University of Southampton

DEVELOPMENT OF ENANTIOSELECTIVE RECEPTORS FOR SEPARATIONS OF RACEMIC MIXTURES OF CARBOXYLIC ACID DERIVATIVES

By David Douhéret

A dissertation submitted in partial fulfillment of the requirements for the Master of Philosophy Degree

FACULTY OF SCIENCE

DEPARTMENT OF CHEMISTRY

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ABSTRACT

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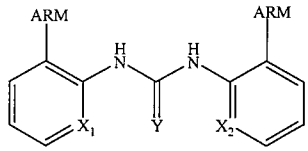
This thesis is concerned with the synthesis and subsequent investigation of the properties of thiourea based receptors for carboxylic acid derivatives. Chapter two describes the synthesis of different phenyl and pyridyl thioureas as Carboxylic Binding Sites (**59-61, 65-67**) for U-shape receptors. Binding studies indicate the suitability of these thioureas for further work on the development of the receptors.

Attention is also given to the level of conformational control (preorganisation) present in the receptor.



$X_1 = X_2 = CH, N$
$Y = S, NH_2+$

($Y = S$, $X_1 = X_2 = CH$) **59**

($Y = S$, $X_1 = CH$, $X_2 = N$) **60**

($Y = S$, $X_1 = X_2 = N$) **61**

($Y = NH_2^+$, $X_1 = X_2 = CH$) **65**

($Y = NH_2^+$, $X_1 = CH$, $X_2 = N$) **66**

($Y = NH_2^+$, $X_1 = X_2 = N$) **67**

L'homme aux quarante écus

« On passe sa vie à espérer, et on meurt en espérant. Adieu, monsieur ; vous m'avez instruit, mais j'ai le cœur navré. »

Le géomètre

« C'est souvent le fruit de la science. »

(*L'homme aux quarante écus*, Voltaire)

Content

Acknowledgement

I would like to thank the following people:

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This time spent in the wonderful world of research will have taught me a few important values.
Firstly, it is now clear to me that some people spend their lives as researchers, others as finders.

Finally, I do understand the meaning of this famous sentence by Voltaire: "Science sans conscience n'est que ruine de l'âme". As the translation would not reflect all the niceties of this sentence, I shall invite you to learn French.

1. Introduction

A molecule is said to be chiral if it is non superimposable with its mirror image. Chirality is an issue of great importance for all molecules with biological relevance. The two mirror images (enantiomers) of a molecule that is intended to act on a biological receptor or enzyme will show different interactions, and hence give rise to different biological effects. A striking example is the sweetener aspartame: whereas the natural (S,S-isomer) is sweet tasting, its mirror image (the R,R-isomer) has a bitter taste. The study of olfaction in the fifties and sixties clearly set up the basis of the importance of chirality, it had become evident that chirality plays a role in the olfactory properties of perfumes and fragrances[1,2,3]. Enantiomer discrimination in odour perceptions is nowadays well recognised. Cases are known in which the two enantiomers of a pair possess significantly different olfactory properties. The experimental results on the carvone and limonene enantiomers are particularly striking: (S)-carvone possesses the odour perception of caraway while (R)-carvone has a spearmint odour. (R)-limonene has an orange odour while its enantiomer has that of lemon.

Although the problem of chirality is of general importance, it had a particular impact on the flavours and fragrances industry and on the pharmaceutical industry. A large number of drugs that are chiral used to be sold as racemates (50/50 mixture of mirror images), but it is now recognised that this is less desirable, because only one of the enantiomers will lead to the desired effect and the other isomer is at best ballast and in the worst case can lead to unwanted side effects - as in the notorious case of thalidomide. This drug given as an anti-inflammatory to pregnant women led to disastrous consequences for the new born babies. As a consequence, in recent years, the regulatory authorities have tended to the view that all the new drugs should be supplied in enantiopure form. In the field of agrochemicals, the switch from racemates to single enantiomers is also a good strategy to reduce the amount of agrochemicals in the soil and therefore also in surface water, thus reducing possible damage to other ecosystems.

The efficient and economical production of enantiomerically pure compounds, particularly from racemic mixtures, is thus one of the major challenges facing the modern

chemical industry. A number of methods mainly used in the field of biotechnologies are available for the production of enantiomerically pure compounds including the use of enzymes, asymmetric synthesis, or fermentation. For small amounts of enantiomerically pure compounds (e.g. for drug discovery programmes), the production is now straightforward in most cases using asymmetric synthesis. However, to achieve good enantioselectivities it is usually necessary to use quite sophisticated chiral reagents.

If they are required in stoichiometric quantities, the need to scale up for clinical trials and production lead to serious cost and waste-disposal problems for the industry.

Recent developments in supramolecular chemistry suggest an alternative approach to the resolution of racemates that avoids problems associated with conventional resolution techniques. Certain "synthetic receptors" are capable of binding their substrates with sufficient power to draw them across phase boundaries, e.g. from an aqueous medium into an organic solvent. If the phase containing the receptor forms a barrier between two others (e.g. an aqueous-organic-aqueous system), it can facilitate transport between the separated phase. If the receptor is enantioselective, only one enantiomer of racemic substrate will be transported, and resolution will be effected.

Enantiopure carboxylic acid derivatives are suitable targets for this methodology because :

- they are usually soluble in water as carboxylate salts,
- they can be extracted into organic phases by agents which "quench" the charge and hydrophilic character of the carboxylate groups
- many important chiral molecules contain the carboxyl group (e.g. amino acids) and,
- the conversion of the unwanted enantiomer back into the racemate, for reprocessing, is generally straightforward.

The overall aim of the proposed research is to develop effective enantioselective receptors, and test these receptors for the medium to large scale separation of racemic carboxylic acids and amino acid derivatives using novel economical membrane devices.

We propose to develop a new class of methods that are economical, environmentally beneficial, and hold out the promise of greater generality than classical resolution techniques.

2. Supramolecular Chemistry

In 1828, Fredrich Wöhler demonstrated the first natural product synthesis by assembling urea[4]. Since then, chemistry has evolved into a mature science that has seen an increasing mastery of the covalent bond, allowing elegant synthesis of more and more complex natural and unnatural products. In 1894, Emil Fischer introduced the idea of geometric complementarity and therefore selectivity through his famous and evocative concept of the lock and key[5], Alfred Werner introduced the idea of co-ordination chemistry[6] and Paul Ehrlich recognised that molecules do not act if they do not bind[7]. Building on these and later developments, Jean-Marie Lehn introduced the concept of supramolecular chemistry in 1978[8].
In 1987, along with D.J. Cram and C.J. Pedersen, he received the Nobel Prize for chemistry for laying the foundations of this rich area of enquiry.

Supramolecular chemistry is defined as the study of the intermolecular bond. By using non-covalent interactions the association of two or more chemical species maybe encouraged resulting in a supermolecule being formed. Supermolecules are composed of a molecular receptor and substrate.

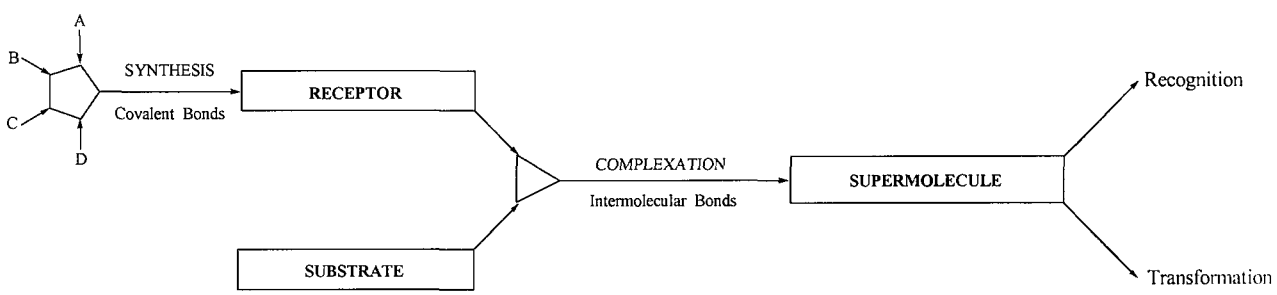


Figure 1 shows the processes involved in the formation of supermolecules.

Individual molecules (A-D) come together through synthesis to form the receptor which complexes the substrate through intermolecular bonds. Once a supermolecule is formed several processes may occur including: binding and selection of a substrate (recognition) and transformation of bound species into products (transformation)[9].

Supramolecular chemistry can also be described as "the chemistry beyond the molecule" [9]. At its heart is the study of non-covalent forces that allow separate molecules to communicate and to associate into complex assemblies. Inspiration for this field lies in Nature's many complex functions which are all facilitated by intermolecular processes. Examples include a virus entering a cell, transfer of genetic information from DNA to RNA and the recognition and transformation of a substrate by an enzyme.

The field of supramolecular chemistry is highly interdisciplinary and overlaps with many branches of science, relating to the physics of condensed matter and the biology of natural polymers.

One can also consider supramolecular chemistry as an information science. Individual molecules communicate instructions through space giving rise to order and complexity. The recognition process implies the storage and read out of information presented by the complementary surfaces of the receptor and the substrate in a system. This is analogous to the interaction between a lock and a key, while the speed that reading takes place is related to the rate of their association and dissociation. Attention is drawn again to Nature. The DNA in the nuclei of our cells is a massive digital recipe for our formation and an archive of our evolution. The two hydrogen bonds of the association of adenine with thymine and the three of guanine with cytosine correspond respectively to the 0 and 1 of binary computer code.

The chemist may act as an artist as well as a scientist developing new molecular architectures, drawing inspiration from the relationship between the three dimensional structure of biopolymers and their function. Aided by the abiotic freedom of the reaction vessel, the chemist is able to create new molecules that further expand the function and complexity of nature.

Since the term of 'supramolecular chemistry' was coined, the imagination of many research teams has been captured. There is an ever-growing volume of literature describing the development of many novel designs. Receptors for many substrates including nucleotide bases[10], carbohydrates[11], amino acids and derivatives[12], artificial catalysts[13], numerous processes by which molecules have been programmed to self assemble *in situ*[14] and even a few systems that are capable of self replication[15] have been reported.

The challenge for the chemist is the development of molecules that are increasingly effective in their function, to generate systems that reflect and complement the incredible complexity that has evolved in biology. The future may see programmed systems containing the necessary information set into their covalent scaffold to carry out desired tasks, perhaps even systems capable of learning, of adapting their structure in response to environmental stimuli and evolving. This would bridge the gap between the closed, controlled systems of the laboratory and open systems, connecting chemistry to the environment.

It would be impossible to provide a comprehensive overview of the immense volume of literature in this area. Instead the interactions that contribute to binding will be introduced using a few representative examples.

There are many useful reference books[16-19] and reviews[20-22] that will provide the interested reader with more general information. These references should also explain the nomenclature that has evolved with supramolecular chemistry. These names may appear gratuitous and are often confusing, with blurred boundaries of definition.Their function however, is merely to provide distinction between certain types of molecule without reference to lengthy systematic names and as such they are indispensable. They should be considered akin to trivial names for living things, which are less cumbersome than the taxonomic name.

3. Host-Guest chemistry

Molecular recognition lies at the heart of biochemistry, and involves the investigation of the selective interactions between biomolecules that control or initiate specific physical functions. Vital biochemical processes such as protein assembly, generic information processing, and molecular transport all inherently require selective molecular recognition and complexation to be successful. The degree of exquisite control and efficiency exhibited by natural systems is a challenging goal for the host-guest chemist to emulate, and has led to much interest into the design of a diverse range of synthetic receptors.

Research into all areas of host guest chemistry has led to the development of a plethora of novel hosts for important biological substrates such as nucleotides, carbohydrates, amino acids and derivatives. All utilize the same fundamental principle, namely that there must exist a complementary relationship between a receptor and its substrate for effective recognition. Firstly, the receptor must contain a cleft or cavity whose size and shape must closely fit the form of the substrate. Secondly, the binding groups lining the interior of this cavity must have a chemical complementarity to the external chemical features of the guest. This premise is illustrated schematically in *Figure 2.*

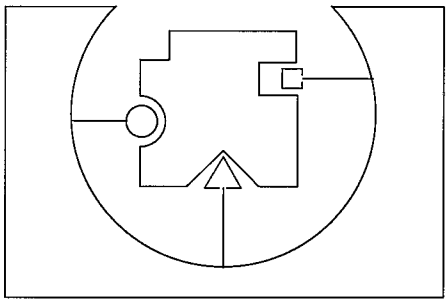


Figure 2: representation of the complementary structural features between a receptor and its substrate.

Ideally, a receptor would be perfectly preorganised to have, as its sole conformation, the structural complement of the substrate to be bound. As the number of low energy conformations of a receptor increases, binding becomes less discriminating and diverges from maximum selectivity. The host then has the opportunity to use whatever state is most appropriate to bind any substrate it may encounter. The host-guest chemist thus strives to

reduce the conformational flexibility of a receptor by introducing as much preorganisation as possible in an effort to achieve selective molecular recognition[23].

A number of factors must be taken into account when a host molecule is designed. The nature of the substrate to be bound (for instance, whether it is charged, cyclic, aromatic or peptidic) will enable prioritisation of the principal molecular interactions involved in the recognition to be made, and evaluation of the functional group arrays to be included in the target molecule.

3.1. Stabilisation of a complex and Energy of Binding

Prior to a discussion of the strategy required for designing effective synthetic receptors, it is important to have a good understanding of the types of molecular interactions involved in complex stabilisation, also called binding interactions.

Indeed, noncovalent interactions are of fundamental importance to all biological process.

The level of binding can be expressed as an equilibrium constant called the association constant, or K_a , which describes the position of the equilibrium between separate host (receptor) [H], and guest (or substrate) [G] and the complex of the bound species HG](*Equation 1*).

$$[H] + [G] \underset{}{\overset{K_a}{\rightleftharpoons}} [HG]$$

Equation 1

This can also be expressed as:

$$K_a = \frac{[\text{ Complex }]}{[\text{ Host }]\,[\text{ Guest }]}$$

This equilibrium constant reflects the free energy of binding (ΔG^0) on complexation (*Equation 2*). As with all thermodynamic processes the free energy change must be negative to be favourable:

$$\Delta G^0_{\text{binding}} = - RT\log K_a \qquad \textit{Equation 2}$$

The free energy contains contribution from enthalpy, (ΔH^0), and entropy, (ΔS^0), and is related to a number of factors (*Equation 3*).

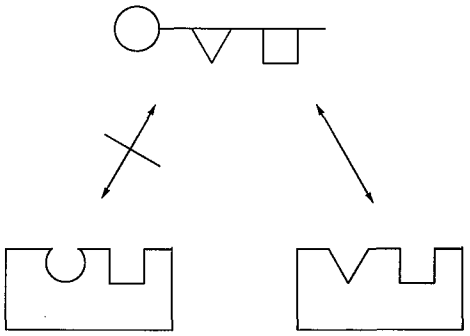
$$\Delta G^0 = \Delta H^0 - T\Delta S^0 \qquad \textit{Equation 3}$$

ΔH^0	ΔS^0
Electrostatic Interactions	Conformational Changes
Hydrogen Bonding	Solvophobic Effects
Van der Waals's Forces	
Aromatic Interactions	
Solvent Competition	
Desolvation	
Dielectric Constant	

None of the binding interactions act independently. It has been shown that the binding of an individual site can be greatly enhanced by co-operative interaction with its neighbours[24,25].

In general, a good Host-Guest complex will have:

- a steric complementarity (lock-key analogy)



- interactions complementarity (as enumerated above)

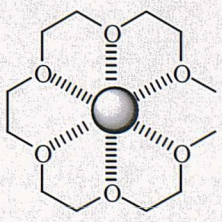
3.1.1. Entropy

Entropy can be explained as a measure of the randomness of a system, the greater the entropy the more disorganised it is and the more favoured it is. Entropy can also be related to atoms and molecules in terms of their spatial freedom. The association of two or more molecules increases order resulting in a loss of entropy (ΔS becomes more negative causing ΔG to become more positive and therefore less favourable).

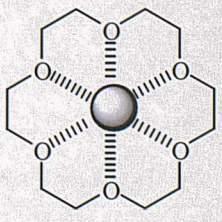
A molecule possesses translational, rotational and internal (vibrational) degrees of freedom. Association of two free molecules to form one complex results in the loss of three translational and three rotational degrees of freedom. The energetic cost for freezing out either the rotational, or the translational degrees of freedom is high at 120 $J.K^{-1}$ mol^{-1}, representing about 40 kJ mol^{-1} for a 1M solution at 25°C[25]. Significantly both rotational and translational terms have a weak mass dependence. Internal degrees of freedom, such as vibrations, make only a small contribution to the entropy[26]. We shall see later that the low mass dependence of translational terms has a profound effect on the role of solvent in molecular recognition.

A receptor, or substrate, that is constrained into the appropriate binding geometry will lose fewer degrees of freedom so that binding will be more entropically favourable. Receptors that are designed to spend most of their time in the appropriate conformation to allow binding to a specific substrate are said to be preorganised[27]. Building rigidity into a receptor pays for entropic losses during synthesis rather than complexation. Highly preorganised systems are also less able to adapt their structure to accommodate other substrates and are consequently more selective.

The concept of preorganisation is demonstrated in *Figure 3*. The acyclic ligand **1** is called a podand and it binds to a potassium cations in anhydrous methanol with log $K_a = 2.3$. The corresponding macrocycle **2** is called a crown ether and binds under the same conditions with log $K_a = 6.08$. The macrocyclic effect therefore accounts for 6000-fold increase in binding strength[18].



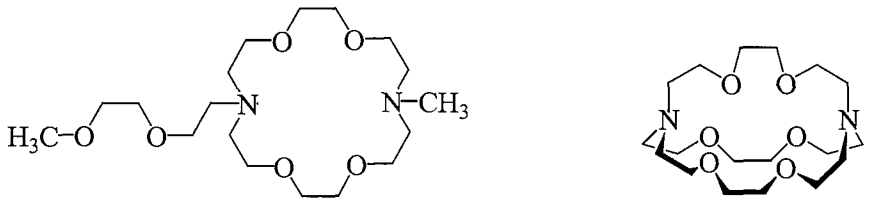
Podand **1**



18-Crown-6 **2**

Figure 3

In a similar study, potassium cations in 95% methanol/water were bound tricyclic [2-2-2]-cryptand **3** log K_a = 9.75, while under identical conditions, the open chained equivalent of this compound called a lariat crown ether **4** showed a much weaker association of log K_a = 4.80. The additional preorganisation in this case is worth an approximate 90,000 fold increase in binding[18] (*Figure 4*).



Lariat Crown - **4**
$\log K_a = 4.80$

[2.2.2] Cryptand - **3**
$\log K_a = 9.75$

Figure 4

However these systems are not fully preorganised. In the unbound structure 18-crown-6 occupies a crumpled conformation in which the methylene hydrogens are *anti*. Complexation forces the hydrogens to be *gauche*, the change of course carrying an energetic penalty, which ultimately decreases the complexation energy.

3.1.2. Enthalpy

3.1.2.1. Hydrogen Bonding

The hydrogen bond is a particularly important phenomenon in recognition processes, especially in biological systems.

The bond between a hydrogen atom and an electronegative element, such as nitrogen, is highly polarised. If this bond is directed towards another electronegative atom bearing a lone pair of electrons, such as oxygen, a weak bond is formed and is termed a hydrogen bond.

Liquids possessing hydroxy groups or other groups with a hydrogen atom bound to an electronegative atom X are strongly associated and have abnormal boiling points. this observation led to the contention that particular intermolecular forces apply here. These are designated as hydrogen bridges, or hydrogen bonds, characterised by a co–ordinative divalency of the hydrogen atom involved. A general definition of the hydrogen bond is: when a covalently bound hydrogen atom forms a second bond to another atom, the second bond is referred to as a hydrogen bond[28].

The concept of hydrogen bonding was introduced in 1919 by Huggins[29]. The first definitive paper on hydrogen bonding- applied to the association of water molecules- was published in 1920 by Latimer and Rodebush[30].

A hydrogen bond is formed by the interaction between the partners R-X-H and :Y-R' according to the equation:

$$R\text{-}X\text{-}H \; + \; :Y\text{-}R' \rightleftharpoons R\text{-}X\text{-}H\text{------}Y\text{-}R'$$

R-X-H is the proton donor and :Y-R' makes available an electron pair for the bridging bond. Thus, hydrogen bonding can be regarded as a preliminary step in a Bronsted acid-base reaction that would lead to a dipolar reaction product :

$$R\text{-}X^{\ominus}\text{------}\ H\text{-}Y^{\oplus}\text{-}R$$

X and Y are atoms of higher electronegativity than hydrogen (e.g. C, N, P, O, S, F, Cl, Br, I). Both inter- and intramolecular hydrogen bonding is possible, the latter when X and Y belong to the same molecule.

The most important electron pair donors (i.e. hydrogen bond acceptors) are the oxygen atoms in alcohols, ethers, and carbonyl compounds, as well as nitrogen atoms in amines and *N*-heterocycles. Hydroxy-, amino-, carboxyl- and amides are the most important proton donor groups.

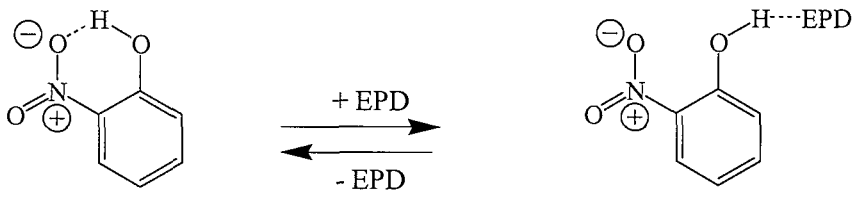
Strong hydrogen bonds are formed by the pairs :

$$O\text{-}H\text{----}O\ ,\ O\text{-}H\text{----}N\ ,\ N\text{-}H\text{----}O$$

When two or more equal molecules associate, so-called homo-intermolecular hydrogen bonds are formed . The association of different molecules results in hetero-intermolecular hydrogen bonds. The designation homo- and heteromolecular[31] as well as homo- and heteroconjugated hydrogen bond are also in use.

Hydrogen bonds can be either intermolecular or intramolecular. Both types of hydrogen bonds are found in solution of 2-nitrophenol, depending on the Lewis basicity of the solvent[32]. The intramolecularly hydrogen-bonded form exists in non-hydrogen-bonding solvents (e.g. cyclohexane, tetrachloromethane). 2-Nitrophenol breaks its intramolecular

hydrogen bond to form an intermolecular one in electron pair donor (EPD) solvents (e.g. anisole, HMPT).



Circular hydrogen bonds have been found in the hexahydrate of α-cyclodextrin (cyclohexaamylose)[33]. Hydration water molecules and hydroxy groups of the macromolecule cooperate to form a network-like pattern with circular O-H---O hydrogen bonds. If the O-H---O hydrogen bonds run the same direction, the circle is called homodromic. Circles with the two counter-running chains are called antidromic, and circles with more randomly oriented chains are designated heterodromic. Such circular hydrogen bonds can be of importance with respect to the inner molecular structure of water and alcohol.

The distance between the hydrogen atom and the non-covalently bound electronegative atom is a little less than a typical Van der Waals contact distance. The energies of such bonds have been estimated by various sources to be 3-30 $kJ.mol^{-1}$ in the optimal linear configuration; significant bending can be tolerated with minimal energy loss. An example of hydrogen bonding used in a host-guest system is the range of synthetic receptors for barbiturates developed by Hamilton[34]. These utilize the triple hydrogen bonding relationship that exists between 2,6-diamidopyridines and imides, as illustrated in *Figure 5.*

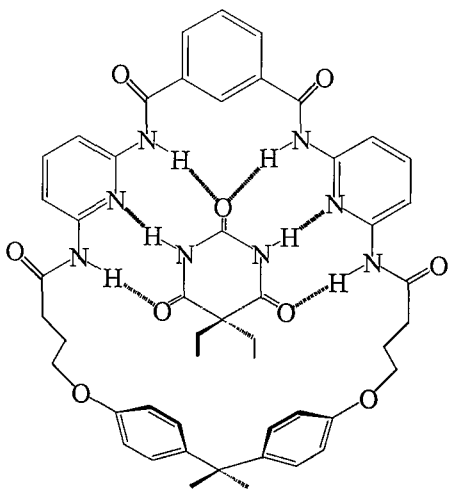


Figure 5

The molecule incorporates this binding site into a rigid framework to form a total of six hydrogen bonds to the barbiturate substrate in the cavity.

3.1.2.2. Electrostatic interactions

All forces between atoms and molecules are electrostatic in origin, even those between non-polar molecules. The term "electrostatic or coulombic forces" is often reserved for those interactions between species bearing opposite charges, but also apply to ionic/dipole and dipole/dipole interactions.

Electrostatic forces play a central role in molecular recognition, both in biological and synthetic systems. As the potential between two ions is a function of their separation and charge, in a host-guest complex designed around the utility of electrostatics, it is desirable that the system contains several ionised regions and that charged sites approach closely. *Figure 6* illustrates hydrogen bonding between an open, extended polyaza macrocycle[35] and ATP^{4-}, formed as a direct result of electrostatic interactions between the phosphate and ammonium moieties.

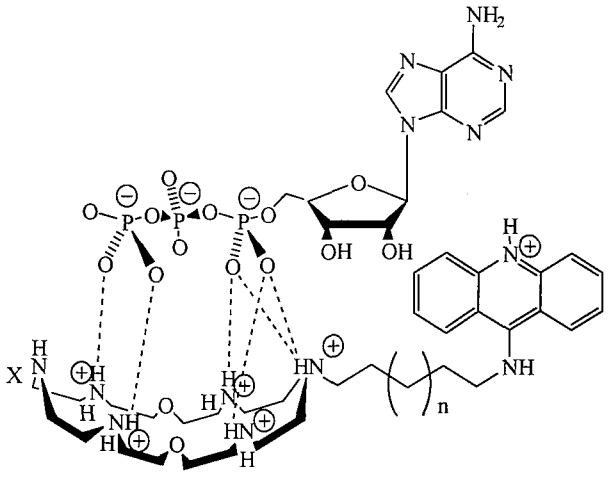
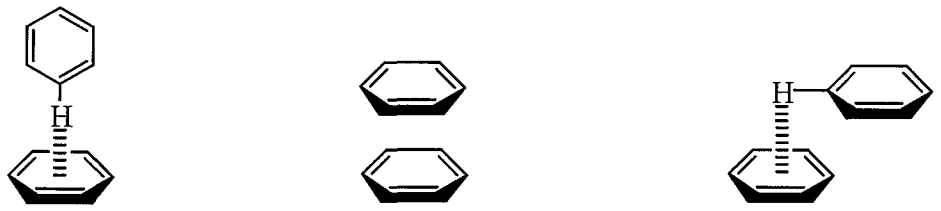


Figure 6

3.1.2.3. Aromatic interactions

Although π-π interactions, or π–stacking, are rather weak interactions, they have an important effect on the geometry of binding. According to a model proposed by Hunter and Sanders[36], the observation of the preferred offset geometry of porphoryn dimers led to the development of a new model. Van der Waals association and solvophobic effects (though weak in chloroform, the solvent of the studies) should prefer face-to-face stacking. It was deduced that electrostatic contributions played a major role in association and the building

geometry. In the model, a positively charged σ framework is sandwiched between negatively charged clouds representing the delocalised π-electrons.



Favoured
Edge To Face

Disfavoured
Face to face

Favoured
Offset stack

Figure 7

The mode of interaction likely to be prevalent between aromatics is that of an offset or edge to face arrangement (*Figure 7)* which places the rings as close together as possible. Face to face stacking is unfavoured as this result in regions of negative charge being in close proximity. Prediction of such aromatic interactions in host-guest systems is complicated as the interactions are not between pure benzene rings, but often heterocyclic species.

3.1.2.4. Van der Waals forces

Unlike electrostatic forces, Van der Waals interactions[37] operate at short range, influencing only over a few molecular diameters, and hence are only significant for molecules in close proximity. They arise from induced dipole-dipole interactions, and consequently their energies are heavily dependent on the polarisability of the substance in question.

The potential energy expression for Van der Waals forces between two atoms is:

$$V = \frac{A}{r^{12}} + \frac{B}{r^{6}}$$

This expression is also know as the Lennard-Jones potential where:

-**A** represents a steeply rising repulsive potential as the two atoms approach within their Van der Waals radii resulting in unfavourable interpenetration of electron clouds[38].

-B represents the attractive potential due to dispersion forces, as a temporary unsymmetrical distribution of electrons in one species induces an opposite polarity in the other.

The attraction is also dependent upon the area of contact of the two molecules: the greater the area the larger the attractive forces. Although the forces are weak, making individual Van de Waals energies low, the interactions are additive and can make significant contributions to binding when summed over the entire system. Van der Waals forces between molecules are dependent upon the nature and polarisability of the solvent in which the system exists, and are reduced in a solvent with respect to a vacuum.

3.1.3. Other factors affecting complex stability

In addition to the four interactions already discussed, other factors affect the stability of the complex. Indeed, the solvent in which the host-guest complex is being formed can affect the binding properties of the receptor due to solvent competition i.e. the solvent molecules can prevent the recognition and binding of substrates by occupying the binding sites themselves. There are two main effects:

3.1.3.1 Hydrogen bonding competition

The term "solvation" refers to the surrounding of each dissolved molecule or ion by a shell of more or less tightly bound solvent molecules. This solvent shell is the result of intermolecular forces between solute and solvent. For aqueous solutions the term used is hydration. Intermolecular interactions between solvent molecules and ions are particularly important in solutions of electrolytes, since ions exert specially strong forces on solvent molecules. Crude electrostatic calculations show that the field experienced by nearest neighbours of dissolved ions is $10^6 \ldots 10^7 V/cm$[39].

The solvation of the host in a polar protic solvent will encourage H-bonding between the host (and the guest) and the solvent. In the presence of a guest, there is competition for the H-bonding sites of the host that results in an enthalpic trade-off, in which the guest needs to form more H-bonds with the host than the solvent molecules that it displaced.

3.1.3.2. Solvophobic effects

Hydrocarbons are poorly soluble in water. Accordingly, the dissolution of a hydrocarbon in water is usually associated with an increase in the Gibbs energy G of the system ($\Delta G>0$). Since it is known that the dissolution of a hydrocarbon in water is exothermic ($\Delta H<0$) it follows from that the entropy of the system must decrease. This can be interpreted as a consequence of the highly ordered structure of the water molecules around the dissolved hydrocarbon molecules. In other words, the water molecules are more tightly packed around the dissolved hydrocarbon molecules than in pure water. This is called a structure increase[40]. If aqueous solutions of two hydrocarbons are mixed, the two hydrocarbons may form an aggregate with simultaneous partial reconstruction of the original undisturbed water structure. This is shown schematically in *Figure 8*.

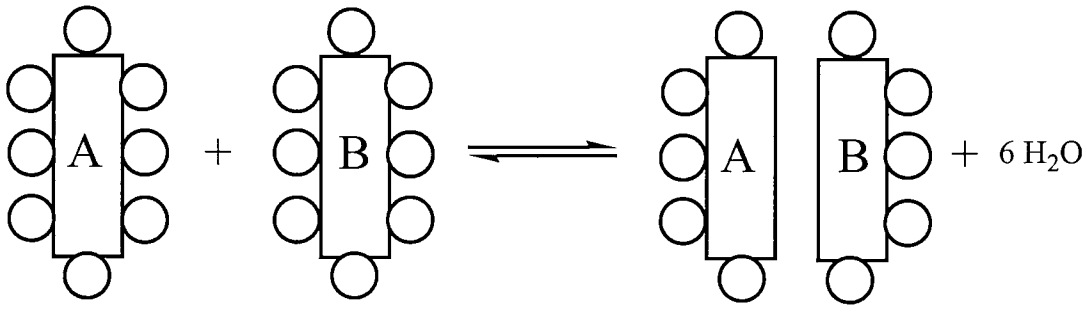


Figure 8: The formation of a hydrophobic interaction between two hydrocarbon molecules A and B (the circles represent water molecules)[40].

Due to the contact between A and B, fewer water molecules are now in direct contact with the hydrocarbon molecules. Thus, the ordering influence of the hydrophobic molecules will be diminished and the entropy increases ($\Delta S>0$). Although thermal energy is required for the destructing of the hydration shells around A and B ($\Delta H>0$), the free energy diminishes upon aggregation ($\Delta G<0$). Therefore, it is energetically advantageous for apolar molecules or apolar groups in large molecules in water to aggregate with expulsion of water molecules from the hydration shells. This phenomenon is known as hydrophobic interaction. This expression reflects the thermodynamic disadvantage of a direct contact between hydrophobic and hydrophilic groups (e.g. alkyl side chains in proteins with water molecules). The system escapes this condition by clustering the hydrophobic groups.

This hydrophobic interaction can be illustrated by considering the thermodynamic parameters for the dissolution of the archetypal apolar hydrocarbon methane in cyclohexane (an apolar, non-associated solvent) and in water (a polar, strongly self associated solvent); *Table 1*.

Solvents	$\Delta G^{\circ}_{s}/(kJ.mol^{-1})$	$\Delta H^{\circ}_{s}/(kJ.mol^{-1})$	$\Delta S^{\circ}_{s}/(J.mol^{-1}.K^{-1})$
Water	26.4	-13.8	-134
Cyclohexane	1.2	-2.5	-54

Table 1: thermodynamic parameters for dissolution of gaseous methane in cyclohexane and water at 25°C[41].

The hydrophobic effect was the first postulated by Franck and Evans in 1945[42].
In principle, such interactions should also apply to other solvents resembling water, and therefore the more general term Solvophobic interaction[43] has been proposed. In fact, analogous water-like behaviour has been observed with self-associated solvents other than water, e.g., ethanol, glycerol and some dipolar non-HBD (hydrogen-bond donor) solvents.

Although it has been widely accepted that hydrophobic interactions are "entropy-driven", there is some contradictory evidence suggesting that they can be "enthalpy driven". Studies on the subject suggest that the major contribution to the hydrophobic interaction between the methylene groups of n-alkanes is an enthalpic and not entropic effect[44].

To summarise, if a molecule is not well solvated, for example, a hydrophobic molecule in water, the solvent forms an ordered structure around it. When the molecule is complexed, solvent molecules are released into the bulk of the solution, hence increasing the entropy of the system, via greater degrees of freedom. Hydrophobic effects are a specific example of solvophobic effects, where an aqueous medium is employed. When a non-polar organic solvent, rather than water, is used as a medium for a host-guest system, the same principles as for hydrophobic effects apply. However, the values of the different thermodynamic terms involved in the binding event, such as desolvation of a guest, may vary considerably. In non-polar solvents such as chloroform, desolvation may represent a less severe barrier (due to the reorganisation of the local environment between solvent and guest) towards complexation than in water.

A multitude of molecular interactions play contributing roles in host-guest chemistry. In designing a receptor for a particular task, those interactions most crucial to the system must be considered, but not to the exclusion of all the others.

3.2. Review of Synthetic Receptors

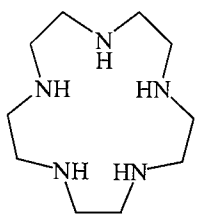
This section reviews the development of receptors for carboxylic acids or carboxylate derivatives. Although our main interest is focused on thiourea and guanidinium receptors and therefore will be discussed in a more detailed way, the review is divided into short sections relating to the site within the receptor to which the carboxylate or carboxylic acid group is bound (i.e. the carboxylate or carboxylic acid binding site or CBS).

We do not aim to deliver an up-to–date review of the different developments of those receptors. We will only introduce the different concepts first created at the early stage of this field of research. Within each section, the examples given reflect the degree to which each CBS moiety has been utilised in receptor design.

3.2.1. Ammonium receptors

3.2.1.1. Polyaza macrocycles

The interaction between a carboxylate and a protonated amine represents the simplest form for the binding of a carboxylate. The use of ammoniums to create carboxylate receptors began with studies on polyammonium compounds as described by the work of Kimura and Lehn. Kimura[45] reported several compounds: pentamines **1-3** and hexamine **4** (as their polyammonium salts), tested as being selective to special carboxylates in water.



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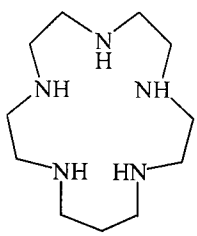

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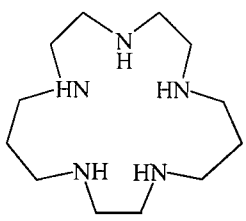

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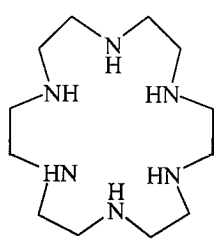
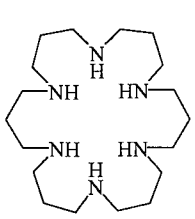


4

At pH neutral, the macrocycles were all triply protonated and formed strong complexes with triscarboxylates such as citrate with electrostatic interactions proving to be fundamental for strong complexation.

Lehn[46] synthesised larger polyaza microcycles **5,6** and **7**. All three fully protonated compounds formed strong complexes with both inorganic and organic polyanions in water. No complexation of monoanions was observed. As previously mentioned, electrostatic interactions were found to play a major role in both the strength and selectivity of anion binding.



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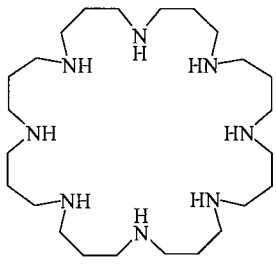

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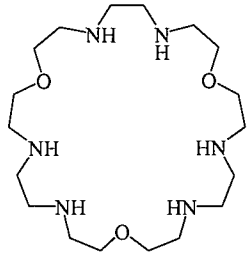
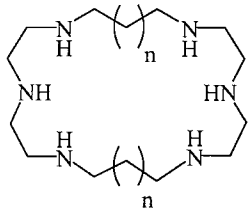


7

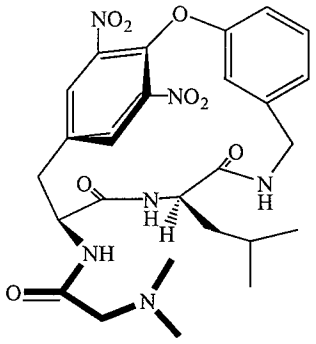
Lehn extended his studies to the preparation of ditopic receptor molecules for dianionic substrates using 1,4,7-triazaheptane moiety separated by various alkyl spacers[47]. The fully protonated forms of hexaaza macrocycles **8-10** were found to complex dicarboxylate substrates with excellent selectivity for substrates whose chain length complemented the size of the cavity.



8 n = 3
9 n = 4
10 n = 5

Other protonated amines receptors with a single protonated amine residue as a carboxylate binding site have also been devised. An elegant example comes from Hamilton[48] who synthesised receptor **11** as a synthetic analogue of the carboxylate binding pocket of vancomycin. Binding of the carboxylate is achieved through a combination of hydrogen bonding from the amide and ammonium functionalities and the formation of a zwitterionic pair. Although no binding constant was reported, large changes in the ^{1}H NMR

spectrum of both host and guest upon complexation in $CDCl_3$ and intermolecular NOE experiments suggest thet binding of the carboxylate **11** resembles the mode of binding exhibited by the antibiotic vancomycin;

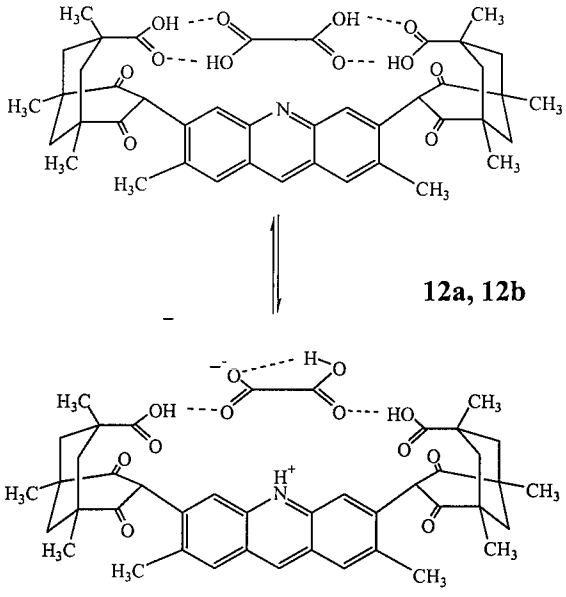


11

3.2.1.2. Cleft receptors

Rebek[49] first described molecular clefts **12a, 12b** as receptors for amino acid derivatives. The well-defined shape of the cleft, derived from condensation of the dye acridine yellow with two of Kemp's triacids, has convergent carboxylic acid groups capable of hydrogen bonding to substrates of appropriate dimensions within the cavity, in a manner similar to enzymes. The molecules were later described as receptors for dicarboxylic acids. A 1:1 stoichiometric complex with oxalic acid in $CDCl_3$ was formed, proposed as tautomeric structures by Rebek.

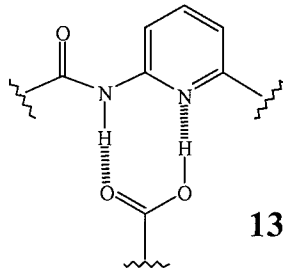
Extra stabilization of these complexes is derived by the prevention of rotations about the C_{aryl}-C_{imide} bonds of the host, restricting its conformations to just those where the carboxyls are convergent.



12a, 12b

3.2.2. Amidopyridines receptors

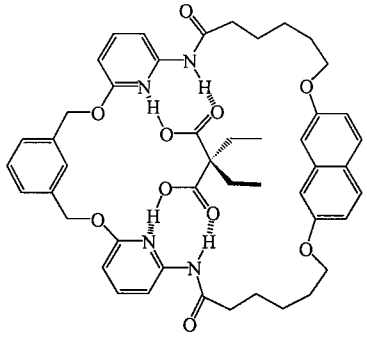
Amidopyridines provide an excellent structural motif for binding carboxylic acids with the ability to form two complementary hydrogen-bonds from the carboxylic acid hydrogen to the pyridine nitrogen and the carboxylic carbonyl to the amide hydrogen as shown by complex **13.**



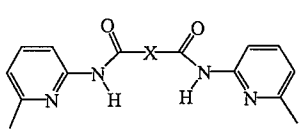
13

In such binding motifs, unfavourable secondary interactions particularly between the relatively electropositive carboxylic acid and amide protons, make amidopyridines a less potent binding site for carboxylic acids than ureas and thioureas are for carboxylates and thus amidopyridines are generally only effective in relatively non-polar solvents.

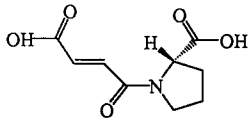
Hamilton[50] was the first to use amidopyridines when he incorporated two amidopyridine units in macrocycle **14** and the structurally simpler **15** to produce receptors for dicarboxylic acids.



14

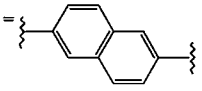


15 X = -pC_6H_4-



17

16 X =

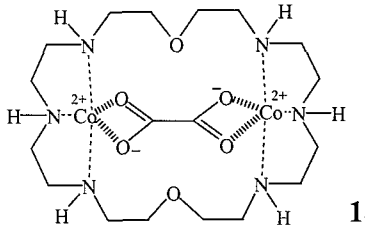


Macrocycle **13** bound ethylmalonic acid ($K_a = 7.3 \times 10^3\ M^{-1}$) and diethylmalonic acid ($K_a = 1.1 \times 10^3\ M^{-1}$) in $CDCl_3$. The relatively low binding constants presumably reflect the unfavourable planar conformation of the diacid required for binding in the cavity of **14.** However, the acyclic receptor **15** forms strong complexes with a range of diacids and particularly with adipic acid ($K_a > 10^5\ M^{-1}$) in $CDCl_3$. An important aspect of this early work was the observation, by X-Ray crystallography, that complexation does not involve proton transfer from the carboxylic acid to the pyridyl nitrogen.

Bisamidopyridine **15** has also been shown to stabilize the (s)-cis rotamer of proline diacid **17** in preference to the (s)-trans, whereas the naphthalene derived bisamidopyridine **16** stabilises the (s)-trans rotamer[51]. Bisamidopyridines have also been cocrystallised with dicarboxylic acids to create self-assembled helical and ribon solid state architctures[52].

3.2.3. Metals

Martell[53] was the first to report the binding of carboxylates by metals. Although the free azacrown of **18** in its fully protonated form is a good host for carboxylate guests ($K_a = 4.8 \times 10^4\ M^{-1}$) for oxalate in water, the cobolt complex **18** forms highly stable complexes with oxalate ($K_a = 1.1 \times 10^9\ M^{-1}$)



18

Bencini Bianchi and Garcia-España have also described a related polyaza macrocycle which forms stable complexes with copper salt of pimelate in water[54].

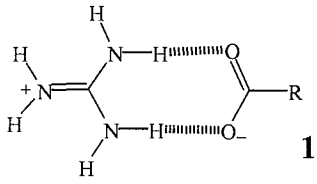
3.2.4. Guanidinium receptors

The guanidinium group as a carboxylate binding moiety possesses several useful features.

Firstly, it remains protonated over a much wider pH range than the ammonium group due to its high p*Ka* (p*Ka* = 13.5 for guanidinium). The group can also form characteristic pairs of

zwitterionic hydrogen-bonds, which provide binding strength due to their charge and structural organization.

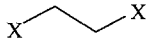
The binding of carboxylates involves a bidentate hydrogen-bonding pattern which is represented by the complex **19**:



19

The guanidinium-anion interaction is important in nature, as can be demonstrated by the function of arginine residues in biological systems[55], and macrocycles containing guanidinium groups have been synthesized for binding purposes[56].

Lehn was the first to utilize the guanidinium group in the complexation of carboxylates by preparing a series of structurally different guanidiniums **20**, **21** and **22** and measuring their association constants with 2 carboxylate salts, acetate and maleate in a 9:1 methanol/water mixture[57].



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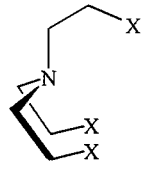

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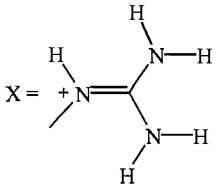
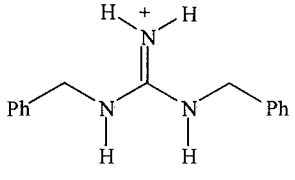


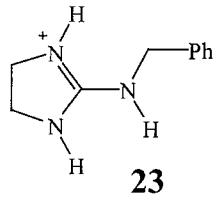


22

The association constant for diguanidinium **20** with acetate was 159 M^{-1} and 15.8 x 10^3 M^{-1} with maleate. The significant increase in the association constant reflects the fact that there are two guanidinium-carboxylate interactions. The same situation occurs with trisguanidinium **21.** Monoguanidinium **22** gave an association constant of 25 M^{-1} with acetate and 79 M^{-1} with maleate.

The association constants observed for **20** and **21** with maleate are significantly greater than between **22** and maleate, this due to the fact that **22** there is only one guanidinium-carboxylate interaction.

Hamilton[50] synthesized guanidinium **23** and found the stabilization of complementary charges led to exceptionally strong binding between acetate and **23** forming complex **24** in DMSO-d_6 (K_a = 12,000 M^{-1}).



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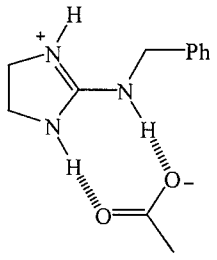
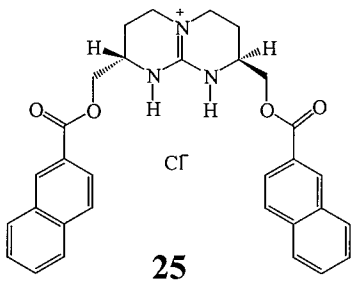


24

Lehn and Mendoza have extended the concept of simple guanidiniums **20-23** by preparing chiral receptor **25**, which contained a rigid bicyclic guanidine and two naphthoyl units[58].



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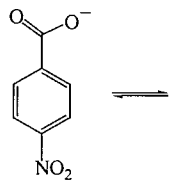

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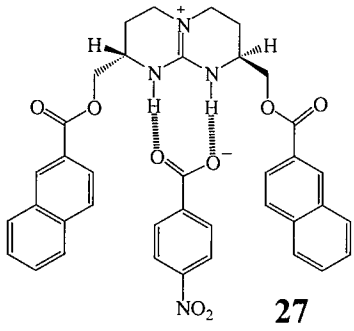
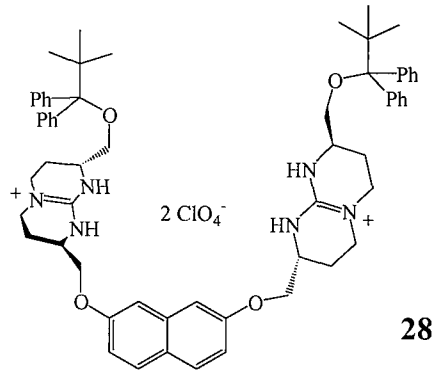


27

Bicyclic guanidine **25** was found to bind *p*-nitrobenzoate **26.** The ^{1}H NMR spectrum of the host-guest complex revealed significant shifts for most signals of both host and guest.
In a separate experiment, sodium *p*-nitrobenzoate **26** was quantitatively extracted from water by a chloroform solution of **25** (K_a = 1609 M^{-1}). This data supported the formation of **27,** which has a well-defined geometry involving double recognition of the guest by the guanidinium cation and the naphtoyl side arms (π-π stacking with the *p*-nitrophenyl moiety).

Mendoza later altered the design of receptor **25** to generate a series of receptors for amino acids by incorporating a crown ether to bind ammonium[59].

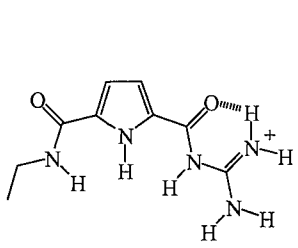
Schmidtchen has also used the rigid bicyclic guanidinium moiety to generate bisguanidinium **28,** which was found to bind a range of dicarboxylate anions in methanol[60]. With monoanions, no change in chemical shifts was observed. Dianions showed complexation and despite its flexibility, **28** exhibits a preference for malonate over shorter or longer analogs. Moreover, even the most rigid and extended guest is bound with considerable stability, indicating the good adaptability of the host to the different guest structure.



28

Diederich[61] also designed receptors for dicarboxylates. His approach consisted of two phenylamidinium units attached to 1,1'-binaphtalene scaffolds. This 1,1'-binaphtalene derivative was found to be a highly efficient receptor for dicarboxylate guests, such as glutarate and isophtalate, even in competitive protic solvents such as methanol.

Schmuck prepared some acyclic guanidinium receptors such as guanidinocarbonyl pyrroles **29** and **30.** These receptors bound carboxylates by ion pairing in combination with multiple hydrogen-bonds[62,63].



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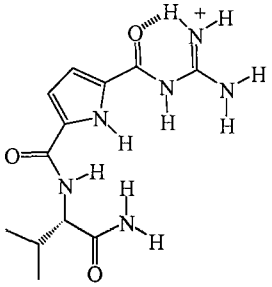

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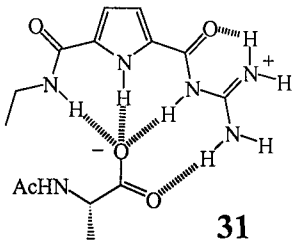


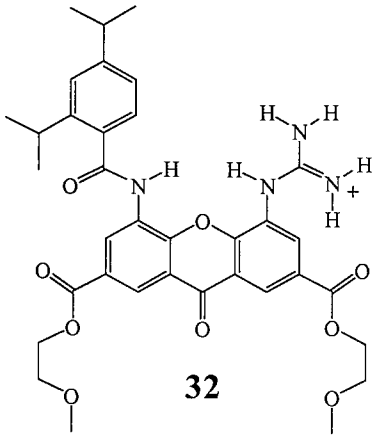
31

Guanidinium **29** incorporated a pyrrole NH to act as an additional hydrogen-bonding donor to carboxylate guests as shown in **31.** For selective binding of *N*-acetyl-α-amino acids, these primary interactions provided the necessary binding energy even in polar solvents, with additional interactions between the amino acid side chain and receptor being used to achieve a selective recognition in **31.**

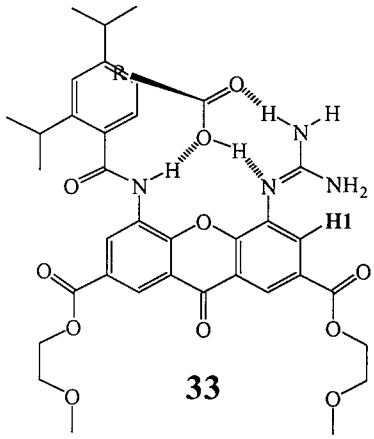
Receptor **29** was found to bind *N*-acetyl-α-amino acid carboxylates in 40% H_2O/DMSO with association constants ranging from K_a = 360 to 1700 M^{-1}, depending on the structure of the aminoacid side chain. Chiral receptor **30** was able to bind amino acid carboxylates enantioselectively (K_a = 350 to 5275 M^{-1} in 40% H_2O/DMSO). This fact was explained by the presence of unfavourable steric repulsion between the isopropyl side chain of the receptor and the alkyl group of certain enantiomers and also by the fact that the aromatic systems of some amino acid carboxylates and the guanidiniocarbonyl pyrolle moiety of the receptor were found to be π-stacked.

Morán[64] has prepared a planar receptor **32** which includes a xanthane scaffold in addition to a guanidinium moiety and also incorporates a third hydrogen-bond from the xanthone NH to the carboxylate oxygens and possible π-stacking interactions with the diisopropylbenzoate residue.

The addition of tetramethylammonium methanesulfonate to a solution of receptor **32** led to a large shift of the methanesulfonate signal in the ^1H NMR spectrum. Attempts to titrate tetramethylammonium actetate in $CDCl_3$ or DMSO with **32** using ^1H NMR spectroscopy did not lead to the expected pattern for movement of acetate methyl group. These results were thought to be related to a proton transfer from the guanidinium to the carboxylate. The acidity of **32** was thought to be a problem as the neutral guanidine **33** could be obtained by washing the ethyl acetate solution with aqueous sodium hydrogenocarbonate. Even though no complex formation was expected for conventional carboxylic acid in DMO, CPK models showed that the free receptor of **33** may well be a good binder of acids. The basicity of the nitrogen atoms were found to favour association with the acidic carboxylic acid hydrogen.



32



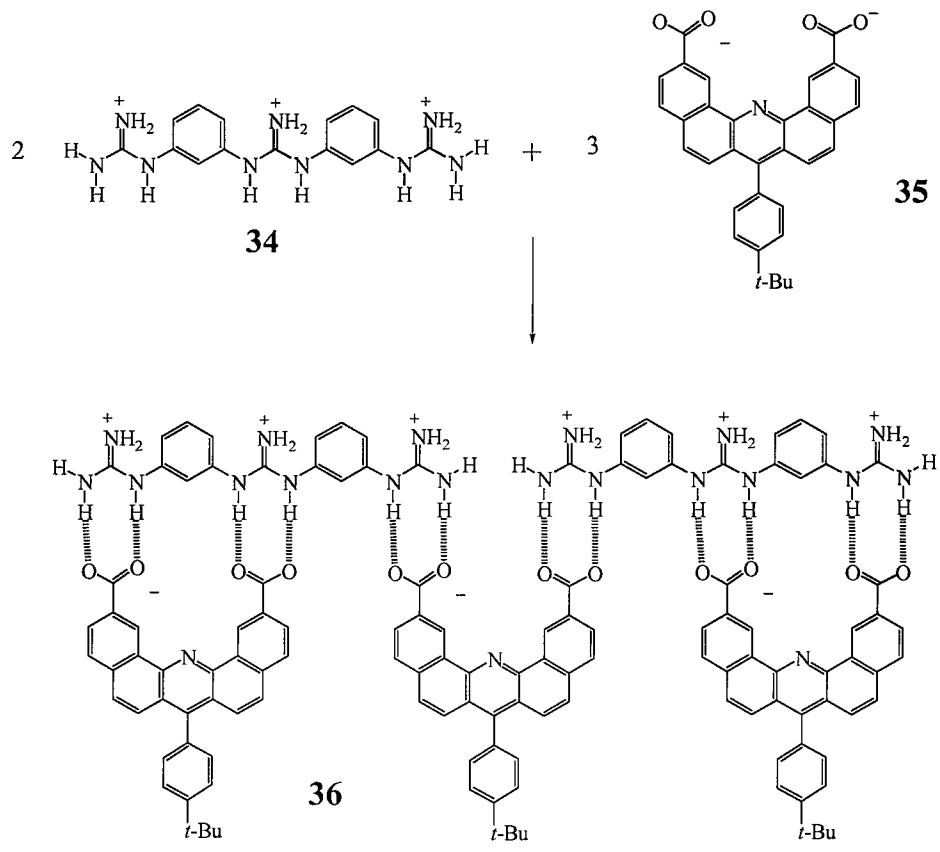
33

In a less competitive solvent such as $CDCl_3$, association takes place with decanoic acid ($K_a = 6 \times 10^4\ M^{-1}$). The association constants of several acids of increasing pK_a were measured by means of a competitive scale to see whether a hydrogen-bond arose when the acidity of the guest matched that of the guanidine. More than a thousand fold increase was observed on passing from decanoic acid to monochloroacetic acid.

A study of the UV spectra of **33** in DMSO was carried out. While acetic and decanoic acid gave no change in the UV spectra, dichloroacetic acid led to the protonated guanidine. Addition of 1.5 equivalents of monochloroacetic acid afforded a soectrum which was similar to that of the protonated species but not superimposable. Larger amounts of monochloroacetic acid did not further change the spectrum. Morán attributed this fact to complex formation. When **33** was titrated with monochloroacetic acid in DMSO, a K_a of $1.8 \times 10^4\ M^{-1}$ was measured. When saturation was reached, the addition of either dichloro or trichloroacetic acid further shifts proton **H1,** in agreement with final guanidinium protonation. It was concluded that monochloroacetic acid associates with receptor **33** in a very competitive solvent such as DMSO and that,, under these circumstances, small differences in the pK_a of the acid may lead to large changes in the association constants.

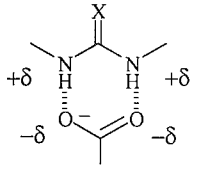
Recent developments in the preparation of guanidinium based receptors include the synthesis of steroidal based guanidinium receptors which are based on a cholic acid scaffold by Davis[(65)].

At last Kelly[(66)] has described the first example of a molecular Vernier **36,** where three molecules of dicarboxylate **35** were found to combine with two molecules of a tris guanidinium **34** to give a pentamer of predetermined dimension **36**. In the Vernier mechanism, two complementary components having different unit lengths undergo side-by-side linear aggregation. Growth continues until the tips of the adjacent aggregates come into register, like the lines of a Vernier, whereupon growth ceases. Generation of **36** was achieved simply by mixing solutions of **34** and **35. 36** spontaneously precipitated from the solution in a very good yield (>95%) and in anatically pure form.

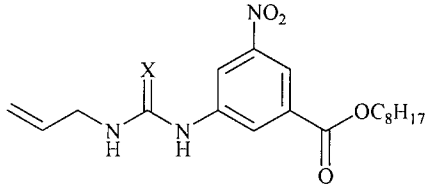


3.2.5. Thiourea and urea receptors

Thiourea and urea units, which have been shown to provide a strong binding site for carboxylate anions[67,68], were developed by Wilcox and then Hamilton. The strong binding of carboxylates was possible through the two hydrogen-bonds from the urea/thiourea N-H hydrogens to the carboxylate oxygens, as shown in complexes **37** and **38.**



37 X = O, **38** X = S



39 X= O, **40** X = S

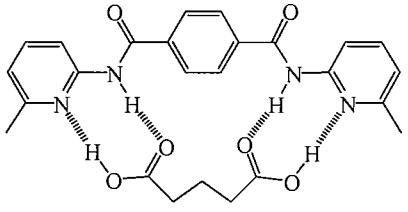
Wilcox was the first to utilise ureas and thioureas such as **39** and **40** in carboxylate binding[69].

Urea **39** was found to bind benzoate with an association constant of 2.7 x 10^4 M^{-1} in $CDCl_3$. Large shifts of the N-H protons were also observed, indicating strong hydrogen-bonding between the urea hydrogens and carboxylate oxygens. Further work by Hamilton led to the use of the urea and thiourea in polar solvents such as DMSO[70]. Addition of

tetramethylammonium acetate to a DMSO-d_6 solution of 1,3-dimethylurea gave large downfield shifts of the urea NH resonance (>1 ppm), which was consistent with the formation of a bidentate hydrogen-bonded complex as in **37** and gave an association constant of 45 M^{-1}. Further gains in the binding energy were achieved by increasing the acidity of the hydrogen-bonding donor sites by replacing the urea for a thiourea.

Thiourea (pK_a = 21.0) is more acidic than urea (pK_a = 26.9), and as a consequence 1,3-dimethylthiourea complex **40** gave nearly a ten fold increase in stability over **39** with an association constant of 340 M^{-1}.

Hamilton modified amidopyridine **41** and replaced both the amidopyridine units as hydrogezn-bonding donors with ureas/thioureasas shown in **42** and **43.** This had the advantages of creating four favourable secondary hydrogen bonding interactions and of increasing the strength of primary interaction through the use of charged hydrogen-bonding acceptors (the carboxylate anion).



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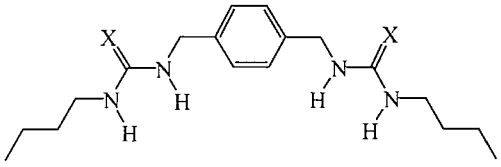
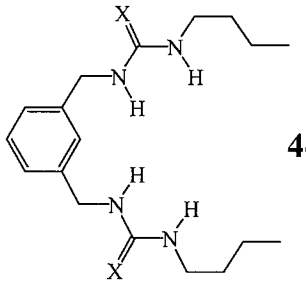


42 X = O, **43** X = S

Compounds **42** and **43** were found to bind the bis-tetrabutylammonium salt of glutaric acid in DMSO-d_6 with association constants of 6.4 x 10^2 M^{-1} and 1.0 x 10^4 M^{-1} respectively. Hamilton showed that by manipulating both the location and charges of hydrogen binding sites, synthetic receptors could be converted from those that function only in nonpolar solvents to those that strongly bind in highly competitive solvents.

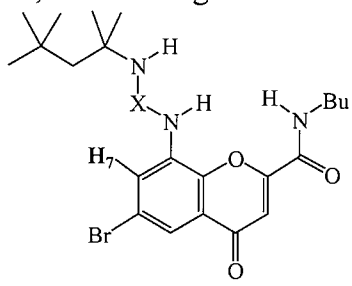
Umezawa[71]) also used the urea and thiourea moieties to bind carboxylates. Urea **44** and thiourea **45** were synthesized and their abilitiy to bind acetate was studied.

The association constant between **44** and acetate was found to be 43 M^{-1} and 470 M^{-1} for **45** with acetate in DMSO-d_6. Umezawa found that the thiourea offered certain advantages over the urea moiety. **44** was insoluble in solvents of low polarity such as $CDCl_3$ whereas thiourea **45** was solvated in this solvent and showed no evidence of self-association.



44 X = O, **45** X = S

Morán prepard a urea and sulfuryl based receptorable to bind carboxylate through the use of both the carboxylate *syn* and *anti* lone pairs[72]. The association constant of urea **46** with benzoate in DMSO was surprisingly small (K_a = 20 M^{-1}) compared to other known urea receptors (K_a = 45 M^{-1} for simple dimethylurea and acetate. Further studies revealed some steric interference between the benzoate aromatic ring of the guest and the receptor butyl substituent. Furthermore, the urea function had to be twisted with respect to the chromenone ring due to the hindrance between the urea carbonyl and the chromenone $\mathbf{H_7}$. This mad ethe cleft wider and prevented the formation of any linear hydrogen-bonds. To overcome this problem, the sulfuryl amide **47** was prepared. The association constant of this receptor with benzoate in DMSO was 330 M^{-1}, which is higher than with **46.**

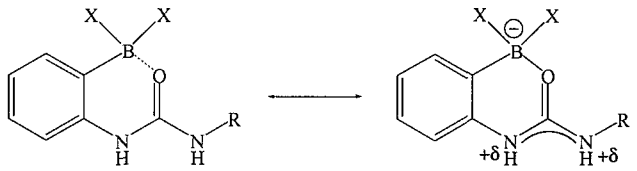


46 X = C=O, **47** X = SO_2

The improved geometry combined with the higher acidity of the sulfuryl amide hydrogens accounted for its better binding properties. The good chloroform solubility of sulfuryl amide **47** allowed titration in this solvent and the association constant with benzoate was over 1 x 10^5 M^{-1} and could not be accurately determined.

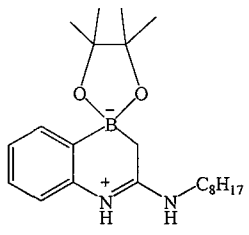
A similar study on a complex combining two chromenone fragments with a urea function was carried out. This receptor was able to form four linear hydrogen-bonds with a carboxylate guest (compared to three with **46** and **47**). The association constant with benzoate in DMSO was 1.5 x 10^4 M^{-1}. The synthesis of a symmetric sulfuryl amide was also carried out and the association constant of this new receptor with benzoate in DMSO was measured and found to be over 1 x 10^5 M^{-1}.

Recently, new developments in the binding of carboxylates have been of importance. Smith[73] has developed neutral urea-based receptors with internal Lewis acid co-ordination for high affinity carboxylate binding. The coordination of the boron to the urea oxygen as shown in **48** increases the polarization of the NH bond leading to increased binding ability.

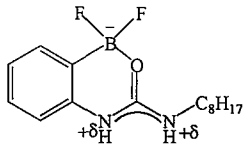


48

Association constants were measured by ^{1}H NMR titration experiments in the highly competitive solvent DMSO-d_6 between **49, 50, 51** and **52** and tetrabutylammonium acetate. The results are given in *Table 2.*



49



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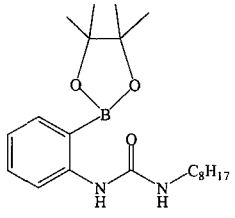

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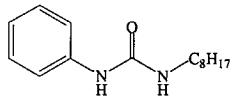


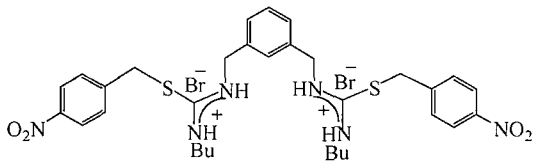
52

Host	K_a (M^{-1})	ΔG_{295}(kcal/mol)	$\Delta\delta_{max}$ (ppm)
52	(3.7±0.4) x 10^2	-3.5	2.14
51	(3.9±0.4) x 10^2	-3.5	2.16
49	(7±2) x 10^3	-5.2	3.75
50	(6±3) x 10^4	-6.5	3.96

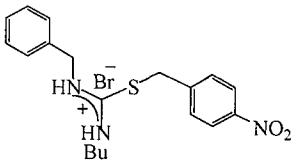
Table 2. Acetate Association constants from 1H NMR titrations in DMSO at 295°K.

There is no major difference between **51** and **52** as the electronegativity of the boron is similar to hydrogen. **49** and **50** showed much better results. This was due to an improved host hydrogen bond donation and the generation of a strong host molecular dipole. the greater binding ability of **50** reflects the structural change to a more withdrawing boron difluoride, which increases the two effects. The strategic use of Lewis acid is an important discovery, this can be further underlined by the fact that **50** is a better acetate binder than guanidinium cation (K_{ass} = 1.2 x 10^4 M^{-1} in DMSO).

Hong[74] developed Smiths' approach by preparing thiouronium-based receptors **53** and **54** through the S-alkylation of the thiourea groups.



53

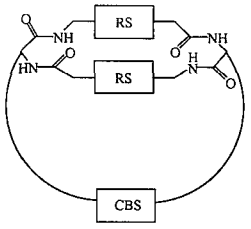


54

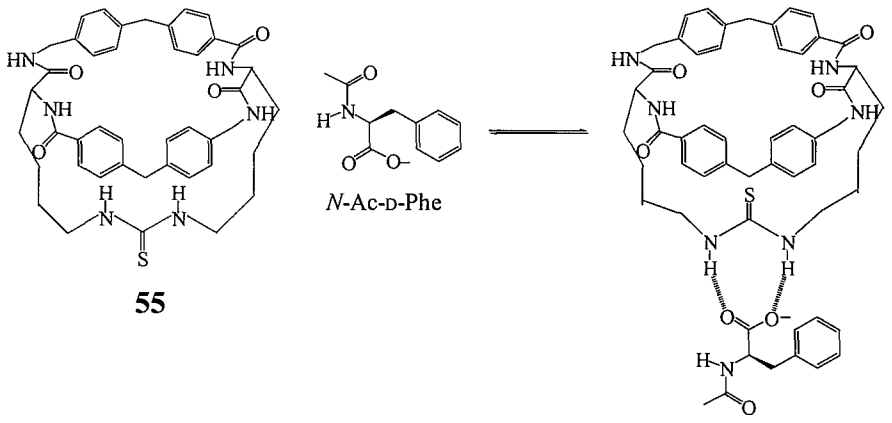
Compared to thiourea groups as an oxoanion binder, thiouronium groups turn out to be relatively stronger binder for oxoanion substrates. For example, mono(thiouronium) receptor **54** binds tetrabutylammonium acetate in DMSO-d_6 more strongly (K_a = 800 M^{-1}) than a mono(thiourea) (K_a = 340 M^{-1}) and a bis(thiourea)(K_a = 470 M^{-1}) respectively. However, it showed poorer binding affinity than guanidinium based ones, although it was very similar in structure.

This fact implied the cationic power of thiouronium was weaker than that of guanidinium, which results from the greater polarisability of sulphur compared with nitrogen. Since anion basicity is a measure of the propensity to form hydrogen bonds, the observed stability trend suggested that the major importance in the formation of thiouronium-oxoanion complex was hydrogen bond formation rather than electrostatic interaction.

Thioureas have been incorporated into more complex architectures for the recognition of more complex carboxylate derivatives[75]. For example, Kilburn has prepared a macrobicyclic receptor **55**, which incorporates a thiourea as the carboxylic binding site, and amide functionality to provide further hydrogen-bonding interactions with suitable guests such as peptidic guests.



CBS = Carboxylate or Carboxylic Binding Site
RS = Rigid Spacer



55

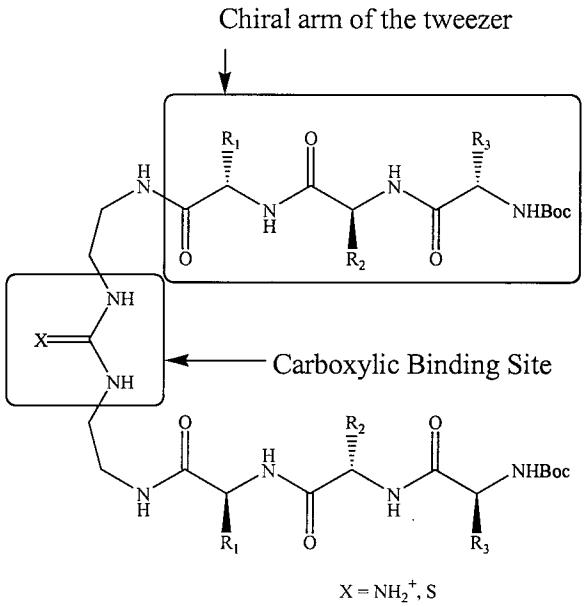
Binding studies showed little selectivity for the various substrates investigated. Nevertheless, Detailed NMR studies revealed that D-amino acid substrates bound predominantly on the outside of the macrobicyclic cavity by a strong carboxylate-thiourea interaction. L-amino acid substrates bound predominantly on the inside of the cavity, but with the acetyl amide in a *cis* amide configuration. Molecular modeling studies suggested that the energetic penalty associated with adopting a *cis* amide configuration in the host-guest complex was compensated by intermolecular hydrogen-bonds between the *cis* amide and the macrocycle amide functionality.

4. Results and Discussion

The aim of the project, part of a European network of research[76], was driven by the need for simple compounds to use as new enantioselective receptors of carboxylates. So far, several types of host-guest complexes have been prepared.

Most synthetic receptors developed by host-guest chemists have incorporated at least one macrocyclic ring because macrocycles have a degree of preorganisation[77]. In a non-macrocyclic receptor reorganisation of the 3D structure of the receptor maybe required so that it is in the correct conformation to bind to the guest. Macrocyclic receptors are locked into a particular conformation and therefore do not need to reorganise as much, which means there is a smaller loss of degrees of freedom upon binding and so the overall binding energy is greater. Although macrocycles have proved to be successful receptors, their synthesis can be long and require numerous steps.

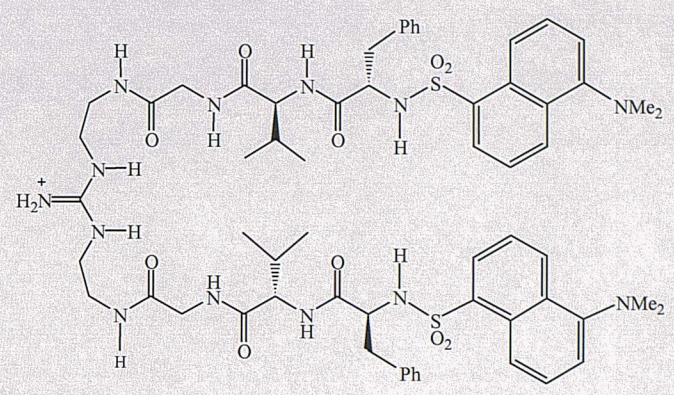
There have been a number of non-macrocyclic receptors developed by host-guest chemists including "tweezer receptors" *(Scheme 1)* or "U-shaped cleft" receptors.



Scheme 1

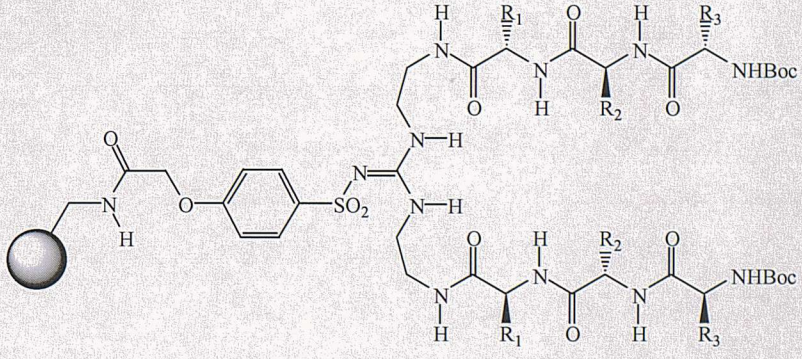
Tweezer receptors are so named because they contain structural features like those of tweezers and their mode of binding can be likened to a pincer. The Kilburn group has synthesised receptors for peptides with a carboxylic acid terminus[78]. Solid-phase synthesis was used to prepare a dansyl-labelled tweezer receptor **56**, which was designed to bind the carboxy terminus of peptides in aqueous system. A guanidinium binding site

was used to provide the primary binding interaction for the carboxylate. The tweezer arms have the potential to form hydrophobic and β-sheet like hydrogen-bonding interactions with the backbone of the peptide substrate.



56

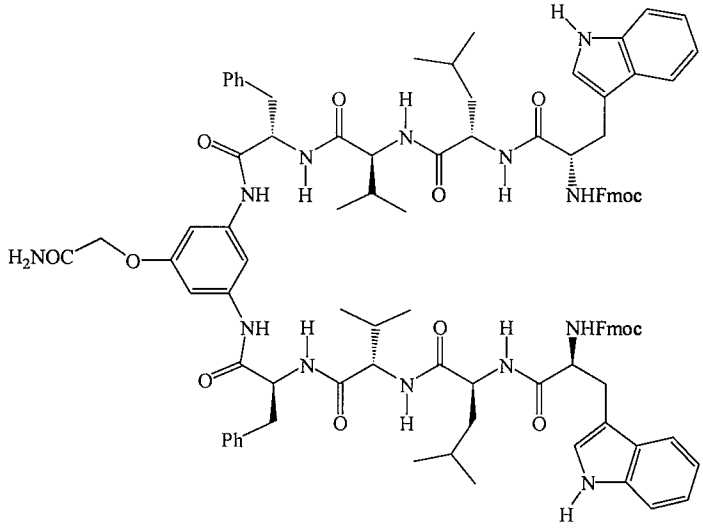
A 1000-member biased library of tripeptides, attached to TentaGel resin via the amino terminus, was screened against tweezer **56** in water. The tweezer receptor was found to bind to approximately 3% of the library members and following sequencing of 20 beads, showed 95% selectivity for valine at the carboxy terminus of the tripeptides and 40% selectivity for Glu(O^{t}Bu) at the amino terminus. Binding of one of the peptides selected from the screening experiments , Cbz-Glu(O^{t}Bu)-Ser(O^{t}Bu)-Val-OH was measured to have an association constant of 4 x 10^5 M^{-1}.



57

It was also possible to screen a library of receptors for the binding of specific tripeptide sequences. However, problems occurred with the direct screening of resin bound receptor library **57**, as the binding strength of the guanidine appeared to have been reduced by the presence of the electron withdrawing sulfonamide linker. It was also thought that the linker might create an unfavourable steric hindrance preventing the binding site orientating into the ideal conformation for binding. It was necessary to find an alternative that could allow anchorage of the tweezer receptors to the solid support without influencing the binding properties.

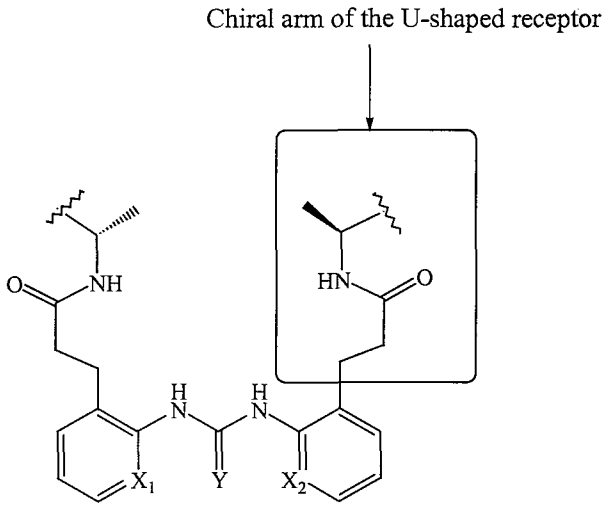
More recently, Kilburn has prepared receptor **58** for peptides with a carboxylic acid terminus[79]. Solid-phase synthesis was used to prepare tweezer receptor **58**, which was designed to bind to the carboxy terminus of peptides in organic media. A diamidopyridyl binding site was used to provide the primary binding interaction for the carboxylic acid. As previously noticed, the tweezer arms have the potential to form hydrophobic and β-sheet like hydrogen-bonding interactions with the backbone of the peptide substrate.



58

Unfortunately, tweezer receptor **58** was insoluble in neat $CDCl_3$ and CD_3CN, thus preventing NMR studies on the formation of a complex with DNS-L-Glu(O^{t}Bu)-L-Ser(O^{t}Bu)-L-Val-OH (a consensus peptide sequence from screening an inverted peptide library against a single tweezer receptor). However, a 500 μM solution of **58** in DMSO:$CHCl_3$ (2:98) could be prepared and complexation studies were carried out on this solution. The intensity of the fluorescence emission maximum for the dansyl group of the peptide guest decreased as successive aliquots of tweezer receptor **58** were added, with the drop in intensity exhibiting typical saturation. The date for this experiment showed a good fit for the presumed 1:1 binding and allowed an estimation of the association constant as 2.6×10^5 M^{-1}. It was concluded that, as anticipated, the incorporation of a specific binding site for the carboxylic acid terminus of peptide guests into a tweezer structure provided a considerably higher affinity than with a non-specific head group.

As a new strategy, the current project was to develop new U-shaped cleft receptors, whose structures are as follows:



$X_1 = X_2 = CH, N$
$Y = S, H_3CS^+, NH_2^+$

(Y = S, $X_1 = X_2$ = CH) *N-N'*-diphenyl thiourea **59**

(Y = S, X_1 = CH, X_2 = N) *N*-phenyl-*N'*-2-pyridyl thiourea **60**

(Y = S, $X_1 = X_2$ = N) *N-N'*-2-dipyridyl thiourea **61**

(Y = H_3CS^+, $X_1 = X_2$ = CH) *N-N'*-diphenyl thiouronium **62**

(Y = H_3CS^+, X_1 = CH, X_2 = N) *N*-phenyl-*N'*-2-pyridyl thiouronium **63**

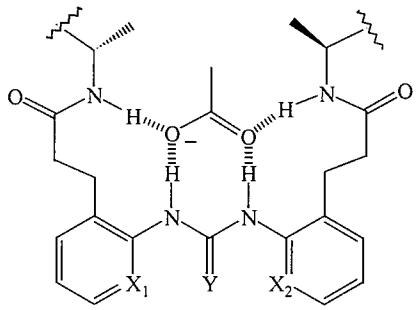
(Y = H_3CS^+, $X_1 = X_2$ = N) *N-N'*-2-dipyridyl thiouronium **64**

(Y = NH_2^+, $X_1 = X_2$ = CH) *N-N'*-diphenyl guanidine **65**

(Y = NH_2^+, X_1 = CH, X_2 = N) *N*-phenyl-*N'*-2-pyridyl guanidine **66**

(Y = NH_2^+, $X_1 = X_2$ = N) *N-N'*-2-dipyridyl guanidine **67**

Like tweezer receptors previously discussed, each arm would consist of a series of chiral amino acids. The thiourea and amide hydrogens were also intended to act as hydrogen-bonding donors to the *syn* and *anti* lone pairs of the carboxylate guest oxygen as shown in *Figure 1*.



$X_1 = X_2 = CH, N$
$Y = S, NH_2+$

Figure 1

Thiourea units, which have been shown to provide a strong binding site for carboxylate anions[67,68], were developed by Wilcox and then Hamilton. The strong binding of carboxylates was possible through the two hydrogen bonds from the thiourea N-H hydrogens to the carboxylate oxygens, as shown in *Figure 2.*

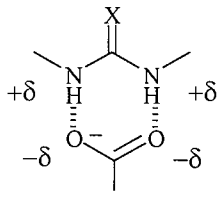


Figure 2

To encourage chiral recognition between the U-shaped receptor and the carboxylate guest, sterically demanding chiral groups could be incorporated in the arms to interact with the amino acid side chain of the guest, leading to a final compound with a good internal structure as well as a good chiral recognition.

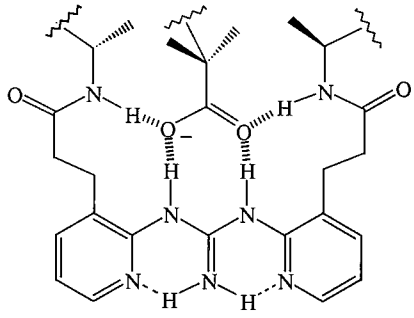


Figure 3

Our main point was to achieve a preorganised structure with the two chiral "arms" aligned as in *Figure 3.*

We thought that the guanidinium derivatives would have a more rigid conformation than the thiourea derivatives as internal hydrogen bonding might take place in the latter (*Figure 4*).

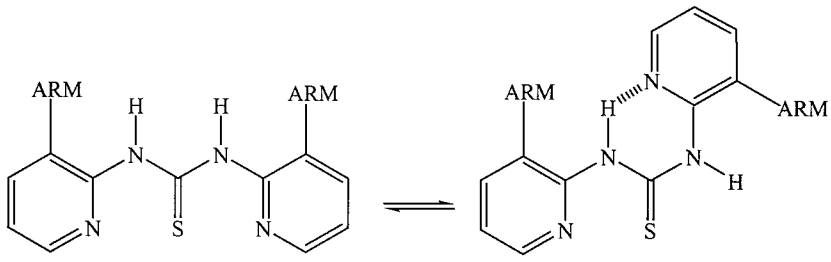
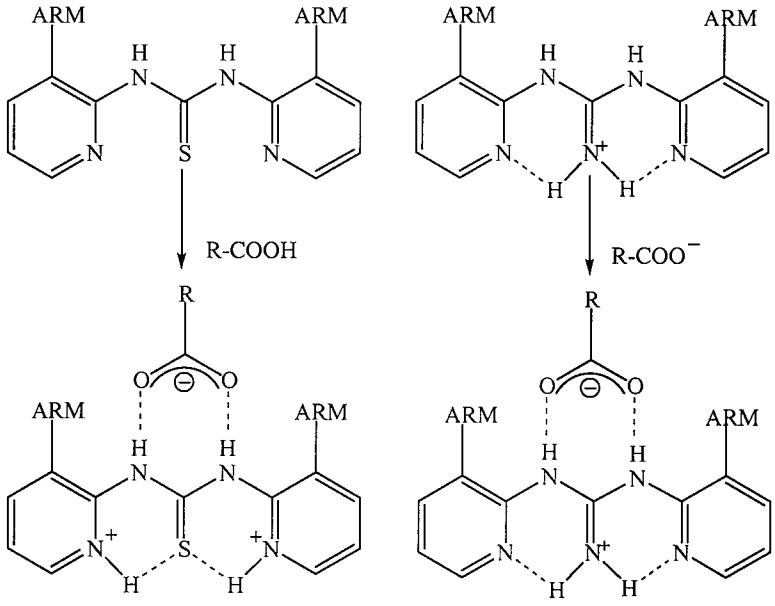


Figure 4: examples of reorganisation and spatial freedom in thioureas.

We anticipated that pyridine rings could interact with the guanidinium group (as in **67**). Also with thiourea **61**, protonation of the pyridines could lead to preorganisation (*Figure 5*). In order to test out this hypothesis, we undertook the synthesis of compounds **59-61** and **65-67** to compare the binding properties and influence of the pyridines.

These effects may have an important consequence on the binding studies that will take place afterwards.



complex of **61** with a carboxylic acid

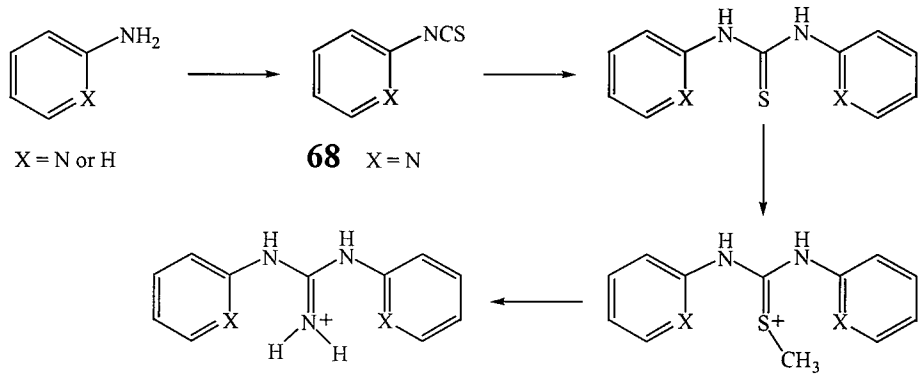
complex of **67** with a carboxylic acid

Figure 5: the hydrogen of the guanidinium could make the molecule more rigid by binding to the nitrogen atoms of the rings allowing a better internal reorganisation to bind a carboxylic acid derivative.

4.1. Synthetic Aspect

4.1.1. General approach and literature background

To prepare the desired compounds, the following schematic synthetic route was proposed:



4.1.2.Methods of preparation of thioureas

The two starting materials were aniline and 2-aminopyridine and the first possible step was the preparation of *N*-2-pyridylisothiocyanate **68** as phenylisothiocyanate was a readily available product.

The major problem encountered in the reactivity of aminopyridines is their very low nucleophilicity of the amine[80].

Aminopyridines exists as amino tautomers, as shown in *Figure 6* :

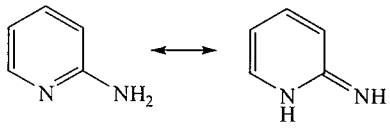


Figure 6: α-aminopyridine resonance structures.

As a consequence, the lone pair electrons on the amino group are not very available to react with an electrophile.

Literature research showed that the preparation of alkyl and aryl isothiocyanates was well documented but less effort had been given to the preparation of heterocyclic derivatives. Pyridyl isothiocyanates were no exceptions and only recently had attention been turned to the preparation of these derivatives[81].

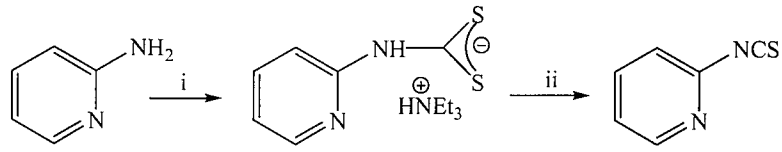
N-2-pyridyl isothiocyanate **68** is described as a liquid, a pale yellow monomer that solidifies at room temperature to a brick-red crystalline compound[82], whose structure was initially thought to be an eight–membered ring[83]. The correct structure of the red dimer, namely the Diels-Alders adduct is now well established[84](*Figure 7).*

Former Structure Established Structure

Figure 7: structures of *N*-2-pyridyl isothiocyanate **68.**

Gerrit L'abbe[81] claims that the dimerization process is reversible in solution. **68** should dissociate completely in dimethylsufoxide at 70°C and this monomer should remain unaltered upon cooling to room temperature. Also in chloroform solution, dissociation should occur readily with a half-life of 22 minutes at 50°C. At room temperature, equilibrium with 83% dissociated dimer is reached after three days. When the chloroform solution is cooled to –50°C, dimerisation occurs again. The reversibility of the process is of interest since the dimmer can be used as the starting material for carrying out chemical reactions on the isothiocyanate.

Procedures to prepare 2-pyridyl isothiocyanate via ammonium *N*-2-pyridyldithiocarbamate **69**, have been given by Fairfull and Peak[82] and also by Le Count and Grundy[85] *(Scheme 2).*



69

i) CS_2, NEt_3, Abs. EtOH,
ii) $FeCl_3$ in H_2O, DCM, NEt_3 or Cl_2CS in dry Toluene, 0°C, Ar

Scheme 2

The first procedure involved the use of concentrated aqueous ammonia (2eq), carbon disulphide (1eq) and 2-aminopyridine (1eq) at 0°C and stirred overnight at room temperature. The crude product was filtered off and washed with a little methanol and

with acetone to afford yellow crystals. The second step involved the use of thiophosgene (1 eq) in dry toluene at 0°C under argon atmosphere. A second procedure involved the treatment of *N*-2-pyridyldithiocarbamate **69** with an aqueous solution of iron chloride[85]. A third procedure given by Schultz and Gauri[86] involved a mixture of 2-aminopyridine with sodium hydrogenocarbonate in water followed by the addition of thiophosgene in water.

Our research also focused on more straightforward preparations to avoid sensitive intermediates such as **68** and **69**. Although thioureas have been reported in the literature since quite a long time, the preparation of compound **61** was not very well documented and proved not to be easy to prepare compared to thioureas **59** and **60**.

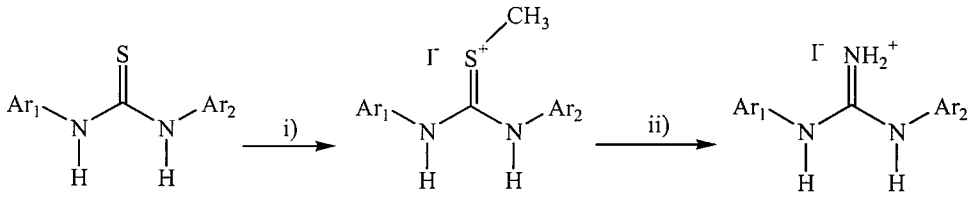
In 1899, Hugershof was the first to report the preparation of symmetrical *N,N'*-diarylthioureas[87]. Thioureas and derivatives have been then studied and found to be tuberculostatic[88] as well as having an antiacetylcholinesterase activity[89]. The Hugershof procedure involved the heating of a primary arylamine with carbon disulphide and sulphur in ethanol. According to the literature, aryl isothiocyanates used in the preparation of unsymmetrical *N,N'*-diarylthioureas were found, to be readily accessible by an extension of the Werner reaction[90].

The preparation of *N,N'*-di-2-pyridilthiourea **61** has been claimed by Fischer[91], Camps[92], Schmid and Becker[93] and Feist[94]. All the procedures described in these articles are dated from the beginning of the century and the compound was described as a side product in the attempted preparation of *N*-2-pyridyl isothiocyanate **68**.

All thioureas undergo thermal decomposition on prolonged heating below their melting points; the melting points therefore depend to a great extent on the speed of heating. This accounts for the wide discrepancies reported. Indeed a search on Beilstein shows that **61** is present in 2 forms: a lower melting form and a higher melting form. The difference of melting points ranges from 136°C to 169°C.

4.1.3. Methods of preparation of guanidiniums salts via thiouronium intermediates

The next step in our work was the synthesis of the guanidinium derivatives. It was thought that we could start with the thioureas by treating them with iodomethane in dichloromethane or acetone to form the isothiouronium iodide. Then treatment of this latter with ethanol saturated with ammonia would give us the guanidinium iodide.



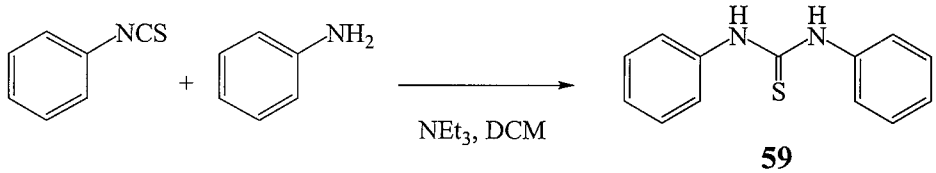
i) CH_3I, CH_3COCH_3
ii) NH_3 in EtOH, 75°C in sealed tube

This approach was thought to be safer and more convenient than the usual preparation involving mercury[95].

4.2. Synthetic results

4.2.1. Synthesis of *N,N'*-diphenyl thiourea 59

The synthesis of *N,N'*-diphenyl thiourea **59**, was our first target. Its preparation involved the following procedure:



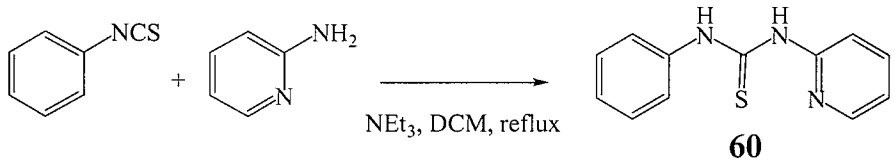
59

This procedure involved the use of an equimolar amount of phenylisothiocyanate, triethylamine and aniline in DCM. The reaction mixture was allowed to stir for 5 days at room temperature with a yield of 44%.

4.2.2. Synthesis of *N*-phenyl-*N'*-2-pyridyl thiourea 60

Our second target compound, *N*-phenyl-*N'*-2-pyridyl thiourea **60** was prepared

using the same procedure used for the preparation of the previous thiourea using 2-aminopyridine, phenyl isothiocyanate, triethylamine and DCM.



60

A first reaction was carried out at room temperature and monitored by TLC. The reaction time was 72 hours, with a yield of 60%.
A second reaction carried out under reflux increased the yield to 75% with a reaction time of 36 hours.
An attempt to make thiourea **60** using the prepared isothiocyanate **68** and aniline in chloroform failed to give us any convincing results as did another attempt to make **61** from **88** and 2-aminopyridine in DMSO.

4.2.3. Synthesis of *N*-2-pyridyl isothiocyanate 68

Attempts to prepare 2-pyridyl isothiocyanate **68** via ammonium *N*-2-pyridyldithiocarbamate **69**, following a procedure by Fairfull and Peak[82] and another by Le Count and Grundy[85] were carried out *(Scheme 2)*.
The first step leading to **69** was successful with a yield of about 55% but each time the second step failed to give us the desired product.

The second step given by Fairfull and Peak[82] involved the use of thiophosgene (1 eq) in dry toluene at 0°C under argon atmosphere. The red dark precipitate was filtered off and washed with toluene, air-dried and triturated with water. The residue was filtered off and washed with water and finally with acetone. Decomposition of the compound was noticed.
The second step given by Le Count and Grundy[85] involved treatment of triethylammonium *N*-2-pyridyldithiocarbamate **69** with an aqueous solution of iron chloride but failed to give us the desired compound.

However, the preparation given by Schultz and Gauri[86] using 2-aminopyridine with sodium hydrogenocarbonate in water followed by the addition of thiophosgene in water gave the desired product.

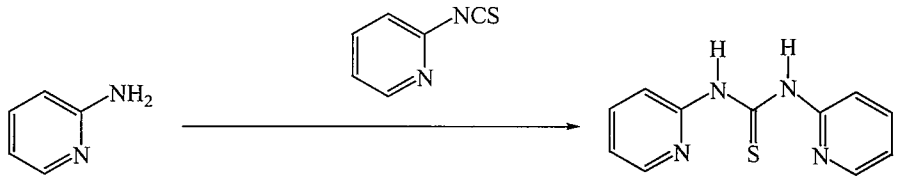
4.2.4. Synthesis of *N,N'*-di-2-pyridilthiourea 61

We carried out the preparation of *N,N'*-di-2-pyridilthiourea **61** using 2-aminopyridine as starting material, both varying the experimental conditions and trying new approaches.

A first attempt was carried out to see whether the reaction between 1 equivalent of thiophosgene, 2 equivalents of 2-aminopyridine and 3 equivalent of triethylamine would be successful, using a mixture of ether and dichloromethane as solvents.

Although the reaction was quite reactive, it yielded thiourea **61** as an amorphous product (55%).

Other experiments were carried out to prepare either *N,N'*-di-2-pyridilthiourea **61** or *N*-2-pyridyl isothiocyanate **68** (*Scheme 3*). A crude dark brown oil was often obtained, showing the presence of a lot by-products.



Experiment A: $CSCl_2$, K_2CO_3 in H_2O, $CHCl_3$, reflux

Experiment B: $CSCl_2$, NEt_3, DCM at 0°C

Experiment C: CS_2, DCC, dry THF, N_2

Experiment D: $CSCl_2$, $NaHCO_3$ in H_2O, Ether

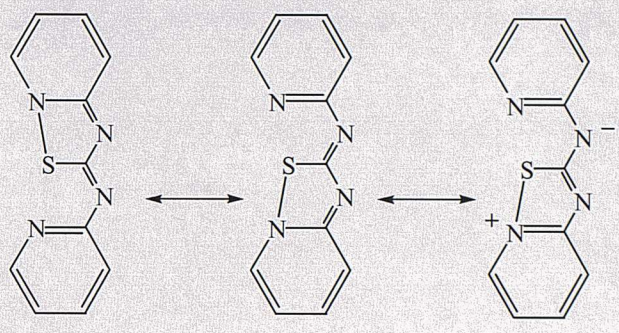
Scheme 3: Attempts to prepare **61** via **68**.

Experiments A, B, C and D led to mixtures of by-products, which were not worth separating.

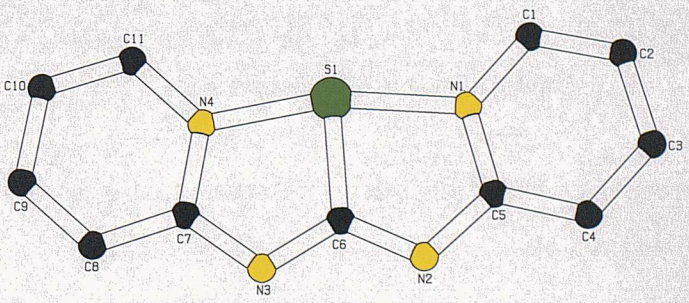
Nevertheless, experiment A led to some interesting results. The reaction using 2 equivalents of 2-aminopyridine, 1 equivalent of thiophosgene and 1 equivalent of aqueous potassium carbonate in chloroform was set up, but this time the reaction mixture was heated under reflux for 5 days. This reaction led to some unexpected results, a crystalline product was obtained and the structure was determined to be (Z)-pyridin-2-yl-[1,2,4]thiodiazolo[2,3,*a*]pyridin-2-ylidene-amine **70**. It is presumed that oxidation of *N,N'*-

di-2-pyridilthiourea **61** has occurred during the synthesis, causing a loss of amine protons in the thiourea moiety.

Figure 8: resonance structure of **70**.



This compound has been reported previously by Harris[96], where spectroscopic data was interpreted in terms of resonance structure (*Figure 8*), which is now confirmed by our work[97]. Harris suggested this resonance hybrid after looking at NMR spectra, the chemical properties and mass spectrum of the compound. The possible participation of a number of structures including some involving the d-orbitals of the sulfur atom may explain the unusual stability of **70**. Crystallographic analysis showed that the fused four-ring formed by this interaction is essentially planar, with the sulfur-nitrogen separations significantly less than the sum of the Van def Waals radii. The length of the carbon sulfur bond is greatly increased from the double bond length normally observed in thioureas derivatives and may be considered to be a formal single bond. Few cases of sulfur in a similar coordination environment were found and none with aromatic moieties.

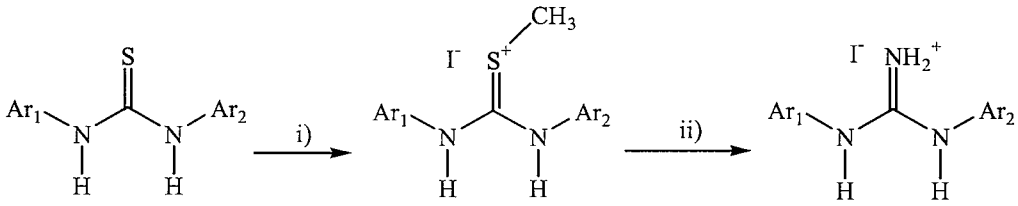


*Crystal structure of the resonance structure of (Z)-pyridin-2-yl-[1,2,4]thiodiazolo[2,3,a]pyridin-2-ylidene-amine **70***

Experiment C involving 1,3-dicyclohexylcarbodiimide (DCC) (1eq), carbon disulphide (6eq) and dry THF mainly yielded the coupling compound of the reaction: dicyclohexylthiourea.

4.2.5. Synthesis of guanidiniums salts via thiouronium intermediates

The next step in our work was the synthesis of the guanidinium derivatives. It was thought that we could start with the thioureas by treating them with iodomethane in dichloromethane or acetone to form the isothiouronium iodide. Then treatment of this latter with ethanol saturated with ammonia would give us the guanidinium iodide *(Scheme 4)*.

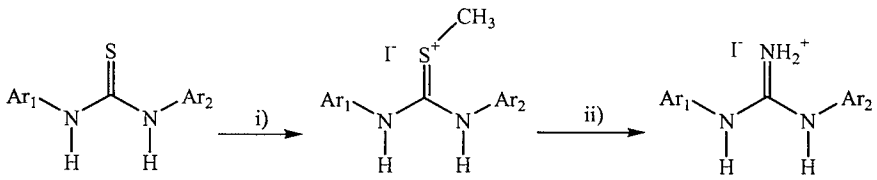


i) CH_3I, CH_3COCH_3
ii)NH_3 in EtOH, 75°C in sealed tube

Scheme 4

This scheme was not thought to be a problem with thiourea **59**. On the other hand, the use of iodomethane with thiourea **60** could be more difficult as the methylation of the nitrogen atom of the pyridyl ring might occur. Nevertheless, due to the strong intramolecular hydrogen bonding, it was thought that the experiment should not be a problem. Indeed, when a first equivalent of iodomethane was added a new product appeared by TLC then another equivalent was added showing no further reaction.

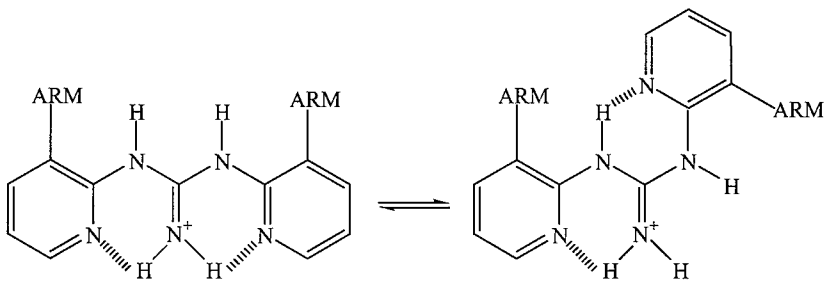
For thiourea **61**, it was thought that the methylation of the non-bonded nitrogen atom could occur but the experiment using 1 equivalent of iodomethane gave only one product. The reaction was stopped and the ^1H NMR spectrum of the isolated compound showed that we had prepared the isothiouronium intermediate **64**. Unfortunately, the second step of the reaction failed to give us the final compound **67.**



Compound **59**	Compound **62** Yield **99%**	Compound **65** Yield **75%**
Compound **60**	Compound **63** Yield **95%**	Compound **66** Yield **60%**
Compound **61**	Compound **64** Yield **70%**	Compound **67** (not prepared)

In conclusion, we successfully prepared **59-66** but were unable to prepare **67**.

4.3. Structure studies



Having prepared thioureas **59**, **60** and **61**, it was decided to focus on the degree of preorganisation that these compounds could show.

4.3.1. Studies on N-phenyl-N'-2-pyridyl thiourea 60

The ^{1}H NMR of **60** showed a very acidic proton (δ 13.8 ppm). The X-ray crystal structure of **60** was also determined and showed that a strong hydrogen bond exists between the hydrogen atom (as shown overleaf) from the thiourea group and the nitrogen atom from the pyridyl ring (*Figure 9*):

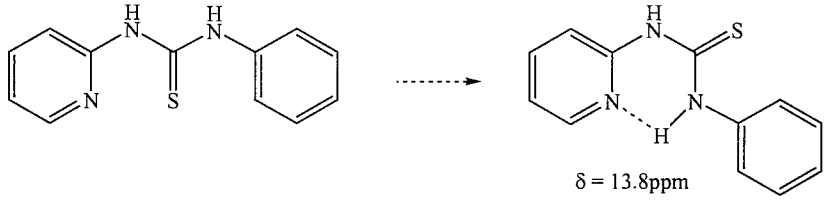
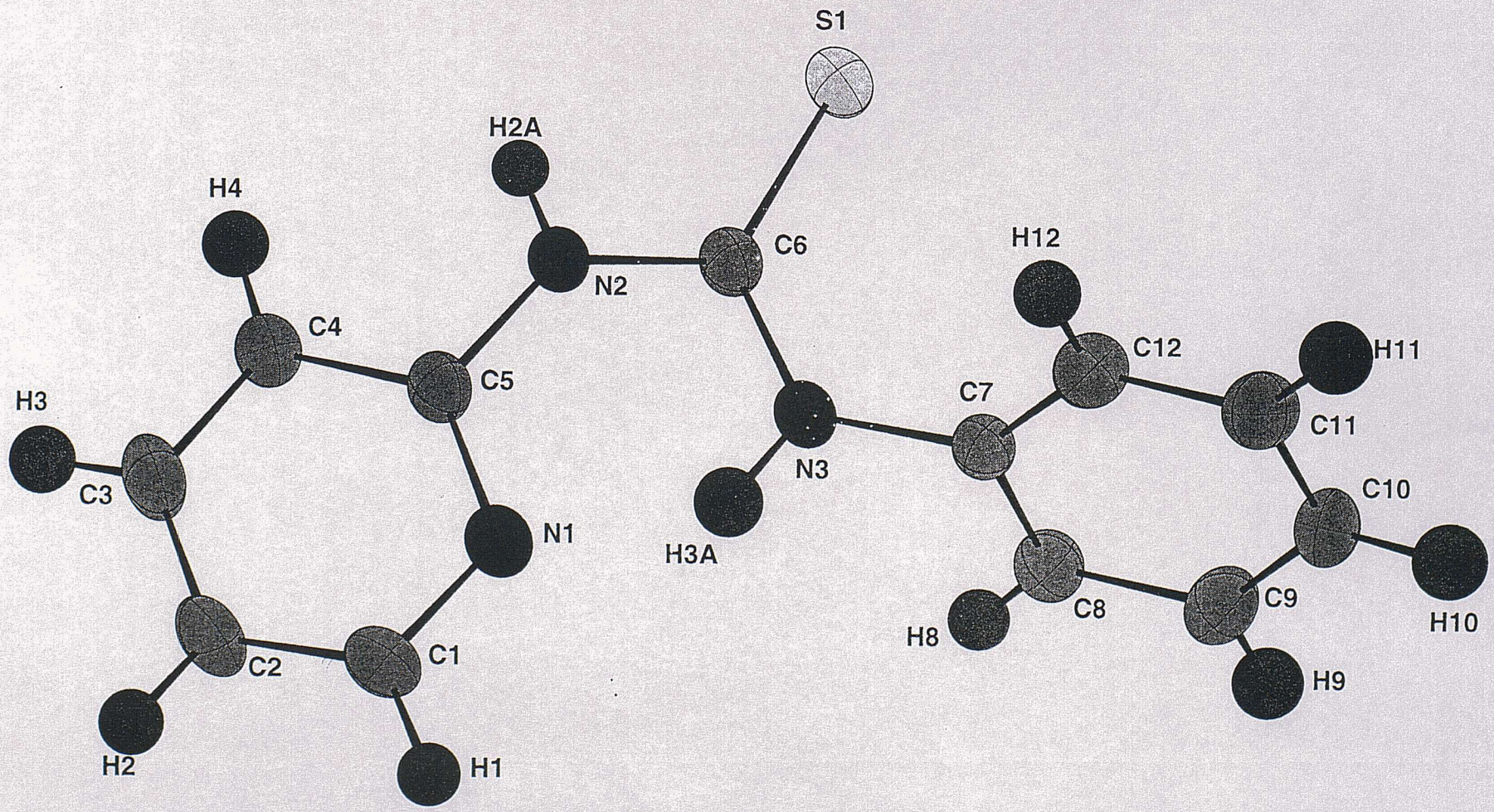


Figure 9: internal organisation of N-phenyl-N'-2-pyridyl thiourea **60**

During the course of our work, the crystal structure was published by another team[98]. Of course, this sort of internal preorganisation is not very interesting when our aim is to bind a carboxylic acid derivative as we need the two hydrogen atoms to bind with the guest.

Therefore, it was decided to study the effect of the addition of acid to the molecule. Like thiourea **27**, it was thought that the addition of acid could protonate the nitrogen atoms of the pyridyl groups so that the sulphur atom could bind to the protonating hydrogen atoms, allowing the carboxylate salt to bind with the hydrogen atoms of the thiourea group. This reorganisation would make the molecule more rigid (*Figure 10*).


S1
H2A
H4
C6
H12
N2
C4
C12
H11
C5
C7
C11
H3
N3
C10
C3
N1
H3A
C8
C9
H10
H8
C2
C1
H9
H2
H1

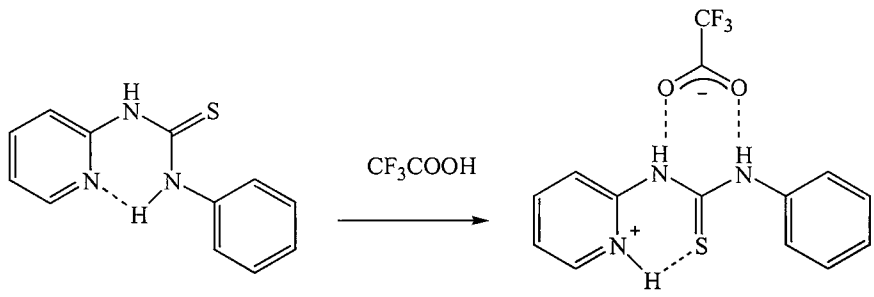


Figure 10

To this purpose, a ^{1}H NMR study of *N*-phenyl-*N'*-2-pyridyl thiourea with different concentrations of acids was carried out.

Test A:

Using phenylacetic acid

1 equivalent of **60** + 0.5 equivalent of Acid

1 equivalent of **60** + 1 equivalent of Acid

1 equivalent of **60** + 2 equivalents of Acid

Test B

Using trifluoroacetic acid

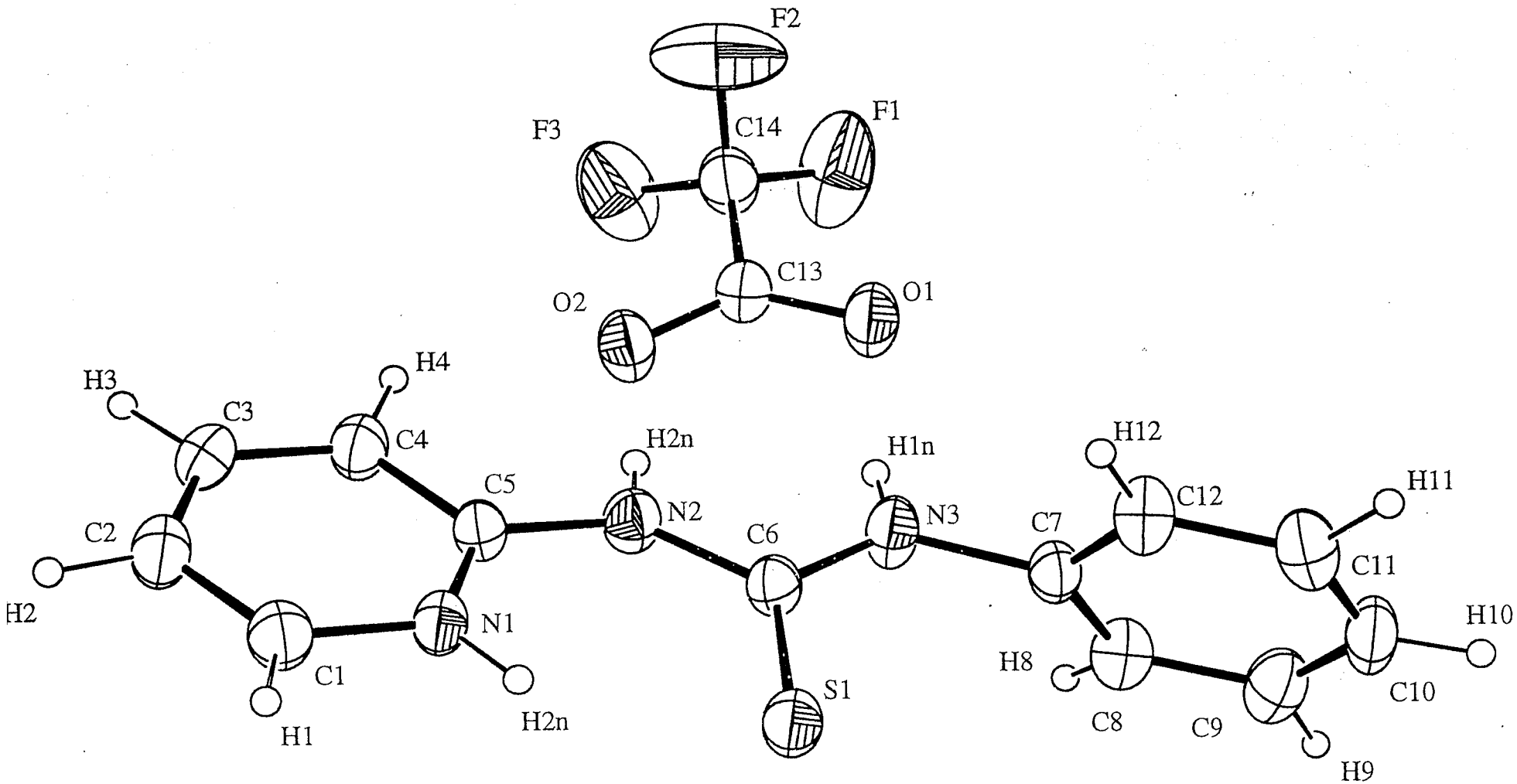
1 equivalent of **60** + 0.5 equivalent of Acid

1 equivalent of **60** + 1 equivalent of Acid

1 equivalent of **60** + 2 equivalents of Acid

The spectra for Test A did not show any change in the chemical shifts. On the other hand, the spectra for Test B using 1 and 2 equivalent of acid showed some important changes. Furthermore, the presence of crystals in the NMR tubes was noticed. These crystals were isolated and a crystal structure was determined (as shown overleaf).

We noticed that the crystals had the same structure and a reorganisation was observed, confirming our expectations.


F2
F3
C14
F1
C13
O2
O1
H4
H3
C3
C4
H2n
H1n
H12
C5
N2
C6
N3
C7
C12
H11
C2
C11
H2
N1
H10
C1
H8
C10
S1
H2n
C8
C9
H1
H9

4.3.2. Studies on *N,N'*-di-2-pyridilthiourea 61

A similar test with thiourea **61** and trifluoroacetic acid was carried out but no crystals appeared in the NMR tube and the concentration in vacuo of the content of these tubes did not give valuable crystals.

No crystal structure of thiourea **61** has been made so far but some ^{1}H NMR studies reported in the literature[99] claim that the compound can exist in 4 different forms (*Figure 11*). Nevertheless, no evidence has been reported for the existence of the E,E isomer[100]. Dreiding models show that the E,Z or Z,E isomers possess the ideal geometry for the formation of a strong intramolecular hydrogen bonding between the hydrogen of the thiourea group and the nitrogen atom from the pyridyl ring as previously seen for thiourea **60**.

It is worth noting that the ^{1}H NMR spectrum of the thiourea **61** was not easy to interpret at room temperature, so the NMR was run at –60°C and the chemical shifts were much clearer allowing a better interpretation of the spectra.

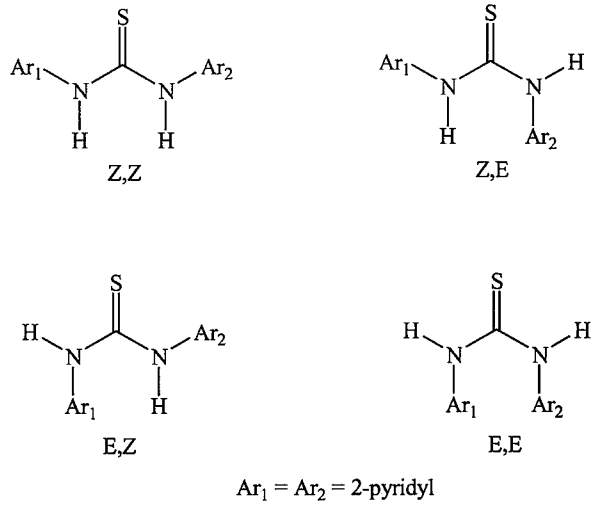
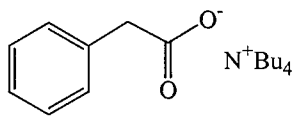


Figure 11: conformational isomers of 1,3-disubstituted thioureas

4.4. Binding studies

Having prepared the series of receptors, we wished to measure their relative binding properties with a simple carboxylate, the tetrabutylammonium salt of phenylatic acid **71**.



71

The binding efficiency is measured in terms of an equilibrium constant K_a where:

$$K_a = \frac{[\text{ Complex }]}{[\text{ Host }][\text{ Guest }]}$$

This equilibrium constant reflects the free energy change (ΔG^0) on complexation:

$$\Delta G^0_{binding} = - RT\log K_a$$

which combines enthalpic (ΔH^0) and entropic (ΔS^0) factors:

$$\Delta G^0 = \Delta H^0 - T\Delta S^0$$

The binding constants are to be compared so that the optimum system can be found. It was hoped that the guanidines should give the highest binding constant because of the presence of favourable intramolecular hydrogen bonds (*Figure 12*)

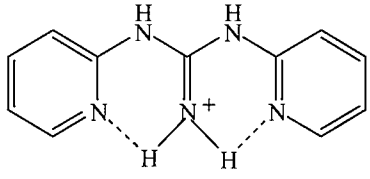


Figure 12: internal organisation of guanidines.

The solvent effect is a very important factor as a polar solvent can bind to the host competing with the guest for complexation. So, chloroform was used to carry out the binding studies as it is a relatively non-polar solvent.

The procedure for the binding studies in chloroform by UV/Visible is as follows:

Solution A : 1 eq Host in $CHCl_3$

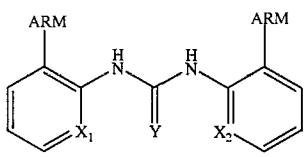
Solution B : 1 eq Host + 10 eq Guest in $CHCl_3$

Solutions A and B are quite dilute ([A] = 2.6 x 10^{-5} mol.l^{-1}) and all the solutions contain molecular sieves to be sure to avoid the presence of water.

1 ml of solution A is transferred into a cuvette and 20µl of solution B are added at each time, a change in the absorbance is observed and monitored. Using a software, the binding constant is assessed.

3 binding studies in $CHCl_3$ have been carried out for each compound. The results are summarised in the following table:

Compound	Average Ka
59 (Y = S, $X_1 = X_2$ = CH)	(1.49±0.62) x 10^4 M^{-1}
62 (Y = H_3CS^+, $X_1 = X_2$ = CH)	(1.40±0.44) x 10^5 M^{-1}
65 (Y = NH_2^+, $X_1 = X_2$ = CH)	(1.93±0.62) x 10^5 M^{-1}
60 (Y = S, X_1 = CH, X_2 = N)	(1.65±0.44) x 10^2 M^{-1}
63 (Y = H_3CS^+, X_1 = CH, X_2 = N)	(1.71±0.32) x 10^5 M^{-1}
66 (Y = NH_2^+, X_1 = CH, X_2 = N)	(1.04±1.19) x 10^5 M^{-1}
61 (Y = S, $X_1 = X_2$ = N)	No interactions
64 (Y = H_3CS^+, $X_1 = X_2$ = N)	(1.40±0.60) x 10^6 M^{-1}



$X_1 = X_2$ = CH, N
Y = S, NH_2+

62, 63 and **64** represent the thiouronium salts of the corresponding thioureas **59,60** and **61**. From these experiments, we can notice that the thiouronium salts as well as the guanidines give higher binding constants than the thioureas.

The difference in binding constants for thioureas **59**, **60** and **61** can be explained by the presence of internal hydrogen bonding. This fact was confirmed by crystallography for thiourea **60** (*Figure 9*) and by the literature for thiourea **61**[99,100] (*figure 11*). Thiourea **61** possesses the ideal geometry for the formation of a strong intramolecular hydrogen bonding between the hydrogen of the thiourea group and the nitrogen atom of the pyridyl ring.

The thiouronuim derivatives **62**, **63** and **64** gave much higher binding constants due to missing internal hydrogen bonding. These experimental results confirmed the work of Yeo and Hong[101] who found that compared to thiourea groups as an oxoanion binder, thiouronium groups turned to be relatively stronger binder for oxoanion substrates.

The guanidinium derivatives **65** and **66** are also good receptors although not appreciably better than the thiouronium ones. **66** is not appreciably better than **65** as might have been expected. **67** was unfortunately not prepared.

To conclude, it appears that the thiouronium derivatives as well as the guanidinium derivatives may help to preorganise the receptor in such a way that the guest can bind to the hydrogens of the Carboxylic Binding Site of the receptors. They could be good receptors according to these experimental data.

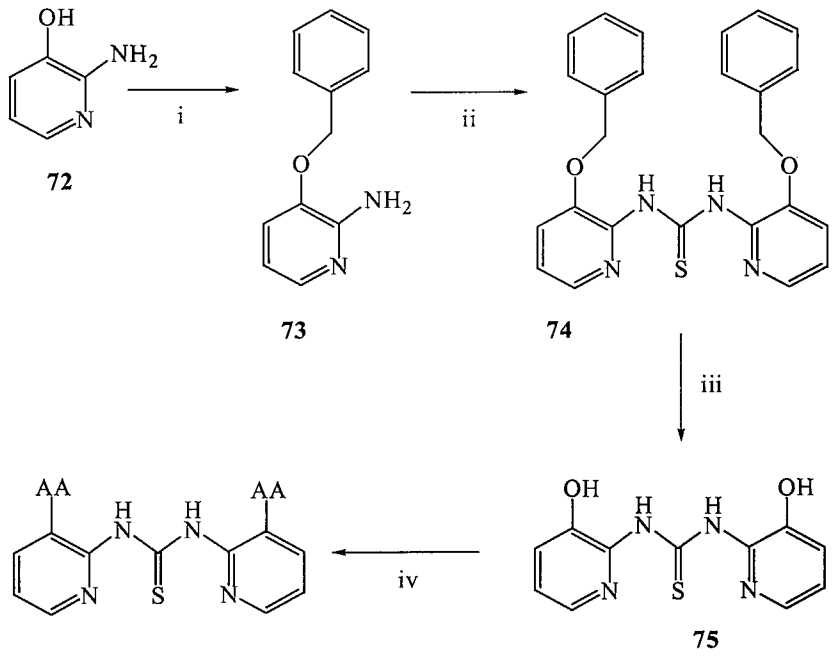
^{1}H NMR binding studies were carried out for thioureas **59**, **60** and **61** using carboxylate **71** in chloroform-d_3. Thiourea **59** was studied and a binding constant of 5 x 10^5 M^{-1} was found. This result can be considered as relevant compared to the value given by UV titration. Binding studies using thioureas **60** and **61** led to spectra with very poor resolution preventing any interpretation of the results.

4.5. Further synthetic work

The second part of the work was to start the addition of the so-called arms on the CBS. The first selected approach starting from 3-hydroxy 2-aminopyridine **72** is given in *scheme 5.*

The preparation of 3-benzyloxy-2-aminopyridine **73** proved to be a real challenge although it was found in the literature[102]. The success of this procedure could not be predicted since there are several possible ambident nucleophilic sites in **72,** but the phase-transfer catalysed alkylation of this compound was said to be very good.

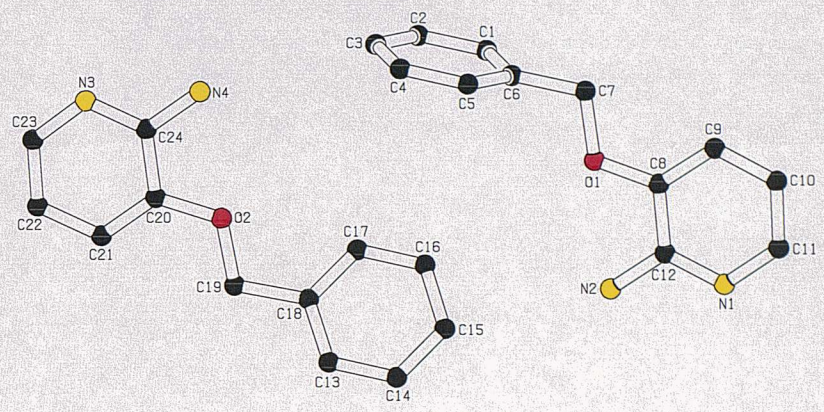
Several attempts to prepare **73** have been tried all leading to a poor yield (between 10 and 13%). Some parameters were changed in order to improve the yield, such as the quantity of Adogen 464 (the phase-transfer catalyst), the solvent system, the reaction scale and the reaction time. All these attempts were affording an oily red crude instead of a yellow solid. Nevertheless, after trituration of this oil with ether, a recrystallisation of the product in ethanol was possible, leading to a yellow solid.



i) Adogen 464 1%mol, 40% NaOH in H_2O, $C_6H_5CH_2Cl$, DCM, Reflux
ii) CCl_2S, $CHCl_3$, K_2CO_3 (0.4M), Reflux
iii) Pd/C
iv) Addition of an amino-acid.

Scheme 5

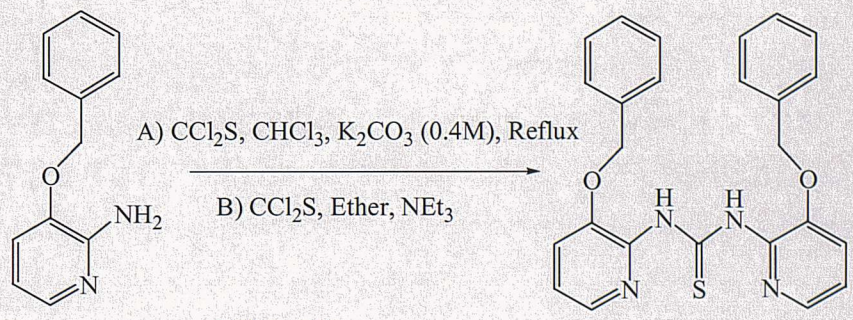
However, a last attempt refluxing the mixture was successful, as a yellow crude product was obtained, which was recrystallised in ethanol but giving a different sort of crystals. The most important point is that the yield increased to 50%.



Crystal structure of **73**

The next step, the formation of **74,** could be carried out according to 2 approaches as described in *Scheme 6*:

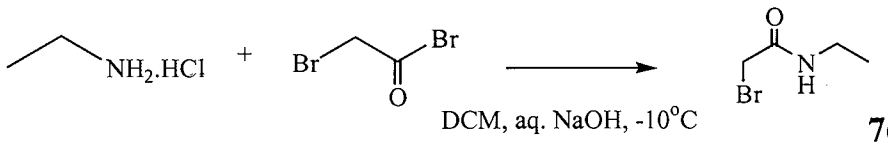
The experiment A was not found to be successful whereas experiment B is following a procedure already known used in the group and successfully used for the preparation of thiourea **61.**



Scheme 6

Unfortunately, these two approaches failed to give us the desired product. It is thought that the benzyl functionality is too bulky to allow the preparation of our product.

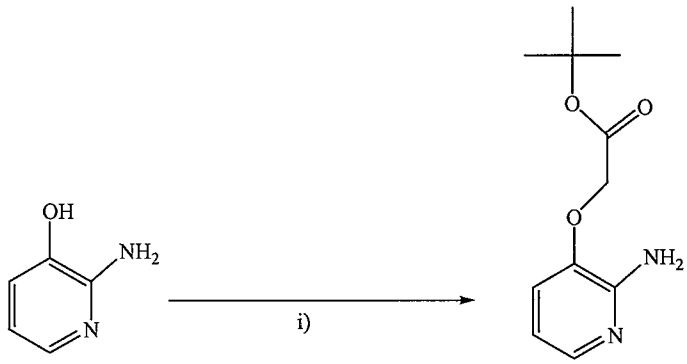
In the meantime, another approach to the preparation of the receptor **75** was carried out.



76

The preparation of **76** was successfully achieved following a known procedure[103] but reaction with **72** failed to give us the right product. The amide proton can be too reactive for such a reaction

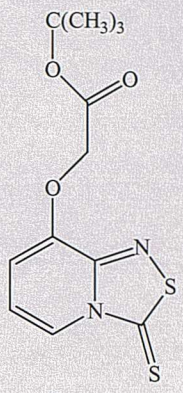
The reaction between **72** and tert-butyl bromoacetate gave compound **77,** 2-[(2'-amino-3'-pyridyl)oxy]-tert-butyl acetate. It was anticipated that treatment with acid would deprotect the tert-butyl ester suitable for attachment of amino acids.



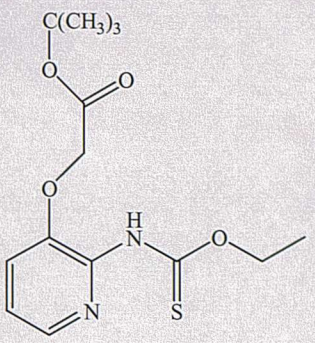
77

i) Adogen 464, DCM, 40% aq. NaOH, tert-butyl bromoacetate

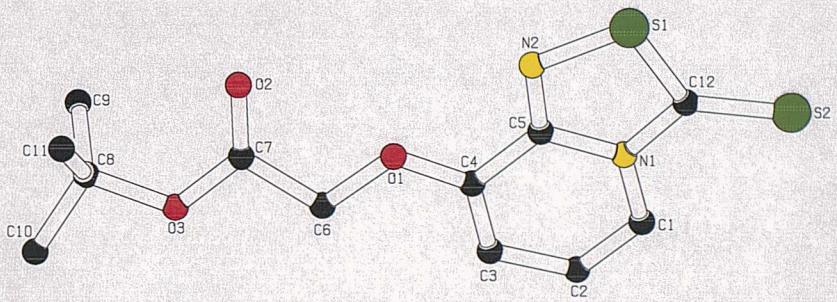
Surprisingly, the attempt to prepare the substituted thiourea from **77** gave some unexpected results. Indeed, two products, **78** and **79** were identified and characterised by X-Ray crystallography[104]. It is supposed that the ethanol used to stabilize chloroform can react to produce **79.** The formation of **78** is not completely understood, it is thought that an oxidation process may occur during the reaction.



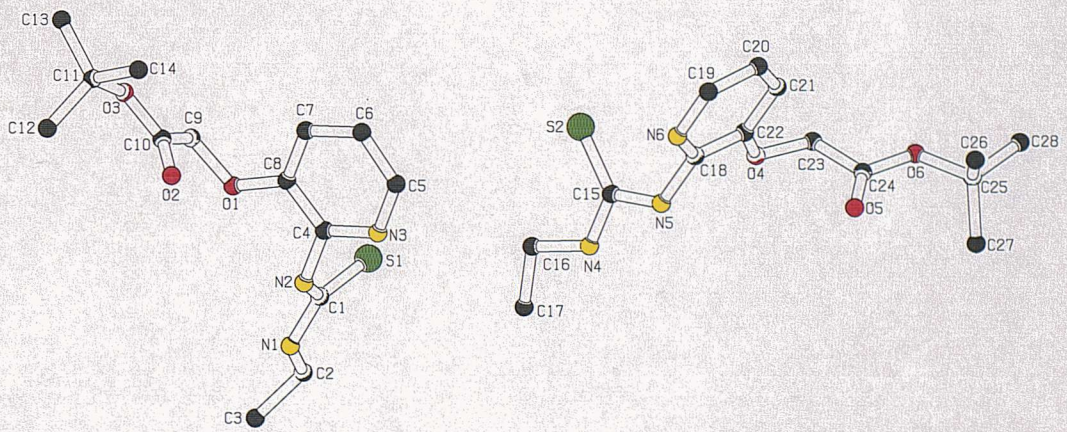
78



79



Crystal structure of **78**



Crystal structure of **79**

In conclusion, the addition of the so-called arms on the CBS proved to be impossible to achieve. Nevertheless, we found some interesting compounds which were identified and characterized by X-Ray crystallography.

5. Conclusion

The project failed to deliver the desired products in a very straightforward way. The chemistry is not very amenable and the yields are not as good as we would like. These points are not compatible with the goals fixed by the research network. Indeed, the receptors should be easy to prepare and the yields should be good enough for the project to be commercially viable.

The chemistry involved, as easy as it may seem on paper, appeared not to be so simple. We experienced difficulties during the work-up of the reactions and we noticed stability problems during purification by column chromatography. Most of the procedures dated from the beginning of the century and like most sciences, techniques were different from the ones used today. Chemistry was more a craft than a science. Nevertheless, the chemistry involved gave useful and interesting data on a crystallographic point of view.

After a few months of further research, work and dialogue between the different members of this European collaboration, it was decided that other kinds of receptors should be developed.

6. Experimental

6.1. General methods and instrumentation

General experimental

Solvents were of commercial grade and were used without further purification unless otherwise stated. Where further purification was required the procedures are outlined in *Purification of Laboratory Chemicals* (Perrin and Armarego, Pergamon Press: Oxford, 3rd edition (1989)) were followed. Where petrol has been used, the fraction boiling between 40°C and 60°C was used.

Thin layer chromatography (TLC) was performed on aluminium backed sheets coated with silica gel (SiO_2 ; 0.25 mm) containing fluorescent indicator UV_{254}. Column chromatography was performed on Sorbasil C60, 40-60 mesh silica.

Instrumentation

All melting points were determined in open capillary tubes using a Gallenkamp Electrothermal Melting Point Apparatus and are uncorrected.

Infrared spectra were recorded on a BIO-RAD Fourier Transform spectrophotometer. Samples were applied neat on a diamond supported by a golden gate anvil surface.

Proton NMR spectra at 300 MHz were obtained on a Bruker AC 300 spectrometer and at 400 MHz on a Bruker DPX 400. Peak positions are quoted against the δ scale relative to the residual chloroform (δ7.27), DMSO (δ2.53) or to an internal standard of tetramethylsilane (δ0.00), using the following abbreviations: (s) singlet, (d) doublet, (t) triplet, (q) quartet,(m) multiplet and (b) broad.

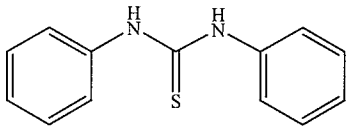
Carbon NMR spectra were obtained at 75.5 MHz on a Bruker AC 300 spectrometer and at 100 MHz on a Bruker DPX 400. The multiplicities of the carbon-13 signals were

elucidated using distortionless enhancement by phase transfer (DEPT) spectral editing technique with second pulses at 90° and 135°.

Mass spectra were obtained on VG Open Lynx FISONS

All ES^+ data were acquired using capillary voltage of 3.5 kV, a source temperature of 120°C, and injecting the sample into a mobile phase stream of CH_3CN.

6.2. Experimental



***N-N'*-diphenyl thiourea**

Phenylisothiocyanate (1.28ml, 10.75 mmol) in 10 ml of DCM, triethylamine (1.49 ml, 10.75 mmol) and aniline (1g, 10.75 mmol) in 10 ml of DCM were charged under stirring. The reaction mixture was allowed to stir for 5 days at room temperature and worked up using 2*40 ml of 2M HCl and then 50 ml of water. The organic layer was concentrated in vacuo to give yellow crystals.

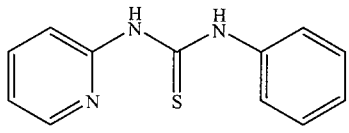
The product was recrystallised in ethanol to give shiny yellow crystals (1.07g, 4.7 mmol, 44%), m.p.= 152-154°C (lit.[105] 152°C).

^{1}HNMR (300 MHz, $CDCl_3$), δ 8.06 (2H, s, N*H*), 7.45-7.20 (10H, m, Ar).

^{13}C NMR (300 MHz, $CDCl_3$), δ 174(0), 138.5(0), 129.7(1), 127.2(1), 125.4(1).

IR ν/cm^{-1}: 3196, 3031, 1596, 1526, 1450, 1343, 1241, 933, 757.

LRMS (ESIPOS) 229 (MH^+, 100%).



***N*-phenyl-*N'*-2-pyridyl thiourea**

2-aminopyridine (1 g, 10.6 mmol) in dichloromethane (10 mL) was added to a solution of triethylamine (1.43 mL, 10.6 mmol) and phenylisothiocyanate (1.26 mL, 10.6 mmol) in dichloromethane (10 mL).

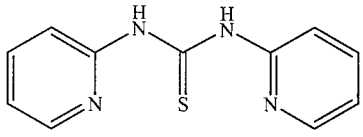
The reaction was refluxed for 36 hours and concentrated in vacuo to afford a yellow solid which was recrystallised from ethanol to give the desired product as a yellow solid (1.43 g, 75%), mp = 168-171°C (lit.[106] 169°C).

^{1}H NMR (300 MHz, $CDCl_3$), δ 13.8 (1H, s, -NH), 9.6 (1H, s, -NH), 8.19 (1H, dd, J = 1, 6 Hz, pyr H), 7.62 (3H, m, aromatic H), 7.39 (2H, m, aromatic H), 7.26 (1H, m, aromatic H), 6.95 (2H, m, aromatic H).

^{13}C NMR (300 MHz, $CDCl_3$), δ 178.9(0), 153.5(0), 145.7(1), 139.2(1), 138.8(0), 129.9(1), 126.5(1), 125.3(1), 118.4(1), 112.8(1).

IR ν/cm^{-1} : 3214, 3171, 3034, 1593, 1529, 1469, 1342, 1267, 1187, 924.

LRMS (ESIPOS) 230 (MH^+, 100%).



***N-N'*-2-dipyridyl thiourea**

A mixture of thiophosgene (0.8 mL, 10.6 mmol) in diethyl ether (5 mL) was cooled to 0°C and triethylamine (4.4 mL, 31.8 mmol) was slowly added dropwise affording a thick orange mixture. A solution of 2-aminopyridine (2 g, 21.2 mmol) in dichloromethane (40 mL) was added with vigorous stirring. The reaction mixture was stirred overnight at room temperature and concentrated in vacuo to give a brown dark powder which was recrystallised from methanol to give the desired product as a brown powder (1.42 g, 65%), mp = 137-139°C (lit.[107] 152-154°C).

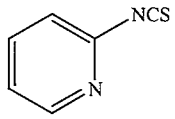
^{1}H NMR (300 MHz, $CDCl_3$ at 213°K), δ 14.6 (1H, s, -NH), 10.2 (1H, s, -NH), 8.74 (1H, d, J = 8 Hz, H_{pyr}), 8.44 (1H, dd, J = 1.5, 5 Hz, H_{pyr}), 8.29 (1H, dd, J = 1.6, 5 Hz, H_{pyr}), 7.79 (1H, ddd, J = 1.7, 8, 8 Hz, H_{pyr}), 7.66 (1H, ddd, J = 1.5, 8, 8 Hz, H_{pyr}), 7.16 (1H, dd, J = 7, 5 Hz, H_{pyr}), 7.06 (1H, d, J = 8 Hz, H_{pyr}), 7.01 (1H, dd, J = 7, 12 Hz, H_{pyr}).

^{13}C NMR (300 MHz, $CDCl_3$), δ 177.5(0), 152.7(0), 146.9(1), 137.8(1), 118.6(1), 112.5(1).

IR ν/cm^{-1} : 3243, 1596, 1526, 1422, 1352, 1310, 1188, 1142, 1048, 819.

LRMS (ESIPOS) 231 (MH^+, 100%).

^{1}H NMR spectrum identical to that reported.



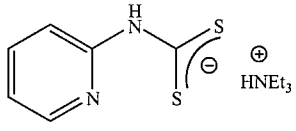
2-isothicyanato pyridine

Thiophosgene (1.32 mL, 17 mmol) in diethyl ether (20 mL) was added with strong stirring to a mixture of 2-aminopyridine (1.41 g, 15 mmol) and sodium hydrogenocarbonate (1.5 g) in water (20 mL). The reaction became warm and turned dark orange. The mixture was stirred for 3 hours, the ether layer was separated, dried over magnesium sulfate, and the filtrate was concentrated in vacuo to give the title compound as a yellow powder (1.10 g, 45%) which turned dark orange after a few hours in the air. mp = 110°C. (lit.[108] 106-108°C).

^{1}H NMR (300 MHz, $CDCl_3$), δ 8.35 (1H, ddd, J = 1.1, 1.4,5.8 Hz, H_{pyr}), 7.74 (1H, ddd, J = 1.4, 6.9, 8.4 Hz, H_{pyr}), 7.53 (1H, ddd, J = 0.7, 0.7, 8.5 Hz, H_{pyr}), 6.93 (1H,ddd, J = 1.1, 5.8, 6.2 Hz, H_{pyr}) .

^{13}C NMR (300 MHz, $CDCl_3$), δ 188.2(0), 151.5(0), 148.4(1), 138.4(1), 119.7(1), 115.2(1).

IR ν/cm^{-1} : 3094, 2982, 1583, 1503, 1311, 1228, 1029, 994, 745.



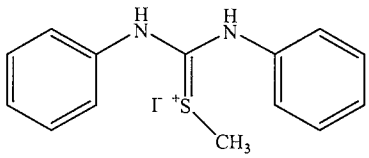
Triethylammonium *N*-2-pyridyldithiocarbamate

A mixture of 2-aminopyridine (3.13 g, 32.5 mmol), carbon disulfide(2.36 mL, 40 mmol), triethylamine (7.56 mL, 55 mmol) in absolute ethanol (6 mL) was stirred for two days at room temperature. The product which separates was filtered off and washed with a little ethanol and with acetone affording a yellow powder (4.64 g, 53%). mp = 85-87°C.(lit.[108] 88-89°C).

^{1}H NMR (300 MHz, $CDCl_3$), δ9.84 (1H, bs, -NH), 9.01 (1H, dd, J = 1.8, 8 Hz, H_{pyr}), 8.28 (1H, dd, J = 1.8, 4.8 Hz, H_{pyr}), 7.65 (1H, ddd, J = 1.8, 7.3, 8.4 Hz, H_{pyr}), 6.95 (1H, ddd, J = 1.1, 5.2, 7.4 Hz, H_{pyr}), 3.23 (1H, q, J = 7.3 Hz, CH_2), 1.37 (1H, t, J = 7.3 Hz, CH_3).

^{13}C NMR (300 MHz, $CDCl_3$), δ 214.8(0), 153.5(0), 147.9(1), 137.1(1), 118.9(1), 115.1(1), 46.1(2), 9.0(3).

IR ν/cm^{-1} : 3188, 2971, 1569, 1468, 1427, 1279, 1217, 985, 840.



***N-N'*-diphenyl isothiouronium iodide**

Iodomethane (55 μL, 0.88 mmol) was added to a mixture of *N-N'*-diphenyl thiourea (0.2 g, 0.88 mmol) in dichloromethane (10 mL), iodomethane (55 μL, 0.88 mmol) was added under stirring. After stirring temperature overnight, tlc analysis showed that unreacted starting material remained so a further quantity of iodomethane (220 μL, 3.52 mmol) was added and the reaction was stirred for 16 hours. The organic fraction was dried over magnesium sulphate and concentrated *in vacuo* to give a crude product as a dark yellow foam (310 mg, 99%), R_f = 0.56. mp = 68-71°C.

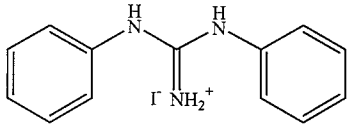
^{1}H NMR (300 MHz, $CDCl_3$), δ9.72(2H, bs, NH), 7.44-7.37 (10 H, m, aromatic H), 2.53 (3H, s, CH_3).

^{13}C NMR (400 MHz, $CDCl_3$), δ169.6(0), 135.2(0), 130.3(1), 129.1(1), 125.8(1), 17.6(3).

IR ν/cm^{-1} : 3050, 2981, 2874, 2158, 1595, 1545, 1482, 1430, 1241, 1140, 1076, 986, 939, 843, 758, 687.

LRMS (ESIPOS) 243 (M^+, 100%).

HRMS (FAB) 243 (M^+, 33%).



***N-N'*-diphenyl guanidinium iodide**

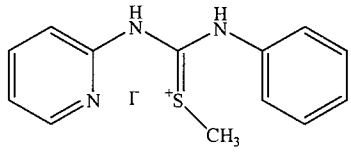
N-N'-diphenyl isothiouronium iodide (0.1 g, 0.26 mmol) in ethanol (7 mL) saturated with ammonia was heated in a sealed tube at 60°C for 6 hours. After tlc analysis showed that unreacted starting material remained, the reaction was heated at 90°C for further 6 hours. The organic fraction was dried over magnesium sulphate and concentrated *in vacuo* to afford a brown oil which was purified by column chromatography on silica gel, eluting with methanol –dichloromethane (5:95,v/v), to produce a white solid (70 mg, 75%), R_f = 0.26. mp = 138-140°C.

^{1}H NMR (300 MHz, $CDCl_3$), δ 7.53-7.34 (14H, bm, aromatic H, NH and NH_2^+).

^{13}C NMR (400 MHz, $CDCl_3$), δ155(0), 133.1(0), 130.9(1), 129.1(1), 126.2(1).

IR ν/cm^{-1} : 3336, 3261, 3147, 3081, 3031, 2985, 1664, 1628, 1575, 1493, 1460, 1441, 1371, 1222,1084, 755, 679.

HRMS (FAB) 243 (M^+, 100%).



_N_-phenyl-_N'_-2-pyridyl isothiouronium iodide

Iodomethane (27 μL, 0.44 mmol) was added to a mixture of _N_-phenyl-_N'_-2-pyridyl thiourea (0.1 g, 0.44 mmol) in acetone (5 mL) and dichloromethane (1 mL). After stirring overnight, tlc analysis showed that unreacted starting material remained so a further quantity of iodomethane (27 μL, 0.44 mmol) was added and the reaction was stirred for 18 hours. The mixture was concentrated in vacuo to give crude product as a dark yellow sticky foam (146 mg, 95%) $R_f = 0.63$.

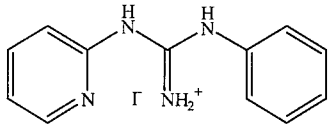
^{1}H NMR (300 MHz, $CDCl_3$), δ8.42 (2H, s, NH), 8.3 (1H, ddd, J = 1, 2, 5 Hz, H_{pyr}), 7.87 (1H, ddd, J = 2, 7, 8 Hz, H_{pyr}), 7.5-7.33 (7H, m, aromatic H), 7.26 (1H, ddd, J = 1, 2, 5 Hz, H_{pyr}), 2.95 (3H, s, -CH_3).

^{13}C NMR (400 MHz, $CDCl_3$), δ 167.5(0), 151.6(1), 142.9(1), 139.4(1), 133.7(1), 128.8(1), 127.8(1), 124.7(1), 120.4(1), 117.2(1), 17.2(3).

IR ν/cm^{-1} : 3048, 2979, 2868, 1592, 1544, 1480, 1433, 1242, 1143, 989, 849, 763, 688.

LRMS (ESIPOS) 244 (M^+, 100%).

HRMS (FAB) 244 (M^+, 100%).



_N_-phenyl-_N'_-2-pyridyl guanidinium iodide

_N_-phenyl-_N'_-2-pyridyl isothiouronium iodide (0.1 g, 0.26 mmol) in ethanol (5 mL) saturated with ammonia was heated in a sealed tube at 75°C for 7 hours. The organic fraction was dried over magnesium sulphate and concentrated *in vacuo* to afford a brown oil which was purified

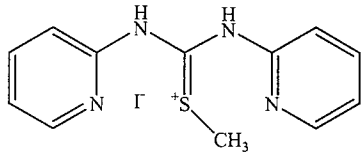
by column chromatography on silica gel, eluting with methanol-dicloromethane (5:95,v/v), to produce the above product as a white powder (55 mg, 60%), $R_f = 0.36$. mp = 153-155°C.

^{1}H NMR (400 MHz, $CDCl_3$), δ9.18 (4H, bs, NH and NH_2^+), 8.17 (1H, ddd, J = 2, 8, 8 Hz, H_{pyr}), 7.78 (1H, ddd, J = 2, 7, 8 Hz, H_{pyr}),7.5-7.2 (6H, m, aromatic H and –NH), 7.16 (1H, ddd, J = 1, 2, 5 Hz, H_{pyr}),.

^{13}C NMR (400 MHz, $CDCl_3$), δ 153.3(0), 150.6(1), 144.9(1), 138.5(1), 131.1(1), 129.7(1), 128.2(1), 125.0(1), 119.1(1), 113.0(1).

IR ν/cm^{-1} :3285, 3141, 3036, 2983, 1634, 1569, 1463, 1370, 1227, 1142, 1013, 898.

HRMS (FAB) 213 (M^+, 100%).

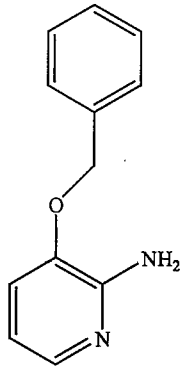


***N-N'*-2-dipyridyl isothiouronium**

Iodomethane (27 μL, 0.44 mmol) was added to a mixture of *N-N'*-2 dipyridyl thiourea (0.1 g, 0.44 mmol) in acetone (5 mL) and the reaction mixture was stirred overnight. The mixture was concentrated in vacuo to give a dark yellow oil which was purified by column chromatography with diethyl ether in petroleum ether (50:50. v/v), to give the desired product as a brown foam (11mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$), δ 8.38 (2H, s, -NH), 7.7 (2H, m, H_6 and H_6), 7.3-7 (6H, m, pyr H), 2.58 (3H, s, $-CH_3$).

LRMS (ESIPOS) 245 (M^+, 100%).



3-benzyloxy-2-aminopyridine

A mixture of 3-hydroxy-2-aminopyridine (1.10g, 10 mmol), benzyl chloride (1.35g, 10.7mmol) and Adogen 464 (53mg) in aqueous 40% sodium hydroxide (5ml) and dichloromethane (5ml), was stirred under reflux for 24 hours. The dichloromethane layer was separated and the aqueous layer was diluted with water (5ml) and extracted with dichloromethane (30ml). The dichloromethane phases were combined, dried with potassium carbonate, and evaporated to give a crude product, which was recrystallised from ethanol to afford big yellow crystals (1g, 50%).m.p.= 89-91°C (Ref.[109], m.p.= 93-94°C).

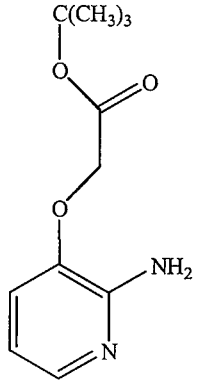
^{1}H NMR (300 MHz, $CDCl_3$), δ 7.72 (1H, d, J = 4.4 Hz, pyr), 7.51-7.31 (5H, m, Ar), 7.08 (1H, d, J = 7.3 Hz, pyr), 6.65 (1H, dd, J = 5.1, 8 Hz, pyr), 5.12 (2H, s, CH_2), 4.84 (2H,s, NH_2).

^{13}C NMR (300 MHz, $CDCl_3$), 70.3(2), 113.7(1), 116.9(1), 127.7(1), 128.4(1), 128.8(1), 136.4(0), 139.2(1), 141.6(0), 150.4(0).

IR ν/cm^{-1} : 3467, 3276, 3117, 1628, 1563, 1484, 1452, 1380, 1283, 1206, 1082, 1052, 994, 736.

LRMS (ESIPOS) m/z 201 (MH^+, 100%).

Further characterised by X-Ray crystallography.



2-[(2'-amino-3'-pyridyl)oxy]-tert-butyl acetate

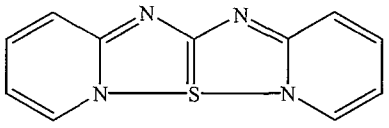
A mixture of 3-hydroxy-2-aminopyridine (1.10g, 10 mmol), tert-butyl bromoacetate (1.47ml, 10.2mmol) and Adogen 464 (53mg) in aqueous 40% sodium hydroxide (5ml) and dichloromethane (5ml), was stirred 24 hours. The organic layer was separated and the aqueous layer was diluted with water (5ml) and extracted with dichloromethane (30ml). The

organic phases were combined, dried over magnesium sulfate, and evaporated to give a crude orange oil, which was purified by column chromatography on silica gel with dichloromethane-methanol (95:5, v/v) as eluent to afford the title product as a yellow oil.(222.5mg, 10%).

^{1}HNMR (400 MHz, $CDCl_3$), δ 7.62 (1H, dd, J = 1.5, 5 Hz, H_{pyr}), 6.76 (1H, dd, J = 1.5, 7.5 Hz, H_{pyr}), 6.5 (1H, dd, J = 5, 7.5 Hz, H_{pyr}), 4.82 (2H, s, NH_2.), 4.43 (2H, s, CH_2), 1.4 (9H, s, $(CH_3)_3$)

^{13}C NMR (400 MHz, $CDCl_3$), 28.8(3), 66.9(2), 83(0), 113.7(1), 117.9(1), 140.3(1), 141.2(0), 151(0), 167.9(0).

IR ν/cm^{-1} : 3462, 3322, 3181, 2985, 2935, 1746, 1626, 1473, 1367, 1294, 1230, 1201, 1152, 1086, 848, 782, 756,736.



(Z)-pyridin-2-yl-[1,2,4]thidoiazolo[2,3,*a*]pyridin-2-ylidene-amine

Thiophosgene (0.4 mL, 5.3 mmol) was slowly added to a mixture of 2-aminopyridine (1.00 g, 10.6 mmol) in chloroform (20 mL). After addition of 0.4 M aqueous potassium carbonate (23.8 mL, 9.5 mmol), the mixture was heated under reflux for 24 hours. After allowing to cool to r.t. The organic layer was concentrated *in vacuo* to afford a brown solid which was purified by recrystallisation from methanol providing a brown solid (1.75g, 7.6mmol, 72%).

mp > 250°C.(lit.[110] 251-253°C).

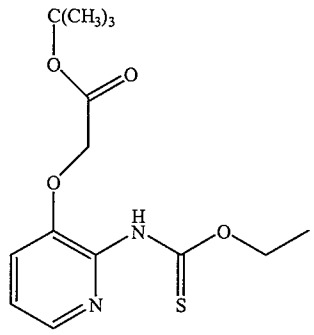
^{1}H NMR (300 MHz, $CDCl_3$), δ 8.74 (2H, ddd, J = 0.7, 1.5, 5.9 Hz, H_{pyr}), 8.44 (2H, ddd, J = 1.7, 6.9, 8.7 Hz, H_{pyr}), 8.29 (2H, ddd, J = 0.9, 1.2, 8.6 Hz, H_{pyr}), 7.79 (2H, ddd, J = 0.9, 5.9, 6.9 Hz, H_{pyr}).

^{13}C NMR (300 MHz, $CDCl_3$), δ 168.0(0), 156.3(0), 137.6(1), 134.0(1), 118.9(1), 113.9(1).

IR ν/cm^{-1} : 3057, 3016, 1612, 1545, 1510, 1480, 1415, 1316, 1291, 1189, 1014, 929, 846, 763.

LRMS (ESIPOS) 229 ($(M+H)^+$, 100%).

Further characterised by X-Ray crystallography.



Ter-butyl-2-[(2-{[(ethoxy)carbothioyl]amino}-3-pyridyl)oxy]acetate

Thiophosgene (1.23mL, 3.0 mmol) was slowly added to a mixture of 2[(2'-amino-3'-pyridyl)oxy]tertbutylacetate (1.34 g, 6.0 mmol) in chloroform (40 mL) and 0.4M aqueous potassium carbonate (15 mL, 6.0 mmol). The reaction was heated under reflux for 5 days. After allowing to cool to room temperature the mixture was transferred into a separating funnel. The organic layer was then separated and aqueous was extracted with chloroform (30 mL). The organic fraction was dried over magnesium sulphate and concentrated *in vacuo* to afford a brown oil which was purified by column chromatography on silica gel, eluting with ethyl acetate-petroleum ether (30:70,v/v), to produce a brown solid which was recrystallised from methanol (208.4 mg, 16%), $R_f = 0.1$. mp = 88-91°C.

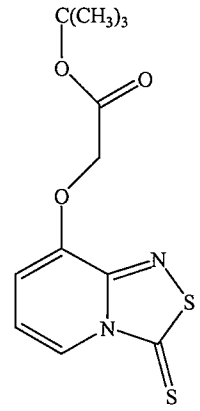
^{1}H NMR (300 MHz, $CDCl_3$) δ8.88 (1H, s, NH), 8.10 (1H, dd, J = 1.8, 4.4 Hz, H_{pyr}), 7.05 (2H, m, H_{pyr}), 4.63 (2H, q, J = 7 Hz, $O\underline{CH_2}CH_3$), 4.60 (2H, s, CH_2), 1.49 (9H, s, $(CH_3)_3$), 1.39 (3H, t, J = 7.3 Hz, $OCH_2\underline{CH_3}$).

^{13}C NMR (300 MHz, $CDCl_3$) δ189.0(0), 167.2(0), 144.5(0), 141.6(0), 140.9(1), 120.9(1), 120.4(1), 83.4(0), 68.1(2), 66.9(2), 28.1(3), 14.1(3).

IR ν/cm^{-1} : 3271, 3153, 2980, 2936, 1727, 1579, 1513, 1446, 1368, 1236, 1191, 1158, 1038, 789, 737.

LRMS (ESIPOS) m/z 313 (MH^+, 100%).

Further characterised by X-Ray crystallography.



Ter-butyl-2-[(3-thioxopyrido[2,1-c][1,2,4]thiadiazol-8-yl)oxy]acetate

Thiophosgene (1.23mL, 3.0 mmol) was slowly added to a mixture of 2[(2'-amino-3'-pyridyl)oxy]tertbutylacetate (1.34 g, 6.0 mmol) in chloroform (40 mL) and 0.4M aqueous potassium carbonate (15 mL, 6.0 mmol). The reaction was heated under reflux for 5 days. After allowing to cool to room temperature the mixture was transferred into a separating funnel. The organic layer was then separated and aqueous was extracted with chloroform (30 mL). The organic fraction was dried over magnesium sulphate and concentrated *in vacuo* to afford a brown oil which was purified by column chromatography on silica gel, eluting with ethyl acetate-petroleum ether (30:70,v/v), to produce a brown solid which was recrystallised from methanol (60.4 mg, 5%), $R_f = 0.28$. mp = 110-112°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ8.14 (1H, dd, $J = 1$, 7.2 Hz, H_{pyr}), 6.57 (1H, dd, $J = 7.2$, 7.2 Hz, H_{pyr}), 6.49 (1H, dd, $J = 0.7$, 7.5 Hz, H_{pyr}), 4.69 (2H, s, CH_2), 1.41 (9H, s, $(CH_3)_3$).

^{13}C NMR (400 MHz, $CDCl_3$) δ192.4(0), 165.1(0), 148.4(0), 147.1(0), 119(1), 112.1(1), 106.9(1), 82.3(0), 65.9(2), 27.0(3).

IR ν/cm^{-1} : 3091, 2977, 2925, 1754, 1546, 1504, 1461, 1358, 1308, 1228, 1155, 1069, 980, 836, 762.

LRMS (ESIPOS) m/z 299 (MH^+, 100%), 337 (MK^+,), 339(MCH_3CN^+,).

Further characterised by X-Ray crystallography.

6.3. Experimental for binding studies

Obtaining association constants by ^{1}H NMR or UV/Visible titration experiments involves titration of a solution of host with guest and recording a spectrum after each addition. Protons in the host or guest may undergo a change in chemical shift or absorbance upon complexation. Any protons involved in hydrogen bonding usually undergo a more dramatic shift and are therefore commonly used to determine association constants. After the data from the titration experiment has been acquired, curve fitting software is employed to determine the association constant. Free host and free guest are in equilibrium with host-guest complex and as association and dissociation occur on a timescale faster than that of NMR, the observed chemical shift of any proton (δ_{obs}) involved in binding will be a weighted average of the fully bound (δ_{bound}) and the fully unbound (δ_{free}) chemical shift. After an initial estimate for K_a and $\Delta\delta$, the theoretical (δ_{obs}) can be obtained for each data point. The theoretical values for the chemical shifts are compared with the experimentally observed ones and the sum of the difference between each point is determined using the following equation:

$$\text{Sum of the differences} = \Sigma\ (\delta_{obs(experimental)} - \delta_{obs(theoritical)})$$

If the sum of the differences is positive (or negative), the K_a is increased (or decreased) and the value $\Delta\delta$ is recalculated and the whole calculation repeated until the values converge. The shape of the binding curve is wholly dependent on K_a, $[H]_{total}$ and $[G]_{total}$. At K_a's or higher concentrations, the observed binding curve will be steeper. A more detailed explanation of the theoretical basis to the above discussion has been published[111].

Method Used for Obtaining Binding Constants

All ^{1}H NMR or UV/Visible titration experiments were conducted on either a Brüker AM 300

or a Shimadzu UV-1601 UV-visible spectrometer at 298 K. All $CDCl_3$ or $CHCl_3$ was passed over apad of basic alumina prior to use and collected over molecular sieves (4Å). Guest stock solutions were typically made up such that 10μL of that solution contained 0.1 equivalents of

guest with respect to host. The hydrogens or changes in absorbance monitored during binding studies were the thiourea in the host unless otherwise stated. For a greater degree of accuracy, association constants quote in the discussion chapter are taken as the average of all the association constants obtained.

The software used to determine binding constants was kindly provided by Prof C.A. Hunter, University of Sheffield, where a 1:1 binding mode was assumed. All data obtained corresponded well with the theoretical model for 1:1 binding stoichiometry.

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **59.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.6×10^{-4} mol/l
Association constant:	1.49×10^{4} M^{-1}

Volume added/μL	Abs @ 275 nm
0	0.468
20	0.472
40	0.477
60	0.483
80	0.486
100	0.487
120	0.489
140	0.496
160	0.501
180	0.504
200	0.501
240	0.511
280	0.511
320	0.511
360	0.515
400	0.515

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **59.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	3.05×10^{4} M^{-1}

Volume added/μL	Abs @ 275 nm
0	0.321
20	0.324
40	0.327
60	0.331
80	0.335
100	0.337
120	0.343
140	0.345
160	0.349
180	0.353
200	0.355
240	0.360
280	0.365
320	0.369
360	0.373
400	0.383

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **59.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	1.01×10^{4} M^{-1}

Volume added/μL	Abs @ 275 nm
0	0.468
20	0.472
40	0.477
60	0.483
80	0.486
100	0.487
120	0.489
140	0.496
160	0.501
180	0.504
200	0.501
240	0.511
280	0.511
320	0.511
360	0.515
400	0.515

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **60.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	1.65×10^{2} M^{-1}

Volume added/μL	Abs @ 265 nm
0	0.465
20	0.467
40	0.472
60	0.479
80	0.481
100	0.493
120	0.497
140	0.506
160	0.511
180	0.521
200	0.524
240	0.528
280	0.533
320	0.545
360	0.552
400	0.554

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **60.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	7.42×10^{1} M^{-1}

Volume added/μL	Abs @ 265 nm
0	0.611
20	0.612
40	0.612
60	0.612
80	0.614
100	0.614
120	0.615
140	0.615
160	0.616
180	0.617
200	0.620
240	0.620
280	0.622
320	0.623
360	0.623
400	0.623

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **60.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	1.03×10^{1} M^{-1}

Volume added/μL	Abs @ 265 nm
0	0.577
20	0.577
40	0.578
60	0.579
80	0.579
100	0.580
140	0.582
180	0.583
220	0.585
260	0.586
300	0.587
340	0.588
400	0.590

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **62.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	1.40×10^{5} M^{-1}

Volume added/μL	Abs @ 242 nm
0	0.272
20	0.279
40	0.301
60	0.311
80	0.324
100	0.336
120	0.345
140	0.350
160	0.351
180	0.358
200	0.361
240	0.357
280	0.354
320	0.353
360	0.351
400	0.355

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **62.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	2.89×10^{5} M^{-1}

Volume added/μL	Abs @ 242 nm
0	0.413
20	0.416
40	0.445
60	0.458
80	0.485
100	0.495
120	0.502
140	0.502
160	0.503
180	0.503
200	0.515
240	0.508
280	0.506
320	0.505
360	0.507
400	0.506

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **62.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	2.46×10^{5} M^{-1}

Volume added/μL	Abs @ 242 nm
0	0.377
20	0.375
40	0.396
60	0.420
80	0.434
100	0.442
120	0.451
140	0.452
160	0.457
180	0.461
200	0.468
240	0.471
280	0.469
320	0.468
360	0.471
400	0.464

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **63.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	1.71×10^{5} M^{-1}

Volume added/μL	Abs @ 269.5 nm
0	0.341
20	0.340
40	0.331
60	0.330
80	0.339
100	0.352
120	0.360
140	0.366
160	0.377
180	0.385
200	0.380
240	0.381
280	0.384
320	0.392
360	0.405
400	0.409

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **63.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	2.81×10^{5} M^{-1}

Volume added/μL	Abs @ 269.5 nm
0	0.0262
20	0.0280
40	0.0289
60	0.0294
80	0.0299
100	0.0302
120	0.0304
140	0.0308
160	0.0311
180	0.0320
220	0.0326
260	0.0336
310	0.0332
360	0.0345

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **63.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	2.30×10^{5} M^{-1}

Volume added/μL	Abs @ 269.5 nm
0	0.0398
20	0.0406
40	0.0416
60	0.0425
80	0.0424
100	0.0427
120	0.0430
140	0.0430
160	0.0433
180	0.0430
200	0.0436
240	0.0446
280	0.0448
320	0.0448
360	0.0449
400	0.0463

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **64.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	6.01×10^{4} M^{-1}

Volume added/μL	Abs @ 242 nm
0	0.380
20	0.382
40	0.399
60	0.405
80	0.424
100	0.435
120	0.445
140	0.449
160	0.460
180	0.465
200	0.468
240	0.474
280	0.473
320	0.478
360	0.475
400	0.475

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **64.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	1.96×10^{6} M^{-1}

Volume added/μL	Abs @ 242 nm
0	0.0220
20	0.0487
40	0.0436
60	0.0530
80	0.0492
100	0.0549
120	0.0571
140	0.0568
160	0.0585
180	0.0626
220	0.0614
260	0.0576
310	0.0586
360	0.0604

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **64.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	1.39×10^{6} M^{-1}

Volume added/μL	Abs @ 242 nm
0	0.0149
20	0.0339
40	0.0366
60	0.0416
80	0.0466
100	0.0470
120	0.0514
140	0.0509
160	0.0551
180	0.0614
200	0.0631
240	0.0643
280	0.0667
320	0.0703
360	0.0687
400	0.0660

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **65.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	2.80×10^{5} M^{-1}

Volume added/μL	Abs @ 242 nm
0	0.454
20	0.461
40	0.480
60	0.487
80	0.515
100	0.532
120	0.541
140	0.550
160	0.548
180	0.547
200	0.551
240	0.553
280	0.557
320	0.557
360	0.559
400	0.559

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **65.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	1.07×10^{5} M^{-1}

Volume added/μL	Abs @ 242 nm
0	0.401
20	0.409
40	0.431
60	0.452
80	0.463
100	0.477
120	0.482
140	0.490
160	0.492
180	0.499
200	0.504
240	0.516
280	0.512
320	0.525
360	0.516
400	0.514

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **66.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	1.04×10^{5} M^{-1}

Volume added/μL	Abs @ 242 nm
0	0.408
20	0.420
40	0.439
60	0.473
80	0.498
100	0.505
120	0.511
140	0.518
160	0.528
180	0.528
200	0.526
240	0.539
280	0.545
320	0.550
360	0.552
400	0.565

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **66.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	4.40×10^{5} M^{-1}

Volume added/μL	Abs @ 242 nm
0	0.436
20	0.436
40	0.460
60	0.482
80	0.504
100	0.507
120	0.507
140	0.514
160	0.516
180	0.520
200	0.524
240	0.524
280	0.526
320	0.527
360	0.528
400	0.527

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **66.**

Solvent:	Chloroform
Starting volume of host solution:	1 ml
Concentration of host solution:	2.6×10^{-5} mol/l
Concentration of guest solution:	2.7×10^{-4} mol/l
Association constant:	3.84×10^{6} M^{-1}

Volume added/μL	Abs @ 242 nm
0	0.552
20	0.564
40	0.575
60	0.614
80	0.633
100	0.651
120	0.665
140	0.669
160	0.673
180	0.676
200	0.668
240	0.673
280	0.672
320	0.668
360	0.674
400	0.667

Binding data for the tetrabutylammonium salt of phenylacetic acid **71** with receptor **59.**

Solvent:	Chloroform-d_3
Starting volume of host solution:	500 μL
Concentration of host solution:	2.3×10^{-2} mol/l
Concentration of guest solution:	2.3×10^{-3} mol/l
Association constant:	5.01×10^{5} M^{-1}

Volume added/μL	Chemical Shift/ppm
0	7.79
10	8.51
20	9.19
30	9.76
40	10.29
50	10.69
70	11.31
90	11.66
110	11.89
150	12.08
190	12.10
230	12.21

7. References to Introduction

(1) P.M. Muller, D. Lamparski, *Perfumes: Art, Science and Technology*. Elsevier Applied Science, **1991**.

(2) R.H. Wright, *The Science of Smell*, George Allen and Unwin Ltd, **1964**.

(3) E. Theimer, *Fragrance Chemistry: The Science of the Sense of Smell,* Academic Press Inc., **1982**.

(4) F. Wöhler, *Poggendorf Ann. Physik*, **1828**, *12*, 253.

(5) E. Fischer, *Ber. Deutsch. Chem. Ges.*, **1894**, *27*, 2985.

(6) A. Werner, *Zeitschr. Anorg. Chem.*, **1893**, *3*, 267.

(7) P. Ehrlich, Studies on immunity; Wiley: New York, **1906**.

(8) J.M Lehn, *Angew. Chem., Int. Ed. Engl.*, **1978**, *50*, 871.

(9) J.M Lehn, *Angew. Chem., Int. Ed. Engl.*, **1988**, *27*, 89.

(10) F.P. Schmidtchen, *Tet. Lett.*, **1989**, *30*, 4493.
G. Deslonchamps, A. Galán, J. De Mendoza, J. Rebek, *Angew. Chem., Int. Ed. Engl.*, **1992**, *31*, 61.

(11) R.P. Bonar-Law, A.P. Davies, B.A. Murray, *Angew. Chem., Int. Ed. Engl.*, **1990**, *29*, 1407.
R.P. Bonar-Law, A.P. Davies, K.M. Bhattarai, B.A. Murray, *J. Chem. Soc., Chem. Comm.*, **1993**, 752.

(12) W.H. Pirkle, T.C. Pochawski, *J. Am. Chem. Soc.*, **1987**, *109*, 5975.
J.-I. Hong, S.K. Namgoong, A. Bernardi, W.C. Still, *J. Am. Chem. Soc.*, **1991**, *113*, 5111.

(13) M.W. Hosseini; J.-M. Lehn; A.J. Blacker, *J. Am. Chem. Soc.*, **1990**, *112*, 3896.

(14) C.M. Drain, J.-M. Lehn, *J. Chem. Soc., Chem. Comm.*, **1994**, 2313.
C.A. Hunter, *Angew. Chem., Int. Ed. Engl.*, **1995**, 34, 1079.
A.W. Scwhabacher, J.H. Lee, H.Y. Lei, *J. Am. Chem. Soc.*, **1992**, *114*, 7597.
C.A. Hunter, L.D. Sarson, *Angew. Chem., Int. Ed. Engl.*, **1994**, 33, 2313.
C.A. Hunter, L.D. Sarson, *Angew. Chem., Int. Ed. Engl.*, **1994**, 33, 2414.
M. Fujita, S. Nagao, M. Iida, K. Ogata, K. Ogura, *J. Am. Chem. Soc.*, **1993**, *115*, 1574.

(15) D.H. Lee, J.R. Granja, J.A. Martinez, K. Severin, M.R. Ghadiri, *Nature*, **1996**, 525.

J.S. Nowick, Q. Feng, T. Tjivikua, P. Ballester, J. Rebek Jr, *J. Am. Chem. Soc.*, **1991**, *113*, 8831.

T. Tjivikua, P. Ballester, J. Rebek Jr, *J. Am. Chem. Soc.*, **1990**, *112*, 1249.

(16) D.J. Cram, J.M. Cram, *Container Molecules and Their Guests*; The Royal Society of Chemistry: Cambridge, **1994**: Vol. 4.

(17) F. Diedrich, *Cyclophanes*; The Royal Society of Chemistry: Cambridge, **1994**: Vol. 2.

(18) G.W. Gokel, *Crown Ethers and Cryptands,* The Royal Society of Chemistry: Cambridge, **1994**: Vol. 3.

(19) C.D. Gutsche, *Calixarenes*, The Royal Society of Chemistry: Cambridge, **1994**: Vol. 1.

(20) H.-J. Schneider, *Angew. Chem., Int. Ed. Engl.*, **1991**, *30*, 1417.

(21) T.H. Webb, C. S. Wilcox, *Chem. Soc. Rev.*, **1993**, 383.

(22) F.P. Schmidtchen, M. Berger, *Chem. Rev.*, **1997**, *97*, 1609.

Chem. Rev., **1997**, *97* contains a extensive series of reviews on molecular recognition.

(23) J.M. Cram and D.J. Cram, Science, **1974**, *183*, 803.

(24) A. Fersht, *Enzyme Structure and Mechanism*; 2nd ed.; Freeman: New York, **1985**.

(25) P. Groves, M.S. Searle, M.S. Westwell, D.H. Williams, *J. Chem. Soc., Chem. Comm.*, **1994**, 1519.

(26) M.I. Page, W.P. Jencks, *Proc. Natn. Acad. Sci. USA*, **1971**, *68*, 1678.

(27) D.J. Cram, *Angew. Chem., Int. Ed. Engl.*, **1988**, *27*, 1009.

(28) M.D. Joesten, L.J. Schaad, *Hydrogen Bonding*; Dekker, New York, **1974.**

(29) M.L. Huggins, *Angew. Chem., Int. Ed. Engl.*, **1971**, *10*, 147.

(30) W.M. Latimer, W.H. Rodebush, *J. Am. Chem. Soc.*, **1920**, *42*, 1419.

(31) N. Isenberg, *J. Chem. Educ*, **1982**, *59*, 547.

(32) M.J. Kamlet, R.W. Taft, *J. Org. Chem.*, **1982**, *47*, 1734.

(33) W. Saenger, K. Lindner, *Angew. Chem., Int. Ed. Engl.*, **1980**, *19*, 398.

(34) A.D. Hamilton, S.K. Chang, *J. Am. Chem. Soc.*, **1988**, *110*, 1318.

A.D. Hamilton, D.V. Engen, *J. Am. Chem. Soc.*, **1987**, *109*, 5035.

A.D. Hamilton, A.M. Pant, *Pure Appl. Chem.*, **1988**, *60*, 533.

(35) M.W. Hossieni, A.J. Blacker, J.-M. Lehn, *Helv. Chim. Acta.*, **1990**, *112*, 3896.

(36) C.A. Hunter, *Chem. Soc. Rev.*, **1994**, 101.

C.A. Hunter, M.N. Neah, J.K.M. Sanders, *J. Am. Chem. Soc.*, **1990**, *112*, 5773.

(37) A. Fersht, *Enzyme Structure and Mechanism*; 2nd ed.; Freeman: New York, **1985**.

(38) E. Hering, R. Martin, M. Stohier, Physik für Ingeneure, 3. Verbesserte Auflage, **1989**.

(39) G. Zundel, *Hydration and Intermolecular Interaction*, Academic Press, New York, London, **1969**.

(40) B.R. Baker, *J.Chim. Educ*, **1967**, *44*, 610.

(41) J.B.F.N. Engberts, *Pure Appl. Chem.*, **1982**, *54*, 1797.

(42) C. Franck, W. Evans, *J. Phys. Chem.*, **1945**, *13*, 507.
C. Tanford, *The Hydrophobic Effect*, 2nd Ed., Wiley–Interscience, New York, **1980.**

(43) A. Ben-Naim, *J. Phys. Chem.*, **1971**, *54*, 1387.

(44) M.H. Abraham, *J. Am. Chem. Soc.*, **1980**, *102*, 5910.

(45) E. Kimura, A. Sakonaka, T. Yatsunami, M. Kodama, *J. Am. Chem. Soc.*, **1981**, *103*, 3041.

(46) B.Dietrich, M.W. Hosseini, J.-M. Lehn, R.B. Sessions, *J. Am. Chem. Soc.*, **1981**, *103*, 1282.

(47) M.W. Hosseini, J.-M. Lehn, *J. Am. Chem. Soc.*, **1982**, *104*, 3525.
M.W. Hosseini, J.-M. Lehn, *Helv. Chem. Acta*, **1988**, *71*, 749.

(48) N. Pant, A.D. Hamilton, *J. Am. Chem. Soc.*, **1988**, *110*, 2002.

(49) J. Rebek Jr, B. Ashew, D. Nemeth, K. Parris, *J. Am. Chem. Soc.*, **1987**, *109*, 2432.
J. Rebek, D. Nemeth, P. Ballester, F.T. Lin, *J. Am. Chem. Soc.*, **1987**, *109*, 3474.

(50) F. Garcia-Tellado, S. Goswani, S.-K. Chang, S. Geib, A.D. Hamilton, *J. Am. Chem. Soc.*, **1990**, *112*, 7393.

(51) C. Vicent, E. Fan, A.D. Hamilton, *Tetrahedron Lett.*, **1992**, *33*, 4269.

(52) S.J. Geib, C. Vicent, E. Fan, A.D. Hamilton, *Angew. Chem., Int. Ed. Engl.*, **1993**, *32*, 119.
B. Konig, O. Moller, P. Bubenitschek, P.G. Jones, *J. Org. Chem.*, **1995**, *60*, 4291.

(53) A.E. Martell, J. Motekaitis, *J. Am. Chem. Soc.*, **1988**, *110*, 8059.

(54) C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, E. Garcia-Espana, C. Giorgi, J.M. Llinares, J.A. Ramirez, B. Valtancoli, *Inorg. Chem.*, **1999**, *38*, 620.

(55) A.P. Kozikowski, D.S. Dodd, J. Zaidi, Y.-P. Pang, B. Cusack, E; Richelson, *J. Chem. Soc. Perkin Trans. 1*, **1995**,1615.

(56) A. Galán, J. de Mendoza, C. Toiron, M. Bruix, G. Deslongchamps, J. Rebek Jr., *J. Am. Chem. Soc.*, **1991**, *113*, 9424.

(57) B. Dietrich, D.L. Fyles, T.M. Fyles, J.-M. Lehn, *Helv. Chem. Acta*, **1979**, 280.

(58) A. Echavarren, A. Galán, J.-M. Lehn, J. de Mendoza, *J. Am. Chem. Soc.*, **1989**, *111*, 4994.

(59) A. Echavarren, A. Galán, J. de Mendoza, *J. Am. Chem. Soc.*, **1992**, *114*, 1511.

(60) P. Schiessl, F.P. Schmidtchen, *Tetrahedron Lett.*, **1993**, *34*, 2449.

(61) L. Sebo, B. Schweizer, F. Diederich, *Helv. Chem. Acta*, **2000**, *83*, 80.

(62) C. Schmuck, *Chem. Commun.*, **1999**, 843.

(63) C. Schmuck, *Chem. Eur. J.*, **2000**, *6*, 709.

(64) M. Martin, M. Almaraz, J.V. Hernandez, A. Tejeda, M. Cruz Caballero, J.R. Morán, *Heterocycles*, **1999**, *50*, 47.

(65) L.J. Lawless, A.P Davies, *Chem. Commun.*, **1999**, 9.

(66) T. Ross Kelly, R.L. Xie, C.K. Weinreb, T. Bregant, *Tetrahedron Lett.*, **1998**, *39*, 3675.

(67) C. Seel , J. de Mendoza . *In comprehensive Supramolecular chemistry*; J.L. Atwood, J.E. Davies, D.D. Macnicol, F. Vogtleand J.-M. Lehn, Eds Pergamon: Oxford **1996**; Vol 2, 519-552.

(68) F.P. Schmidtchen, M. Berger, *Chem. Rev.*, **1997**, *97*, 1609-1646.

(69) P.J. Smith, M.V. Reddington and C.S. Wilcox, *Tetrahedron Lett.*, **1992**, *41*, 6085.

(70) E. Fan, A. Van Arman, S. Kincaid, A.D. Hamilton, *J. Am. Chem. Soc.*, **1993**, *115*, 369.

(71) S. Nishizawa, P. Buhlmann, M. Iwao, Y. Umezawa, *Tetrahedron Lett.*, **1995**, *36*, 6483.

(72) C. Raposo, M. Crego, L. Mussons, C. Caballero, R.R. Morán, *Tetrahedron Lett.*, **1994**, *35*, 3409.

(73) M.P. Hughes, M. Shang, B.D. Smith, *J. Org. Chem.*, **1996**, *61*, 4510-4511.
J.T. Bien, M.J. Eschner, B.D. Smith, *J. Org. Chem.*, **1995**, *60*, 4525-4529.

(74) W.-S. Yeo, J.-I. Hong, *Tet. Lett.*, **1998**, *39*, 8137-8140.

(75) G.J. Pernia, J.D. Kilburn, M. Rowley, *J. Am. Chem. Soc.*, **1995**, 305.
G.J. Pernia, J.D. Kilburn, J.W. Essex, R.J. Mortishire-Smith, M. Rowley, *J. Am. Chem. Soc.*, **1996**, *118*, 10220.

8. References to Results and Discussion

(76) TMR Research Network "Enantioselective Separations", funded by the EC, Contract ERBFMRXCT980233, in collaboration with the Universities of Dublin (Prof. A.P. Davies), Madrid (Prof. J. de Mendoza), Milano (Prof. C. Gennari) and with DSM Group, The Nertherlands, and Chiroscience UK.

(77) A.D. Hamilton, J.S. Albert, *Tet. Lett.*, **1993**, *34*, 7363.

(78) M. Bonnat, J.D. Kilburn, M. Bradley, *Tetrahedron Lett.*, **1996**, *37*, 5409.

(79) T. Fessmann, J.D. Kilburn, *Angew. Chem., Int. Ed. Engl.*, **1999**, *38*, 1993-1996.

(80) J.A. Joule, G.F. Smith, Heterocyclic Chemistry, Chapt. 3, Van Nostrand Reinhold Company, Ltd., **1978.**

(81) G. L'abbe, *Synthesis,* **1987**, 525-530.

(82) A.E.S. Fairfull, D.A. Peak, *J. Chem. Soc.*, **1955**, 796-802.

(83) J.C. Howard, J.G. Michels, *J. Org.Chem.*, **1960**, *25*, 829-832.

(84) H.M. Blatter, H. Lukaszewski, *Tet. Lett.*, **1964**, 1087. V. Nair, K.H. Kim, *J. Heterocycl. Chem.*, **1976**, *13*, 873.

(85) D.J. Le Count, D.J. Dewsbury, W. Grundy, *Synthesis,* **1977**, 582.

(86) O.-E. Schultz, K.K. Gauri, *Arch Pharm*, **1962**, *295*, 146.

(87) A. Hugershoff, *Chem. Ber .*, **1899**, *32*, 2246.

(88) Jouin and Buu-Hoi, *Ann. Inst. Pasteur*, **1946**, *72*, 580. Mayer, *Chem. Abs.*, **1941**, *36*, 5199.

Huebner *et al, J. Amer. Chem. Soc.*, **1953**, *75*, 2274. Buu-Hoi, Gley, Xuong and Bouffanais, *Compt. rend.*, **1954**, *238*, 2582.

(89) J.-L. Vidaluc, F. Calmel, D. Bigg, E. Carilla, A. Stenger, P. Chopin, M. Briley, *J. Amer. Chem. Soc.*, **1994**, *37*, 689.

(90) Werner, *J.*, **1891**, *59*, 399.

(91) O. Fischer, *Chem. Ber.*, **1899**, *32*, 1301.

(92) Camps, *Arch. Pharm.*, **1902,** *240*, 351.

(93) Schmid, Becker, *Monatsh. Chem.*, **1925**, *46*, 672.

(94) Feist, *Arch. Pharm.*, **1934**, *272*, 104.

(95) G.M. Kyne, PhD Thesis, University of Southampton, **2001**.

(96) R.L.N. Harris, *Aust. J. Chem.,* **1972,** *25*, 993-1001.

(97) S. Coles, D. Douhéret, M. Hursthouse, J. D. Kilburn, *Acta Cryst.*, **2000**, *C56*, 687-688.

(98) D. X. West, A. K. Hermetet, L.J. Ackerman, J. Valdes-Martinez, S. Hernandez-Ortega, *Acta Crystallogr. Sect. C: Cryst. Struct.Commun.*, **1999,** *55,* 811-813.

(99) L.V. Sudha, D.N. Sathyanarayana, *J. Chem. Soc. Perkin Trans.II*, **1986**, 1647-1650.

(100) M.L.Martin, M.L. Filleux-Blanchard, G.J. martin, G.A.Webb, *Org. Mag. Reson.*, **1980**, *13*, 396.

(101) W.-S. Yeo, J.-I. Hong, *Tetrahedron. Lett.*, **1998**, *39*, 8137-8140.

(102) J.A. Bristol, I. Gross, R.G. Lovey, *Synthesis*, **1981**, 971-972.

(103) Weaver, Whaley, *J. Amer. Chem. Soc.,* **1947**, *69*, 516.

(104) S. Coles, D. Douhéret, M. Hursthouse, J. D. Kilburn, S. Rossi, *Acta Cryst.*, **2000**, *C56*, e224-e226.

9. References to Experimental

(105) Feuer, Braunstein, *J. Org. Chem.*, **1969**, *34*, 2024.

(106) Krishnaswami, Bhargawa, *Indian J. Chem.*, **1969**, 710.

(107) R.P. Rao, S.R. Singh, *J. Indian Chem. Soc.*, **1973**, 492-494. L.V. Sudha, D.N. Sathyanarayana, *J. Chem. Soc. Perkin Trans.II*, **1986**, 1647-1650.

(108) A.E.S. Fairfull, D.A. Peak, *J. Chem. Soc.*, **1955**, 796-802.

(109) F. Dennin, D. Blondeau, H. Sliwa, *J. Heterocycl. Chem.*, **1991**, *28*, 1287-1291.

(110) R.L.N. Harris, *Aust. J. Chem.*, **1972**, *25*, 993-1001.

(111) C.S. Wilcox and M.D. Cowart, *Tetrahedron Lett.*, **1996**, *27*, 5563.
C.S Wilcox In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; H.-J. Schneider and H. Durr, Ed; VCH: Weinheim, **1991**; pp 123.

10. Appendix

Table 1. Crystal data and structure refinement.

Identification code	compound **60**	
Empirical formula	$C_{12}H_{11}N_3S$	
Formula weight	229.30	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 5.8720(10) Å	α = 90°
	b = 22.508(5) Å	β = 98.73(3)°
	c = 8.750(2) Å	γ = 90°
Volume	1143.1(4) Å^3	
Z	4	
Density (calculated)	1.332 Mg / m^3	
Absorption coefficient	0.257 mm^{-1}	
F(000)	480	
Crystal	Block; colourless	
Crystal size	0.15 × 0.15 × 0.1 mm^3	
θ range for data collection	2.52 – 24.99°	
Index ranges	$-6 \le h \le 6$, $-24 \le k \le 26$, $-10 \le l \le 10$	
Reflections collected	13692	
Independent reflections	1994 [R_{int} = 0.0904]	
Completeness to θ = 24.99°	96.9 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1994 / 0 / 189	
Goodness-of-fit on F^2	0.913	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0471, $wR2$ = 0.1186	
R indices (all data)	$R1$ = 0.0997, $wR2$ = 0.1530	
Largest diff. peak and hole	0.187 and −0.231 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	455(1)	639(1)	6859(1)	60(1)	1
N1	−6352(4)	1119(1)	3802(3)	59(1)	1
N2	−2963(5)	577(1)	4546(3)	53(1)	1
N3	−3476(5)	1257(1)	6415(3)	53(1)	1
C1	−8258(6)	1217(2)	2772(4)	67(1)	1
C2	−8831(6)	900(2)	1445(4)	65(1)	1
C3	−7394(6)	449(2)	1159(5)	66(1)	1
C4	−5435(6)	336(2)	2182(4)	61(1)	1
C5	−4972(5)	682(1)	3491(3)	47(1)	1
C6	−2118(5)	842(1)	5902(4)	48(1)	1
C7	−2930(5)	1601(1)	7789(3)	46(1)	1
C8	−4438(6)	1598(2)	8848(4)	57(1)	1
C9	−3989(6)	1949(2)	10167(4)	68(1)	1
C10	−2061(6)	2300(2)	10409(5)	68(1)	1
C11	−574(7)	2304(2)	9332(5)	67(1)	1
C12	−997(6)	1958(2)	8041(4)	57(1)	1

Table 3. Bond lengths [Å] and angles [°].

S1–C6	1.676(3)
N1–C5	1.328(4)
N1–C1	1.344(4)
N2–C6	1.353(4)
N2–C5	1.404(4)
N3–C6	1.349(4)
N3–C7	1.424(4)
C1–C2	1.360(5)
C2–C3	1.368(5)
C3–C4	1.370(5)
C4–C5	1.378(5)
C7–C8	1.375(4)
C7–C12	1.381(4)
C8–C9	1.390(5)
C9–C10	1.371(5)
C10–C11	1.378(5)
C11–C12	1.364(5)
C5–N1–C1	117.1(3)
C6–N2–C5	131.4(3)
C6–N3–C7	126.0(3)
N1–C1–C2	124.0(4)
C1–C2–C3	117.8(4)
C2–C3–C4	119.9(4)
C3–C4–C5	118.6(4)
N1–C5–C4	122.7(3)
N1–C5–N2	117.9(3)
C4–C5–N2	119.4(3)
N3–C6–N2	116.2(3)
N3–C6–S1	123.8(2)
N2–C6–S1	120.0(2)
C8–C7–C12	119.5(3)
C8–C7–N3	118.8(3)
C12–C7–N3	121.6(3)
C7–C8–C9	119.8(3)
C10–C9–C8	120.3(3)
C9–C10–C11	119.5(4)
C12–C11–C10	120.5(4)
C11–C12–C7	120.5(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	54(1)	65(1)	56(1)	−11(1)	−10(1)	10(1)
N1	58(2)	68(2)	47(2)	−4(1)	−5(1)	12(1)
N2	50(2)	61(2)	43(2)	−10(1)	−4(1)	12(1)
N3	49(2)	62(2)	44(2)	−8(1)	−5(1)	8(1)
C1	57(2)	77(3)	60(2)	1(2)	−9(2)	16(2)
C2	58(2)	77(3)	53(2)	3(2)	−15(2)	−1(2)
C3	66(2)	78(3)	49(2)	−7(2)	−10(2)	−4(2)
C4	58(2)	71(2)	49(2)	−10(2)	−2(2)	7(2)
C5	50(2)	55(2)	36(2)	2(2)	3(1)	−1(2)
C6	50(2)	51(2)	40(2)	0(1)	1(1)	2(1)
C7	48(2)	44(2)	42(2)	−2(1)	−1(1)	6(1)
C8	47(2)	63(2)	61(2)	−10(2)	8(2)	−6(2)
C9	64(2)	78(3)	63(2)	−19(2)	18(2)	−2(2)
C10	65(2)	67(3)	69(3)	−26(2)	1(2)	1(2)
C11	59(2)	53(2)	88(3)	−18(2)	8(2)	−8(2)
C12	59(2)	54(2)	61(2)	0(2)	14(2)	−5(2)

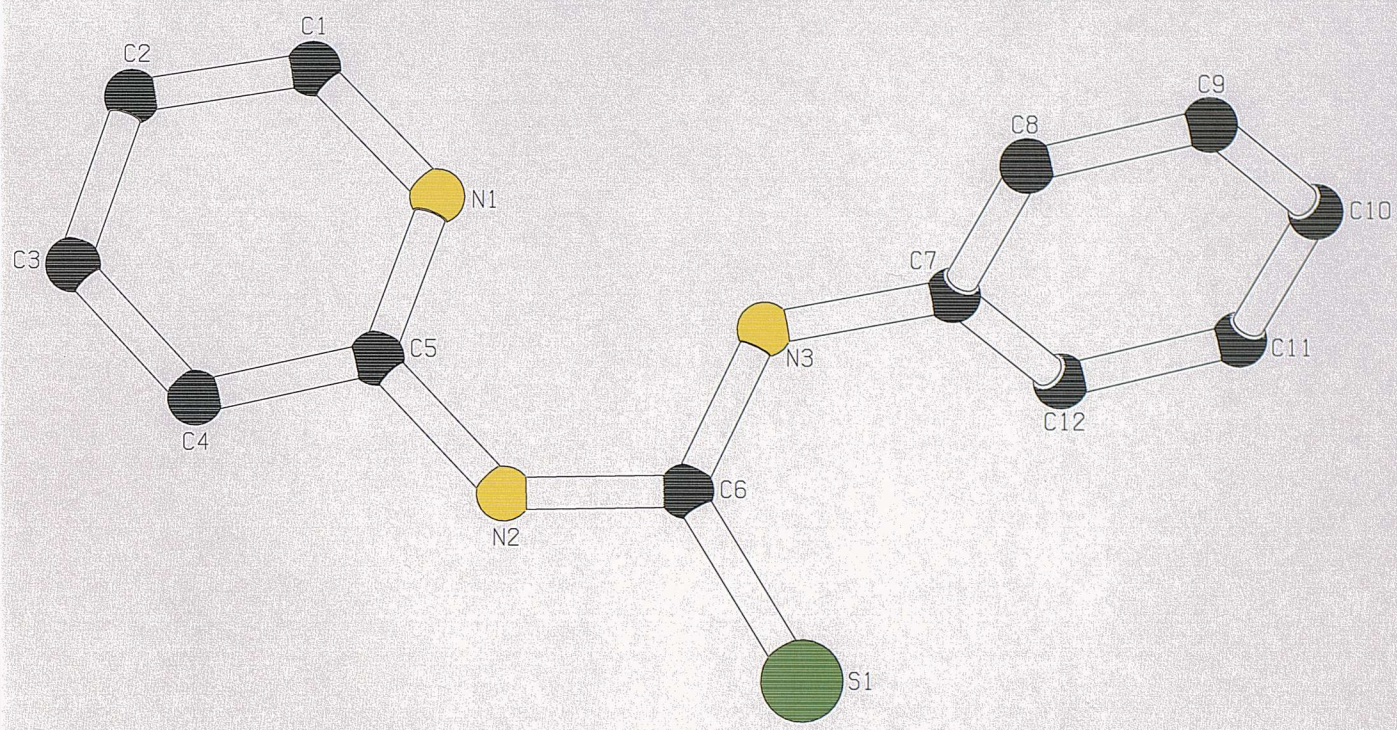

C1
C2
N1
C3
C5
C4
N2
C6
S1
N3
C7
C8
C9
C10
C11
C12

Table 1. Crystal data and structure refinement.

Identification code	Compound **70**	
Empirical formula	$C_{11}H_{10}N_4S$	
Formula weight	230.29	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*C*2/*c*	
Unit cell dimensions	a = 10.970(2) Å	$\alpha = 90°$
	b = 8.986(2) Å	$\beta = 103.66(3)°$
	c = 20.881(4) Å	$\gamma = 90°$
Volume	2000.2(7) Å^3	
Z	8	
Density (calculated)	1.530 Mg / m^3	
Absorption coefficient	0.297 mm^{-1}	
F(000)	960	
Crystal	Plate; pale yellow	
Crystal size	0.1 × 0.1 × 0.025 mm^3	
θ range for data collection	2.96 – 27.46°	
Index ranges	$-14 \le h \le 14, -11 \le k \le 11, -27 \le l \le 26$	
Reflections collected	9713	
Independent reflections	2287 [R_{int} = 0.0522]	
Completeness to θ = 27.46°	93.8 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.994 and 0.957	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2287 / 0 / 145	
Goodness-of-fit on F^2	0.972	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0479, *wR2* = 0.1315	
R indices (all data)	*R1* = 0.0692, *wR2* = 0.1454	
Largest diff. peak and hole	0.325 and –0.674 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	1894(1)	230(1)	5219(1)	26(1)	1
N1	1138(2)	1567(2)	4488(1)	26(1)	1
N2	364(2)	2502(2)	5336(1)	27(1)	1
N3	1106(2)	1060(2)	6282(1)	26(1)	1
N4	2409(2)	−738(2)	6042(1)	24(1)	1
C1	1307(2)	1576(3)	3870(1)	30(1)	1
C2	733(2)	2621(3)	3422(1)	35(1)	1
C3	−41(2)	3679(3)	3619(1)	34(1)	1
C4	−202(2)	3682(3)	4251(1)	32(1)	1
C5	418(2)	2587(2)	4693(1)	27(1)	1
C6	1030(2)	1387(2)	5654(1)	25(1)	1
C7	1884(2)	−92(2)	6499(1)	25(1)	1
C8	2199(2)	−643(3)	7148(1)	30(1)	1
C9	3052(2)	−1769(3)	7305(1)	30(1)	1
C10	3595(2)	−2391(3)	6822(1)	32(1)	1
C11	3256(2)	−1859(2)	6197(1)	29(1)	1

Table 3. Bond lengths [Å] and angles [°].

S1–C6	1.791(2)
S1–N4	1.8902(19)
S1–N1	1.9657(19)
N1–C1	1.345(3)
N1–C5	1.345(3)
N2–C6	1.322(3)
N2–C5	1.359(3)
N3–C6	1.328(3)
N3–C7	1.351(3)
N4–C7	1.355(3)
N4–C11	1.357(3)
C1–C2	1.370(3)
C2–C3	1.400(4)
C3–C4	1.372(4)
C4–C5	1.410(3)
C7–C8	1.407(3)
C8–C9	1.364(3)
C9–C10	1.403(3)
C10–C11	1.357(3)
C6–S1–N4	83.46(9)
C6–S1–N1	82.10(9)
N4–S1–N1	165.55(8)
C1–N1–C5	121.8(2)
C1–N1–S1	128.31(16)
C5–N1–S1	109.89(15)
C6–N2–C5	112.99(19)
C6–N3–C7	112.84(18)
C7–N4–C11	122.1(2)
C7–N4–S1	110.98(15)
C11–N4–S1	126.77(15)
N1–C1–C2	120.9(2)
C1–C2–C3	118.5(2)
C4–C3–C2	120.5(2)
C3–C4–C5	118.5(2)
N1–C5–N2	116.3(2)
N1–C5–C4	119.7(2)
N2–C5–C4	124.1(2)
N2–C6–N3	124.2(2)
N2–C6–S1	118.75(17)
N3–C6–S1	117.09(16)
N3–C7–N4	115.6(2)
N3–C7–C8	125.8(2)
N4–C7–C8	118.6(2)
C9–C8–C7	119.4(2)
C8–C9–C10	120.4(2)
C11–C10–C9	119.0(2)
N4–C11–C10	120.4(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	26(1)	26(1)	26(1)	−3(1)	7(1)	−2(1)
N1	23(1)	26(1)	27(1)	−1(1)	3(1)	−5(1)
N2	25(1)	26(1)	31(1)	−2(1)	8(1)	0(1)
N3	28(1)	28(1)	26(1)	−4(1)	10(1)	0(1)
N4	23(1)	26(1)	25(1)	−1(1)	6(1)	−2(1)
C1	29(1)	34(1)	27(1)	−2(1)	5(1)	−6(1)
C2	34(1)	43(1)	27(1)	0(1)	3(1)	−10(1)
C3	30(1)	36(1)	32(1)	8(1)	−4(1)	−7(1)
C4	28(1)	29(1)	37(1)	1(1)	1(1)	−4(1)
C5	24(1)	26(1)	30(1)	−2(1)	4(1)	−7(1)
C6	21(1)	25(1)	27(1)	−4(1)	5(1)	−5(1)
C7	23(1)	26(1)	27(1)	−4(1)	8(1)	−6(1)
C8	33(1)	32(1)	27(1)	−2(1)	10(1)	−5(1)
C9	31(1)	32(1)	25(1)	4(1)	3(1)	−5(1)
C10	27(1)	27(1)	39(1)	3(1)	3(1)	1(1)
C11	28(1)	28(1)	34(1)	−2(1)	11(1)	−2(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2	–60	3109	5517	33	1
H3	702	1532	6525	32	1
H1	1822	864	3746	36	1
H2A	855	2627	2996	42	1
H3A	–450	4387	3319	41	1
H4	–709	4390	4384	39	1
H8	1830	–243	7467	36	1
H9	3274	–2127	7735	36	1
H10	4178	–3156	6929	38	1
H11	3607	–2265	5872	35	1

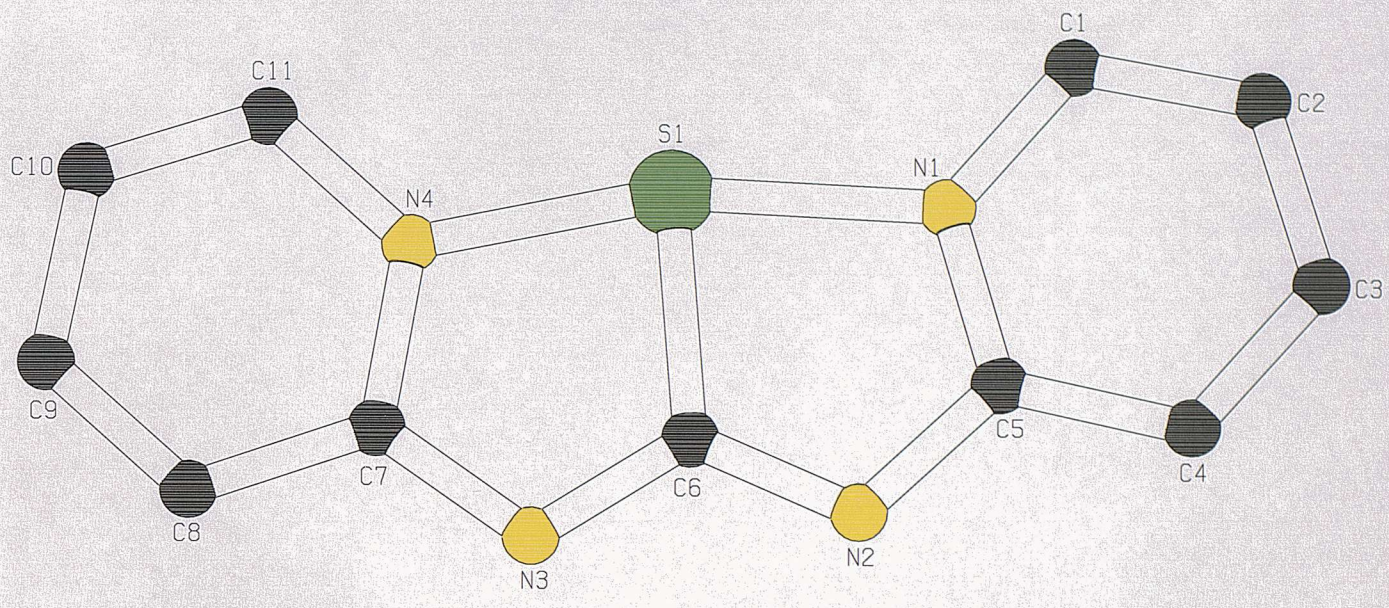

C1
C2
C3
C4
C5
C6
C7
C8
C9
C10
C11
N1
N2
N3
N4
S1

Table 1. Crystal data and structure refinement.

Identification code	Compound **73**	
Empirical formula	$C_{12}H_{12}N_2O$	
Formula weight	200.24	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*Pc*	
Unit cell dimensions	a = 11.112(2) Å	α = 90°
	b = 13.140(3) Å	β = 94.10(3)°
	c = 7.1010(10) Å	γ = 90°
Volume	1034.2(3) Å^3	
Z	4	
Density (calculated)	1.286 Mg / m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	424	
Crystal	Prism; yellow	
Crystal size	0.4 × 0.4 × 0.3 mm^3	
θ range for data collection	1.84 – 25.02°	
Index ranges	$-11 \le h \le 13$, $-15 \le k \le 15$, $-8 \le l \le 8$	
Reflections collected	8286	
Independent reflections	3363 [R_{int} = 0.0320]	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.976 and 0.919	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3354 / 2 / 273	
Goodness-of-fit on F^2	1.362	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0546, $wR2$ = 0.1595	
R indices (all data)	$R1$ = 0.0608, $wR2$ = 0.1764	
Absolute structure parameter	–0.7(15)	
Extinction coefficient	0.09(2)	
Largest diff. peak and hole	0.239 and –0.208 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	464(2)	8759(1)	4194(2)	32(1)	1
O2	6580(2)	6326(1)	4130(2)	32(1)	1
N1	−2131(2)	8255(2)	1028(3)	32(1)	1
N2	−88(2)	7979(2)	788(3)	35(1)	1
N3	9218(2)	6660(2)	7288(3)	33(1)	1
N4	7203(2)	7039(2)	7548(3)	39(1)	1
C1	2885(3)	9838(2)	6098(4)	45(1)	1
C2	4120(3)	9717(3)	6524(4)	52(1)	1
C3	4576(3)	8841(3)	7325(4)	46(1)	1
C4	3810(3)	8062(2)	7709(5)	48(1)	1
C5	2589(3)	8168(2)	7287(4)	41(1)	1
C6	2104(2)	9048(2)	6474(4)	32(1)	1
C7	766(3)	9163(2)	6059(4)	37(1)	1
C8	−735(2)	8768(2)	3606(4)	27(1)	1
C9	−1662(2)	9153(2)	4562(4)	34(1)	1
C10	−2837(3)	9089(2)	3734(4)	37(1)	1
C11	−3027(3)	8629(2)	2013(4)	36(1)	1
C12	−999(2)	8323(2)	1795(3)	28(1)	1
C13	4269(2)	5444(2)	709(4)	42(1)	1
C14	3034(3)	5533(2)	324(5)	48(1)	1
C15	2402(3)	6298(2)	1148(4)	39(1)	1
C16	3015(3)	6973(2)	2359(4)	40(1)	1
C17	4254(2)	6900(2)	2719(4)	35(1)	1
C18	4892(3)	6121(2)	1895(4)	31(1)	1
C19	6231(2)	5987(2)	2271(4)	32(1)	1
C20	7785(2)	6258(2)	4692(4)	28(1)	1
C21	8669(2)	5847(2)	3698(4)	33(1)	1
C22	9854(2)	5834(2)	4514(4)	36(1)	1
C23	10069(3)	6238(2)	6279(5)	35(1)	1
C24	8088(2)	6663(2)	6524(4)	30(1)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C8	1.368(3)
O1–C7	1.444(3)
O2–C20	1.373(3)
O2–C19	1.420(3)
N1–C12	1.337(3)
N1–C11	1.350(4)
N2–C12	1.358(3)
N3–C24	1.332(3)
N3–C23	1.346(4)
N4–C24	1.357(4)
C1–C6	1.391(4)
C1–C2	1.393(4)
C2–C3	1.366(5)
C3–C4	1.372(5)
C4–C5	1.376(4)
C5–C6	1.384(4)
C6–C7	1.502(4)
C8–C9	1.370(4)
C8–C12	1.424(3)
C9–C10	1.396(4)
C10–C11	1.366(4)
C13–C18	1.377(4)
C13–C14	1.385(4)
C14–C15	1.380(4)
C15–C16	1.381(4)
C16–C17	1.385(4)
C17–C18	1.397(4)
C18–C19	1.503(4)
C20–C21	1.361(4)
C20–C24	1.423(4)
C21–C22	1.401(4)
C22–C23	1.366(4)

C8–O1–C7	115.8(2)
C20–O2–C19	116.5(2)
C12–N1–C11	118.1(2)
C24–N3–C23	117.5(3)
C6–C1–C2	119.5(3)
C3–C2–C1	121.1(3)
C2–C3–C4	119.7(3)
C3–C4–C5	119.8(3)
C4–C5–C6	121.7(3)
C5–C6–C1	118.2(3)
C5–C6–C7	121.1(2)
C1–C6–C7	120.7(2)
O1–C7–C6	107.8(2)
O1–C8–C9	127.1(2)
O1–C8–C12	113.9(2)
C9–C8–C12	119.0(2)
C8–C9–C10	118.9(2)
C11–C10–C9	118.9(2)
N1–C11–C10	123.5(3)
N1–C12–N2	118.6(2)
N1–C12–C8	121.5(2)
N2–C12–C8	119.9(2)
C18–C13–C14	120.9(2)
C15–C14–C13	120.3(3)
C14–C15–C16	119.2(3)
C15–C16–C17	120.7(2)

C16–C17–C18	120.0(2)
C13–C18–C17	118.8(3)
C13–C18–C19	118.8(2)
C17–C18–C19	122.5(2)
O2–C19–C18	109.2(2)
C21–C20–O2	126.9(2)
C21–C20–C24	119.4(2)
O2–C20–C24	113.8(2)
C20–C21–C22	118.8(2)
C23–C22–C21	118.1(3)
N3–C23–C22	124.4(3)
N3–C24–N4	118.7(2)
N3–C24–C20	121.7(2)
N4–C24–C20	119.5(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	29(1)	41(1)	25(1)	−5(1)	−3(1)	−2(1)
O2	27(1)	40(1)	29(1)	−6(1)	−2(1)	2(1)
N1	29(1)	32(1)	33(1)	−4(1)	−2(1)	1(1)
N2	29(1)	45(1)	30(1)	−10(1)	−2(1)	3(1)
N3	34(1)	30(1)	34(1)	−3(1)	−5(1)	−2(1)
N4	33(1)	55(1)	28(1)	−9(1)	−3(1)	3(1)
C1	48(2)	51(2)	34(2)	10(1)	−6(1)	−10(1)
C2	44(2)	72(2)	39(2)	10(2)	−2(1)	−23(2)
C3	32(2)	72(2)	34(2)	−8(1)	0(1)	−1(1)
C4	53(2)	47(2)	43(2)	−5(1)	−7(1)	7(1)
C5	45(2)	37(1)	39(2)	−2(1)	−3(1)	−9(1)
C6	37(2)	39(1)	19(1)	−3(1)	−1(1)	−5(1)
C7	38(2)	46(2)	27(2)	−10(1)	−2(1)	−2(1)
C8	29(1)	23(1)	28(1)	1(1)	−1(1)	−1(1)
C9	39(2)	31(1)	31(2)	−3(1)	2(1)	−2(1)
C10	33(2)	36(1)	43(2)	−3(1)	6(1)	3(1)
C11	31(1)	36(1)	39(2)	−2(1)	−1(1)	0(1)
C12	30(1)	27(1)	27(1)	0(1)	0(1)	0(1)
C13	38(2)	47(2)	40(2)	−16(1)	−1(1)	4(1)
C14	41(2)	55(2)	45(2)	−16(1)	−7(1)	−2(1)
C15	32(2)	46(2)	39(2)	2(1)	−2(1)	4(1)
C16	42(2)	40(1)	37(2)	−1(1)	−3(1)	14(1)
C17	40(2)	34(1)	30(1)	−5(1)	−4(1)	0(1)
C18	34(1)	34(1)	26(1)	0(1)	−1(1)	0(1)
C19	33(2)	37(1)	26(1)	−3(1)	−2(1)	1(1)
C20	29(1)	25(1)	31(2)	1(1)	−2(1)	−2(1)
C21	36(2)	32(1)	32(2)	−6(1)	0(1)	−2(1)
C22	30(2)	37(1)	41(2)	−4(1)	3(1)	0(1)
C23	28(1)	34(1)	43(2)	−2(1)	−2(1)	−4(1)
C24	33(1)	25(1)	30(1)	2(1)	−1(1)	0(1)

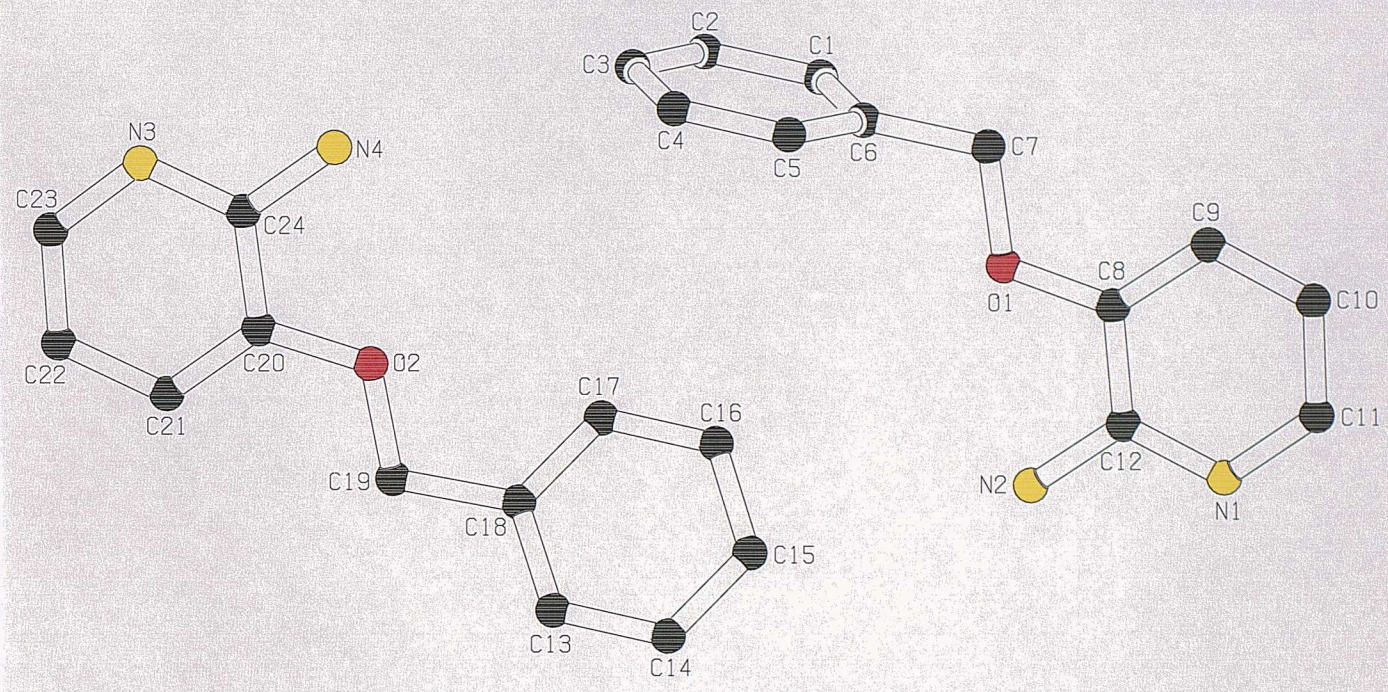

C2
C1
C3
C4
C5
C6
C7
N3
N4
C23
C24
C9
C8
C10
O1
C22
C20
O2
C17
C16
C21
C19
C18
C15
C11
C12
N2
N1
C13
C14

Table 1. Crystal data and structure refinement.

Identification code	Compound **78**	
Empirical formula	$C_{12}H_{14}N_2O_3S_2$	
Formula weight	298.37	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 15.521(3) Å	α = 90°
	b = 6.8270(10) Å	β = 100.06(3)°
	c = 13.574(3) Å	γ = 90°
Volume	1416.2(5) Å^3	
Z	4	
Density (calculated)	1.399 Mg / m^3	
Absorption coefficient	0.381 mm^{-1}	
F(000)	624	
Crystal	Plate; light brown	
Crystal size	0.175 × 0.15 × 0.025 mm^3	
θ range for data collection	2.67 – 27.43°	
Index ranges	$-19 \le h \le 19$, $-8 \le k \le 8$, $-17 \le l \le 17$	
Reflections collected	12963	
Independent reflections	3159 [R_{int} = 0.0583]	
Completeness to θ = 27.43°	98.0 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.998 and 0.888	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3159 / 0 / 175	
Goodness-of-fit on F^2	0.807	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0393, $wR2$ = 0.1033	
R indices (all data)	$R1$ = 0.0679, $wR2$ = 0.1218	
Largest diff. peak and hole	0.278 and –0.292 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	1797(1)	1646(1)	3813(1)	27(1)	1
S2	2678(1)	2169(1)	5971(1)	31(1)	1
O1	−1041(1)	2369(2)	3333(1)	24(1)	1
O2	−2085(1)	1316(2)	1632(1)	33(1)	1
O3	−3255(1)	2608(2)	2181(1)	33(1)	1
N1	945(1)	2276(2)	5158(1)	19(1)	1
N2	724(1)	1847(2)	3449(1)	24(1)	1
C1	658(1)	2565(3)	6060(2)	23(1)	1
C2	−198(1)	2841(3)	6053(1)	23(1)	1
C3	−814(1)	2824(3)	5133(2)	23(1)	1
C4	−539(1)	2480(3)	4255(1)	21(1)	1
C5	375(1)	2175(2)	4244(1)	20(1)	1
C6	−1956(1)	2667(3)	3287(2)	24(1)	1
C7	−2421(1)	2105(3)	2255(2)	24(1)	1
C8	−3916(1)	2016(3)	1309(2)	34(1)	1
C9	−3943(1)	−180(3)	1242(2)	45(1)	1
C10	−4755(2)	2806(5)	1576(3)	65(1)	1
C11	−3714(2)	2968(5)	371(2)	69(1)	1
C12	1818(1)	2046(3)	5063(2)	23(1)	1

Table 3. Bond lengths [Å] and angles [°].

S1–N2	1.6593(17)
S1–C12	1.712(2)
S2–C12	1.653(2)
O1–C4	1.355(2)
O1–C6	1.426(2)
O2–C7	1.196(2)
O3–C7	1.326(3)
O3–C8	1.481(3)
N1–C1	1.388(3)
N1–C5	1.394(3)
N1–C12	1.393(3)
N2–C5	1.308(3)
C1–C2	1.341(3)
C2–C3	1.434(3)
C3–C4	1.355(3)
C4–C5	1.437(3)
C6–C7	1.509(3)
C8–C9	1.502(3)
C8–C11	1.510(4)
C8–C10	1.511(4)
N2–S1–C12	97.23(9)
C4–O1–C6	116.05(15)
C7–O3–C8	121.40(17)
C1–N1–C5	122.74(17)
C1–N1–C12	124.42(17)
C5–N1–C12	112.84(16)
C5–N2–S1	107.91(14)
C2–C1–N1	118.88(18)
C1–C2–C3	120.99(19)
C4–C3–C2	120.21(19)
C3–C4–O1	127.14(18)
C3–C4–C5	119.79(18)
O1–C4–C5	113.06(17)
N2–C5–N1	116.92(17)
N2–C5–C4	125.76(18)
N1–C5–C4	117.30(17)
O1–C6–C7	108.36(16)
O2–C7–O3	127.09(19)
O2–C7–C6	125.05(19)
O3–C7–C6	107.85(17)
O3–C8–C9	109.19(18)
O3–C8–C11	109.85(19)
C9–C8–C11	112.7(2)
O3–C8–C10	102.50(19)
C9–C8–C10	110.7(2)
C11–C8–C10	111.3(2)
N1–C12–S2	126.63(16)
N1–C12–S1	105.06(14)
S2–C12–S1	128.30(13)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	21(1)	38(1)	23(1)	−1(1)	5(1)	2(1)
S2	22(1)	38(1)	30(1)	−2(1)	−4(1)	1(1)
O1	16(1)	38(1)	19(1)	−2(1)	1(1)	−1(1)
O2	21(1)	51(1)	27(1)	−8(1)	6(1)	−5(1)
O3	18(1)	44(1)	35(1)	−9(1)	−3(1)	4(1)
N1	18(1)	20(1)	18(1)	0(1)	1(1)	−1(1)
N2	21(1)	32(1)	19(1)	0(1)	4(1)	0(1)
C1	27(1)	24(1)	17(1)	0(1)	2(1)	−1(1)
C2	30(1)	25(1)	16(1)	−1(1)	6(1)	−2(1)
C3	19(1)	25(1)	24(1)	0(1)	5(1)	−2(1)
C4	21(1)	20(1)	19(1)	2(1)	1(1)	−2(1)
C5	22(1)	18(1)	17(1)	1(1)	0(1)	−1(1)
C6	19(1)	30(1)	24(1)	0(1)	4(1)	0(1)
C7	18(1)	27(1)	27(1)	3(1)	2(1)	−4(1)
C8	15(1)	49(1)	34(1)	−2(1)	−5(1)	−3(1)
C9	26(1)	53(2)	52(2)	−6(1)	−4(1)	−7(1)
C10	26(2)	85(2)	77(2)	−21(2)	−10(1)	14(1)
C11	43(2)	106(2)	50(2)	37(2)	−18(1)	−27(2)
C12	22(1)	22(1)	26(1)	2(1)	4(1)	1(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	1054	2567	6660	27	1
H2A	−396	3048	6653	28	1
H3	−1404	3049	5139	27	1
H6A	−2071	4030	3419	29	1
H6B	−2165	1868	3787	29	1
H9A	−3415	−649	1046	67	1
H9B	−4438	−576	755	67	1
H9C	−3994	−718	1883	67	1
H10A	−4851	2225	2192	97	1
H10B	−5236	2492	1053	97	1
H10C	−4711	4202	1654	97	1
H11A	−3626	4348	483	104	1
H11B	−4194	2764	−169	104	1
H11C	−3193	2397	203	104	1

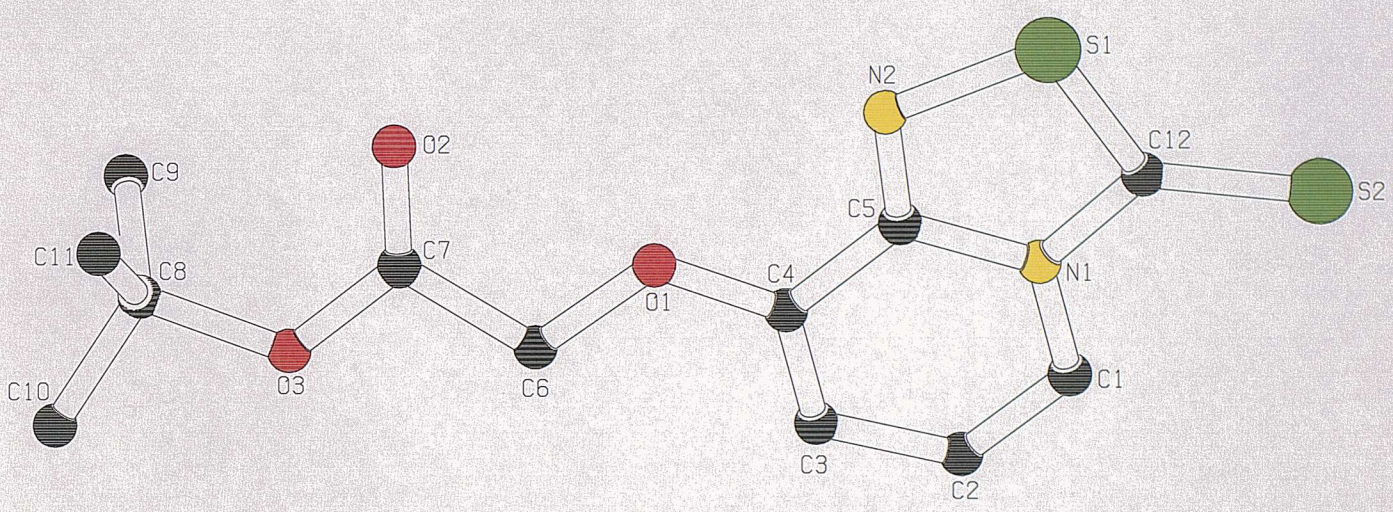

S1
N2
C12
S2
C5
O2
C9
C11
C8
C7
N1
C4
O1
C1
C10
O3
C6
C3
C2

Table 1. Crystal data and structure refinement.

Identification code	Compound **79**	
Empirical formula	$C_{14}H_{21}N_3O_3S$	
Formula weight	311.40	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 10.661(2) Å	α = 76.85(3)°
	b = 11.852(2) Å	β = 81.35(3)°
	c = 13.501(3) Å	γ = 72.12(3)°
Volume	1575.1(5) $Å^3$	
Z	4	
Density (calculated)	1.313 Mg / m^3	
Absorption coefficient	0.219 mm^{-1}	
F(000)	664	
Crystal	Block; colourless	
Crystal size	0.2 × 0.1 × 0.1 mm^3	
θ range for data collection	1.84 – 26.00°	
Index ranges	$-13 \le h \le 13$, $-14 \le k \le 14$, $-16 \le l \le 16$	
Reflections collected	20603	
Independent reflections	6191 [R_{int} = 0.0465]	
Completeness to θ = 26.00°	99.9 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.986 and 0.879	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6191 / 0 / 388	
Goodness-of-fit on F^2	1.192	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0522, *wR2* = 0.1532	
R indices (all data)	*R1* = 0.0681, *wR2* = 0.1652	
Extinction coefficient	0.007(2)	
Largest diff. peak and hole	0.658 and –0.915 e $Å^{-3}$	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	2628(1)	2643(1)	3604(1)	29(1)	1
S2	5860(1)	2371(1)	7762(1)	29(1)	1
O1	495(1)	3460(1)	6265(1)	25(1)	1
O2	355(1)	3865(1)	8201(1)	28(1)	1
O3	−1871(1)	4637(1)	8207(1)	25(1)	1
N1	3298(1)	684(1)	5064(1)	11(1)	1
N2	2968(2)	2383(2)	5571(1)	22(1)	1
N3	3479(2)	4244(2)	5174(1)	26(1)	1
N4	3839(1)	4372(1)	7687(1)	10(1)	1
N5	3261(2)	2688(2)	8097(1)	22(1)	1
N6	3582(2)	861(2)	7567(1)	24(1)	1
O5	868(2)	1237(2)	10643(1)	33(1)	1
O4	3323(1)	1509(1)	10073(1)	24(1)	1
O6	1464(1)	238(1)	12221(1)	26(1)	1
C1	2971(2)	1890(2)	4774(2)	21(1)	1
C2	3469(2)	−65(2)	4312(2)	26(1)	1
C3	3548(2)	−1320(2)	4886(2)	31(1)	1
C4	2578(2)	3654(2)	5536(2)	22(1)	1
C5	3117(2)	5433(2)	5166(2)	27(1)	1
C6	1867(2)	6051(2)	5524(2)	26(1)	1
C7	942(2)	5429(2)	5914(2)	25(1)	1
C8	1300(2)	4204(2)	5915(2)	21(1)	1
C9	−767(2)	3969(2)	6751(2)	24(1)	1
C10	−662(2)	4138(2)	7803(2)	21(1)	1
C11	−2066(2)	5008(2)	9213(2)	30(1)	1
C12	−1708(3)	3882(2)	10037(2)	40(1)	1
C13	−3528(2)	5651(3)	9304(2)	46(1)	1
C14	−1275(2)	5882(2)	9173(2)	34(1)	1
C15	4281(2)	3167(2)	7851(2)	22(1)	1
C16	4775(2)	5075(2)	7312(2)	27(1)	1
C17	4067(2)	6359(2)	7378(2)	33(1)	1
C18	3440(2)	1422(2)	8343(2)	20(1)	1
C19	3742(2)	−328(2)	7771(2)	25(1)	1
C20	3743(2)	−986(2)	8760(2)	26(1)	1
C21	3581(2)	−410(2)	9569(2)	24(1)	1
C22	3436(2)	825(2)	9364(2)	21(1)	1
C23	3043(2)	974(2)	11107(2)	23(1)	1
C24	1648(2)	845(2)	11276(2)	24(1)	1
C25	179(2)	−28(2)	12579(2)	29(1)	1
C26	−71(2)	−791(2)	11912(2)	36(1)	1
C27	−901(2)	1157(2)	12603(2)	43(1)	1
C28	425(3)	−758(3)	13651(2)	44(1)	1

Table 3. Bond lengths [Å] and angles [°].

S1–C1	1.661(2)
S2–C15	1.659(2)
O1–C8	1.374(3)
O1–C9	1.421(2)
O2–C10	1.205(2)
O3–C10	1.333(2)
O3–C11	1.486(3)
N1–C1	1.341(3)
N1–C2	1.451(3)
N2–C1	1.336(3)
N2–C4	1.425(3)
N3–C4	1.329(3)
N3–C5	1.341(3)
N4–C15	1.335(3)
N4–C16	1.453(3)
N5–C15	1.341(3)
N5–C18	1.419(3)
N6–C18	1.330(3)
N6–C19	1.335(3)
O5–C24	1.197(3)
O4–C22	1.359(3)
O4–C23	1.424(3)
O6–C24	1.334(3)
O6–C25	1.485(3)
C2–C3	1.496(3)
C4–C8	1.394(3)
C5–C6	1.383(3)
C6–C7	1.381(3)
C7–C8	1.383(3)
C9–C10	1.504(3)
C11–C13	1.510(3)
C11–C14	1.512(4)
C11–C12	1.518(3)
C16–C17	1.494(3)
C18–C22	1.399(3)
C19–C20	1.384(3)
C20–C21	1.377(3)
C21–C22	1.390(3)
C23–C24	1.519(3)
C25–C26	1.513(4)
C25–C28	1.523(4)
C25–C27	1.522(3)
C8–O1–C9	117.13(16)
C10–O3–C11	120.81(16)
C1–N1–C2	119.84(17)
C1–N2–C4	123.44(17)
C4–N3–C5	117.46(19)
C15–N4–C16	119.16(16)
C15–N5–C18	122.45(17)
C18–N6–C19	118.55(19)
C22–O4–C23	116.34(16)
C24–O6–C25	119.88(16)
N2–C1–N1	109.35(18)
N2–C1–S1	125.64(16)
N1–C1–S1	125.00(17)
N1–C2–C3	107.07(18)
N3–C4–C8	123.4(2)
N3–C4–N2	117.74(18)

C8–C4–N2	118.77(18)
N3–C5–C6	122.9(2)
C7–C6–C5	119.4(2)
C6–C7–C8	118.3(2)
O1–C8–C7	125.50(18)
O1–C8–C4	115.96(18)
C7–C8–C4	118.54(19)
O1–C9–C10	111.66(17)
O2–C10–O3	126.5(2)
O2–C10–C9	124.87(19)
O3–C10–C9	108.66(17)
O3–C11–C13	102.69(18)
O3–C11–C14	109.32(19)
C13–C11–C14	110.0(2)
O3–C11–C12	108.8(2)
C13–C11–C12	111.6(2)
C14–C11–C12	113.8(2)
N4–C15–N5	110.19(17)
N4–C15–S2	125.18(16)
N5–C15–S2	124.63(16)
N4–C16–C17	107.60(18)
N6–C18–C22	122.98(19)
N6–C18–N5	116.93(18)
C22–C18–N5	120.08(19)
N6–C19–C20	122.1(2)
C21–C20–C19	119.8(2)
C20–C21–C22	118.6(2)
O4–C22–C21	125.54(19)
O4–C22–C18	116.41(18)
C21–C22–C18	118.0(2)
O4–C23–C24	110.48(17)
O5–C24–O6	127.2(2)
O5–C24–C23	123.9(2)
O6–C24–C23	108.91(17)
O6–C25–C26	109.58(19)
O6–C25–C28	102.10(17)
C26–C25–C28	110.5(2)
O6–C25–C27	108.87(19)
C26–C25–C27	113.8(2)
C28–C25–C27	111.4(2)

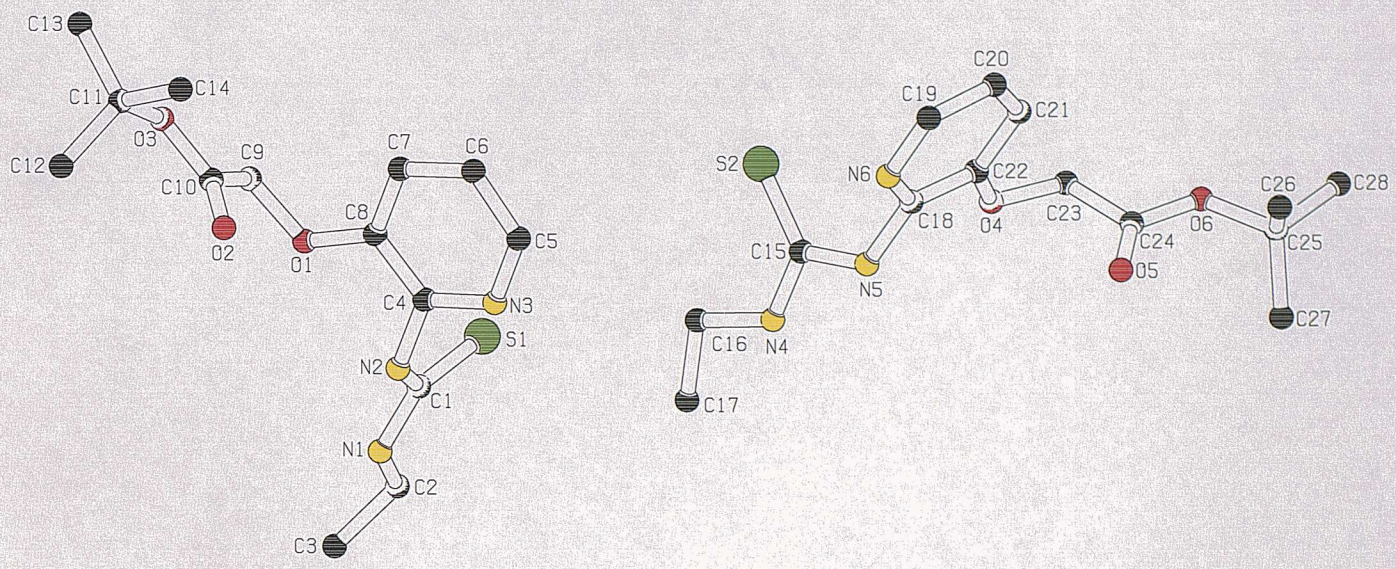
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	37(1)	23(1)	22(1)	−2(1)	−6(1)	−3(1)
S2	21(1)	23(1)	39(1)	−1(1)	−1(1)	−4(1)
O1	26(1)	21(1)	29(1)	−7(1)	5(1)	−7(1)
O2	21(1)	32(1)	29(1)	−4(1)	−4(1)	−4(1)
O3	21(1)	32(1)	23(1)	−9(1)	−1(1)	−5(1)
N1	19(1)	6(1)	6(1)	−1(1)	−2(1)	−1(1)
N2	27(1)	18(1)	18(1)	−2(1)	−2(1)	−3(1)
N3	30(1)	24(1)	24(1)	−5(1)	−1(1)	−7(1)
N4	7(1)	4(1)	18(1)	−2(1)	2(1)	0(1)
N5	20(1)	17(1)	25(1)	−1(1)	0(1)	−2(1)
N6	24(1)	26(1)	22(1)	−4(1)	−2(1)	−8(1)
O5	27(1)	37(1)	31(1)	2(1)	−9(1)	−6(1)
O4	30(1)	21(1)	20(1)	−4(1)	1(1)	−8(1)
O6	23(1)	30(1)	24(1)	−2(1)	1(1)	−10(1)
C1	17(1)	23(1)	24(1)	−6(1)	1(1)	−5(1)
C2	33(1)	25(1)	23(1)	−10(1)	2(1)	−10(1)
C3	37(1)	24(1)	32(1)	−8(1)	0(1)	−8(1)
C4	26(1)	20(1)	18(1)	−3(1)	−3(1)	−5(1)
C5	32(1)	26(1)	25(1)	−5(1)	0(1)	−13(1)
C6	35(1)	18(1)	26(1)	−5(1)	−6(1)	−5(1)
C7	28(1)	24(1)	22(1)	−4(1)	−1(1)	−5(1)
C8	25(1)	21(1)	17(1)	−2(1)	−3(1)	−7(1)
C9	20(1)	25(1)	28(1)	−7(1)	2(1)	−6(1)
C10	19(1)	19(1)	25(1)	−2(1)	−1(1)	−5(1)
C11	26(1)	42(1)	23(1)	−11(1)	−2(1)	−6(1)
C12	41(1)	54(2)	27(1)	−1(1)	−1(1)	−21(1)
C13	26(1)	75(2)	35(2)	−28(1)	2(1)	−2(1)
C14	35(1)	33(1)	35(1)	−13(1)	−9(1)	−2(1)
C15	27(1)	22(1)	17(1)	−3(1)	−2(1)	−8(1)
C16	30(1)	24(1)	30(1)	−4(1)	1(1)	−14(1)
C17	36(1)	24(1)	38(1)	−4(1)	−5(1)	−12(1)
C18	16(1)	20(1)	22(1)	−3(1)	0(1)	−5(1)
C19	25(1)	25(1)	28(1)	−9(1)	0(1)	−9(1)
C20	26(1)	19(1)	33(1)	−3(1)	−2(1)	−7(1)
C21	23(1)	23(1)	24(1)	0(1)	−2(1)	−8(1)
C22	17(1)	22(1)	24(1)	−5(1)	−1(1)	−5(1)
C23	24(1)	24(1)	19(1)	−3(1)	−2(1)	−6(1)
C24	25(1)	20(1)	24(1)	−5(1)	−2(1)	−3(1)
C25	21(1)	34(1)	34(1)	−6(1)	3(1)	−13(1)
C26	34(1)	39(2)	40(2)	−8(1)	−3(1)	−17(1)
C27	27(1)	48(2)	55(2)	−21(1)	8(1)	−9(1)
C28	46(2)	61(2)	29(1)	−2(1)	3(1)	−30(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	3405	355	5694	13	1
H2	3213	1910	6136	27	1
H4	3012	4727	7802	12	1
H5	2470	3166	8106	27	1
H2A	4274	−55	3871	31	1
H2B	2727	232	3894	31	1
H3A	4259	−1588	5321	47	1
H3B	3705	−1852	4412	47	1
H3C	2729	−1325	5294	47	1
H5A	3733	5861	4909	32	1
H6	1652	6879	5501	32	1
H7	101	5823	6170	30	1
H9A	−1323	3443	6798	29	1
H9B	−1184	4744	6340	29	1
H12A	−2215	3352	9999	60	1
H12B	−1900	4107	10695	60	1
H12C	−782	3476	9939	60	1
H13A	−3741	6287	8719	69	1
H13B	−3748	5988	9912	69	1
H13C	−4022	5087	9339	69	1
H14A	−350	5455	9162	52	1
H14B	−1537	6250	9764	52	1
H14C	−1436	6497	8568	52	1
H16A	5099	5010	6611	32	1
H16B	5523	4778	7724	32	1
H17A	3313	6635	6984	49	1
H17B	4654	6851	7114	49	1
H17C	3777	6417	8078	49	1
H19	3857	−728	7231	30	1
H20	3853	−1813	8878	31	1
H21	3568	−838	10237	29	1
H23A	3134	1472	11556	27	1
H23B	3673	184	11273	27	1
H26A	−359	−288	11275	54	1
H26B	−743	−1162	12252	54	1
H26C	731	−1406	11785	54	1
H27A	−617	1653	12943	64	1
H27B	−1693	995	12964	64	1
H27C	−1075	1572	11917	64	1
H28A	1218	−1415	13623	66	1
H28B	−310	−1074	13929	66	1
H28C	521	−247	14076	66	1


C13
C11
C14
C12
O3
C9
C10
O2
C7
C6
C8
O1
C5
C4
N3
S1
N2
C1
N1
C2
C3
C20
C19
C21
S2
N6
C22
C18
O4
C23
C24
O6
C26
C28
C15
N5
O5
C25
C16
N4
C27
C17