DESIGN, SYNTHESIS AND EVALUATION OF NOVEL, METAL COMPLEXING AGENTS

THESIS

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JUSTIN PHILIP HAGEMANN

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Department of Chemistry

Rhodes University

Grahamstown

CONTENTS

ABBREVIATIONS

THF	=	tetrahydrofuran
DMF	=	*N,N*-dimethylformamide
IDA	=	iminodiacetic acid
CDI	=	1,1'-carbonyldiimidazole
en	=	ethylenediamine
dien	=	diethylenetriamine
trien	=	triethylenetetramine
pgm	=	platinum group metals
PLC	=	preparative layer chromatography
TLC	=	thin layer chromatography
s	=	singlet
br s	=	broad singlet
d	=	doublet
dd	=	double doublet
t	=	triplet
m	=	multiplet
IR	=	infrared
NMR	=	nuclear magnetic resonance
COSY	=	^{1}H - ^{1}H correlation spectroscopy

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ABSTRACT

Various chelating ligands have been designed and synthesised; these include amino-amide ligands, tetraacetic acid systems and sulfur-containing amide ligands. Difficulties in the synthesis and purification of the amino-amide ligands were largely overcome, permitting the monoacylation of ethylenediamine and the synthesis of bis(2-aminoethyl)-2-benzylpropanediamide. Novel tetraacetic acid ligands, based on the propanediamide backbone and targeted as EDTA analogues, were obtained from their methyl and benzyl esters; but the instability of the tetraacids prevented their full characterisation.

Bidentate, tridentate and tetradentate sulfur-containing monoamide ligands, based on the *ortho*-thio acetanilide moiety, were designed to specifically chelate platinum and palladium in the presence of base metals. In their synthesis, thiocyanation was used to introduce the *ortho*-thio group on *para*-substituted anilines, and further functionalisation was achieved *via* appropriate protection of nucleophilic sulfur moieties. A range of tetradentate, sulfur-containing diamide ligands was also synthesised by reacting substituted 2-mercaptoacetanilides with 1,2-dibromoethane. Novel ligands were characterised by spectroscopic (^{1}H and ^{13}C NMR; IR and MS) techniques and elemental (combustion and high resolution MS) analysis.

Computer modelling and ^{1}H NMR chemical shift data have been used to explore the conformational preferences of the sulfur-containing acetanilide ligands. The macrocyclic ligands and systems with *ortho*-methylthio substituents appear to exhibit the greatest degree of coplanarity of the aromatic and amide functions.

Solvent extraction studies revealed that the sulfur-containing amide ligands selectively extracted palladium(II) from platinum(II), copper(II), nickel(II) and cobalt(II). Even though the palladium(II) was extracted from an acidic medium, certain monoamide ligands were able to

complex palladium(II) through their sulfur and deprotonated amide nitrogen donors, a trithia monoamide ligand being observed to displace all the chloride ligands on palladium to form a monomeric tetracoordinate complex. The diamide ligands, however, appeared to favour extraction of palladium(II) by coordination through their sulfur donors, forming 5-membered sulfur-sulfur chelates. In basic media (pH 8-9), selected sulfur-containing monoamide and diamide ligands have been shown to complex platinum(II) and palladium(II) through their sulfur and deprotonated amide nitrogen donors. At neutral pH, a dimercapto monoamide ligand has been shown to complex platinum from cisplatin with partial expulsion of the ammine ligands, while a macrocyclic trithia monoamide ligand has been observed to complex platinum from tetrachloroplatinate with concomitant deprotonation of the amide nitrogen. Where possible, the complexes were characterised by infrared and ^{1}H NMR spectroscopy and have also been studied using the computer modelling soft-ware programmes, Momec® and Hyperchem.®

1 INTRODUCTION

Metal-specific ligands have important applications in a wide variety of fields including metallurgy, medicine and environmental control. In metallurgy, metal-specific ligands are finding increasing use as extractants in solvent extraction processes.[1, 2] Medical uses include the treatment of metal intoxication,[3] complexation with radionuclides for scintigraphic imaging and cancer radiotherapy, and metal complexing antibiotics. As the human environment becomes more polluted so the design of chelating agents for removing toxic metals from the human body has grown in importance. Improved clinical treatments require the design of chelating agents which can induce a significant increase in the excretion of a specific, toxic metal. An understanding of the factors influencing complex stability will also elucidate the functioning of many biological systems, including metal-binding proteins and biological cation transport systems. Chelating agents are also frequently used for the extraction of heavy metals from waste waters.[2]

1.1 LIGAND DESIGN FOR SELECTIVE COMPLEXATION

Since Jannik Bjerrum's thesis on metal ammine formation in aqueous solution,[4] considerable quantitative data on metal complex stability has been obtained. The analysis of this data has led to a good understanding of the principles involved in the design of metal-specific ligands. The effect of donor atoms on complex stability is well established and is reflected in the group A or B type acids of Ahrland[5] and Schwarzenbach[6] and the hard and soft acid base principle of Pearson.[7] More recently, the role of steric strain in complexation has been rationalised by Hancock and Martell,[8] and an important tool used in this regard is molecular mechanics (MM) calculations. Such calculations provide a useful indication of the steric constraints involved in complexation. As a result of these developments, steric effects and the nature of the donor atoms are now major considerations in the design of metal-specific ligands. However, design

must also take into account the "operating requirements" of the ligand, *i.e.* in addition to high selectivity, extractants in solvent extraction processes must also have low aqueous solubility, high loading capacity, rapid extraction kinetics and acceptable cost.[9] Biological applications often require the formation of stable complexes with low toxicity and good lipid solubility and, for the treatment of metal intoxication, the chelating agent must have a high stability constant for the toxic metal and must also be tailored to achieve satisfactory interactions with biological systems.

1.1.1 Donor atoms

Trends in coordinating affinities between ligand atoms and metal ions were summarised in 1941 by Sidgwick.[10] Since then, the available quantitative data has increased enormously and the earlier correlations have been revised and extended by Ahrland.[5] Two uniform patterns of relative coordinating affinities have been found:

i) there are great differences between the coordinating affinities of the first and second elements of groups 15, 16 and 17, *i.e.* between nitrogen and phosphorus, oxygen and sulfur, fluorine and chlorine.

ii) there are two types of acceptor, *viz.*, those that form their most stable complexes with the first ligand atom in each group (type A) and those that form their most stable complexes with the second or subsequent ligand atom (type B).

Ahrland further noted that, for a given metal, each oxidation state must be regarded as a different acceptor; for example, Cu(I) is very different to Cu(II) in its coordination chemistry. Most metals in their common oxidation state are type A, while all transition metals in their zero oxidation state belong to class B. The most pronounced class B acceptors are those that form stable olefin complexes, *viz.*, Cu(I), Rh(I), Pd(II), Ag(I), Pt(II), and Hg(II). While many

acceptors are well defined as class A or B, the boundary between them is quite diffuse with many acceptors falling in the border region.

Pearson's approach to the classification of donors and acceptors was more general, covering organic reactions as well as complexation reactions,[7] and thus uses the terminology "ligand" or "Lewis base" for the nucleophilic reagent and "Lewis acid" for the electrophilic acceptor (whether it be an organic compound or metal ion). Again, the classification is based on the stability of the adducts and not on rates of formation. Acids are classified as hard or soft depending on whether they:

i) bind strongly to bases which bind strongly to the proton (hard acids) or

ii) bind strongly to highly polarisable or unsaturated bases, which often have negligible proton basicity (soft acids).

Bases are similarly divided into two categories, *viz.*, those that are polarisable or soft and those that are non-polarisable or hard, hardness being associated with good proton binding. For example, fluorine, oxygen and nitrogen are the hardest in each group and also the most basic to the proton. These elements are also the first elements in each group and so, for the case of metal ions as acceptors, this classification is analogous to Ahrland's.[5] Pearson's classification of Lewis acids thus leaves the classification of metal ions by Ahrland essentially unchanged. Table 1 summarises the classification of acids and bases in terms of Pearson's hard and soft acid and base (HSAB) principle.

For a typically soft metal ion the order of decreasing complex stability for different donors was found to be C~S > I > Br > Cl ~ N > O > F. For a hard metal ion this order is approximately inverted, the inversion is not complete because some soft bases like the sulfide ion are still strong proton acceptors. When using the classification in Table 1 it must be remembered that the class of a given element is not constant and depends on the oxidation state. It must also be

realised that the properties of the central atom can be influenced by the groups attached to it, groups which transfer negative charge to the central atom will increase the softness of that atom. Groups which most readily transfer charge are hydroxide ions, alkanide ions and sulfide ions.

ACIDS

Hard	**Soft**
H^+, Li^+, Na^+, K^+,	Cu^+, Ag^+, Au^+, Tl^+, Hg^+,
Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+},	Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+},
Al^{3+}, Sc^{3+}, Ga^{3+}, In^{3+}, La^{3+},	CH_3Hg^+, $Co(CN)_5^{2-}$, Pt^{4+},
Gd^{3+}, Lu^{3+}, Cr^{3+}, Co^{3+}, Fe^{3+}, As^{3+},	Te^{4+}, Br^+, I^+
Si^{4+}, Ti^{4+}, Zr^{4+}, Hf^{4+}, Th^{4+}, U^{4+},	
Pu^{4+}, Ce^{4+}, WO^{4+}, Sn^{4+},	
UO^{2+}, VO^{2+}, MoO^{3+}	

Borderline

Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+},
Sn^{2+}, Sb^{3+}, Bi^{3+}, Rh^{3+}, Ir^{3+}, $B(CH_3)_3$

BASES

Hard	**Soft**
H_2O, OH^-, F^-, $CH_3CO_2^-$, PO_4^{3-},	R_2S, RSH, RS^-, I^-, SCN^-,
SO_4^{2-}, Cl^-, CO_3^{2-}, ClO_4^-, NO_3^-,	$S_2O_3^{2-}$, R_3P, R_3As, $(RO)_3P$
ROH, RO^-, R_2O, NH_3, RNH_2,	CN^-, RNC, CO, C_2H_4, H^-, R^-
NH_2NH_2	

Borderline

$C_6H_5NH_2$, C_5H_5N, N_3^-, Br^-, NO_2^-, N_2, SO_3^{2-}

TABLE 1: The classification of acids and bases according to the HSAB principle of Pearson.[7,8]

The HSAB classification gives us no indication of the relative stabilities of the hard or soft donors for a given metal ion. For example, which of the hard bases oxygen or nitrogen form the more stable bond with the hard acid Fe^{3+}? It also does not take into account the effect of charge on the donor atom. Thus, Fe^{3+} forms stable complexes with negative oxygen donors but not neutral oxygen donors, while the mercapto group has little affinity for Ni(II) but the sulfide donor complexes well.

Despite giving no indication of the relative affinities of hard/soft acids for hard/soft bases, the HSAB classification is an important starting point for ligand donor atom selection and is often used in conjunction with more sophisticated criteria such as the relative strength and softness of acids and bases.

1.1.2 Estimations of strength and softness of acids and bases[11]

What is meant by acid or base strength, in the context of complexation (equation 1), is that a strong acid and strong base will form a stable adduct A:B, while a weaker acid and base will form a less stable adduct.

$$A + B = A{:}B \qquad \textbf{equation 1}$$

$$\log K = S_A S_B \qquad \textbf{equation 2}$$

The equilibrium constant for complexation can be expressed as a function of the strength factors, S_A and S_B, for the acid and base respectively (equation 2). Both the acid strength of cations and the base strength of anions show increases with increasing charge and decreasing radius. Obviously these factors are dependent on temperature and solvent. A series of standard values of S_A and S_B for 100 acids and 100 bases would permit prediction of the stabilities of 10000 complexes. A scale of base strengths does exist for the special case where the Lewis acid is a proton (pKa's), but this scale is not valid for all Lewis acids and, unfortunately, it is not

possible to write down a universal order of acid or base strength. Equation 2 has been extended to include other parameters which do not measure strength; these are σ_A and σ_B and are termed softness parameters (equation 3).

$$\text{Log } K = S_A S_B + \sigma_A \sigma_B \qquad \textbf{equation 3}$$

Reasonable estimates of hardness and softness for acids and bases can be made. For Lewis acids important properties are size, charge, electronic structure (number of d electrons) and the influence of attached groups. Estimates of base softness can be made by simple examination of the donor atoms; electronegative and non-polarizable atoms (*e.g.* fluorine) are hard, while polarizable and less electronegative atoms (*e.g.* iodine) are soft.

Recently Japanese researchers have applied these concepts to solvent extraction processes, thus facilitating the choice of a suitable extractant for the separation of two or more metal ions.[12, 13] These principles were applied to the separation of indium(III) from gallium(III). Equation 4 was derived from the definition of the separation factor, SF, which relates the amount of one metal in the organic phase to the other (aqueous phase concentrations are also taken into account).

$$SF = (S_{In} - S_{Ga})S_B + (\sigma_{In} - \sigma_{Ga})\sigma_B \qquad \textbf{equation 4}$$

where $S_{A\,(A = In.\,Ga)} = -2\Delta S_h / 2.3RT$ (the acid strength factors for the metals requiring separation);

$\sigma_{A\,(A = In.\,Ga)} = \Delta H_f / 2.3RT$ (the softness parameters for the metals requiring separation);

S_B and σ_B are the base strength and softness factors of a potential extractant;

ΔS_h denotes the hydration entropy;

and ΔH_f the heat of formation of the aqueous Ga(III) and In(III) species.

Values of S_A and σ_A for In(III) and Ga(III) can be calculated from reported data for ΔS_h and ΔH_f, and equation 4 may be reduced to equation 5.

$$SF = -8.7S_B + 19.5\,\sigma_B \qquad \textbf{equation 5}$$

This suggests that the softness factor of a chelating agent (σ_B) is more important for separation than its strength factor (S_B). In practice, for quantitative separation, the SF value should exceed 4, giving the following condition:

$$\sigma_B > 0.21 + 0.45\ S_B \qquad \textbf{equation 6}$$

S_B and σ_B values for common chelating agents were obtained by using extraction data summarised in the literature, and it was found that dithizone (3-mercapto-1,5-diphenylformazan) best fitted this condition for the separation of In(III) from Ga(III). Experimental results verified this prediction, suggesting that the application of HSAB principles incorporating S_B and σ_B factors is practically effective.

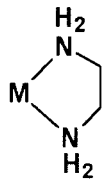
1.1.3 Common donor atoms [8]

Studies of the complexation trends of the common donor atoms has yielded valuable and, sometimes, unexpected information.

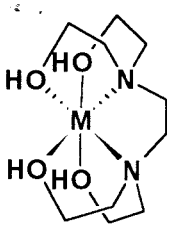
1.1.3.1 The neutral oxygen donor

One might expect that adding groups containing neutral oxygen to an existing ligand might increase the stability of the complexes in aqueous media. In some cases this is true but in others it is not, as evidenced by the data for the Pb^{2+} and Ni^{2+} complexes **1** and **2** detailed in Figure 1.

Figure 1: The effect of neutral oxygen donors on complex stability. [14]



1a,b



2a,b

Metal	Complex	Stability Constant (log K_1)
Pb^{+2}	1a	5.0
Pb^{+2}	2a	7.6
Ni^{+2}	1b	7.4
Ni^{+2}	2b	6.5

What has been found is that the addition of groups containing neutral oxygen donors to an existing ligand leads to an increase in selectivity for large metal ions over small metal ions.[14] This is an important principle for ligand design, permitting a prediction of size selectivity which, remarkably, does not appear to be sensitive to the nature of the metal ion. The rule holds for a large number of ligands, and includes the addition of oxygen donors to straight chain-ligands to form macrocycles and addition to macrocycles to form cryptands. The principle also extends to simple crown ethers, where it is observed that large metal ions form stable complexes while smaller ions do not, even where the ligand cavity is small. This phenomenon is attributed to steric crowding of the oxygen donors, which becomes larger as the metal ion becomes smaller, the increase in steric strain becomes more important than metal-oxygen bond-strength considerations. In some cases, the rule applies up to a certain metal ion size above which steric constraints become negligible and intrinsic metal-oxygen bond-strengths dominate.

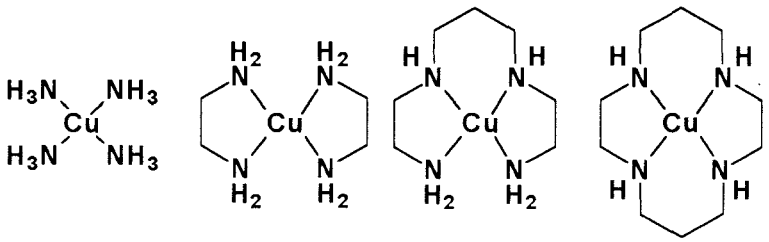
1.1.3.2 The negatively charged oxygen donor

The effect of the negatively charged oxygen donor (*e.g.* the carboxylate and phenolate oxygens) on complex stability is strongly dependent on the acidity of the metal ion concerned,[15] and there is a good linear relationship between the stability of the resulting complex and the affinity of the metal ion for OH^-. Thus, the design of ligands containing these groups for selective separation has to take into account the affinity of the metals for the OH^- ion.

1.1.3.3 The neutral nitrogen donor

Neutral saturated nitrogen donors form strong complexes with a wide variety of metal ions. $LogK_1(NH_3)$ values can be used as indicators of the affinity of metal ions for nitrogen donors. Thus, for any metal ion in water, if $logK_1(NH_3)$ is less than $logK_1(OH^-)$ by more than 4.8 log units, the amine complex will not exist to any appreciable extent. The effect of donor atom basicity on saturated nitrogen donor complexes can be seen in the series of Cu(II) complexes of polyamines detailed in Figure 2.

Figure 2: Enthalpies of complex formation and ligand field strengths for copper-amine complexes.[16]



	3	4	5	6
ΔHf / kcal.mol^{-1}	-22	-25.5	-27.7	-32.4
υ(d-d) /cm^{-1}	17 000	18 300	19 000	19 900

The increases in the enthalpy of complex formation (ΔH_f) and ligand field strength [ν(d-d)] across the series **3** to **6** can be attributed to increasing donor strength as zero order nitrogens are replaced by primary and then secondary nitrogens.[16] Steric effects also appear to play an important role, since alkylation of the secondary amines in cyclam **6** (Figure 2) to afford tertiary amines is accompanied by a drop in complex stability and ligand field strength.[17] Steric effects also account for the decrease in stability of nickel-amine complexes for the ligand series $MeNH_2 > EtNH_2 > i\text{-}PrNH_2$.

1.1.3.4 Heavier donor atoms

The heavier donor atoms S, Se, P and As, when neutral, show limited coordination to small metal ions but coordinate well to the large and poorly solvated Ag(I), Au(I), Hg(II) and Pd(II) cations.[18] The weakly acidic mercapto group binds strongly to many ions, especially Ag(I) and Hg(II).

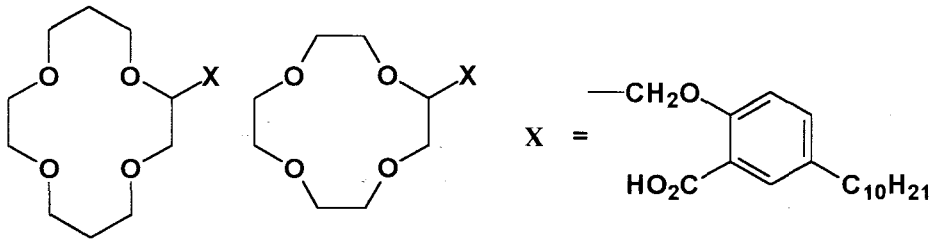
1.1.4 The size of the chelate ring

Ligands which can coordinate at two or more positions (thus producing chelate rings) form more stable complexes than similar ligands which can only coordinate at a single position. This is especially true if five- or six-membered chelate rings are formed. The greater stability of the chelated complex compared with an analogous non-chelated complex is termed the *"chelate effect"*, the effect appears to be mainly a result of entropy contributions.[19]

Increasing the size of the chelate ring from a five-membered ring to a six-membered chelate ring (and further increases in chelate ring size) usually leads to a drop in complex stability. This phenomenon was originally thought to be due to an entropy effect associated with the longer

connecting link between the donor atoms of a particular ligand, but stability constant data[20] have since shown it to be due to less favourable enthalpy contributions as a result of steric strain. Crystal structures of Ni(II)-polyamine complexes with five- or six-membered chelate rings have shown that the bite size, (*i.e.* the non-bonded, N-N distance across the chelate ring), is longer in six-membered rings than in five-membered rings. One would expect this to provide a means of achieving selectivity for large metal ions over small metal ions. Surprisingly the opposite has been found to be true, *i.e.* an increase in chelate ring size leads to greater complex destabilization of complexes of larger metal ions compared to those for smaller metal ions.[20, 21] To a large degree this rule also holds for macrocyclic ligands, for example, the crown ether **7** (Figure 3), which has a larger ring than crown ether **8,** shows greater selectivity for the small Li^+ ion over the larger Na^+ ion.

Figure 3: Crown ether 7 is more selective than 8 for small metal ions. [21]

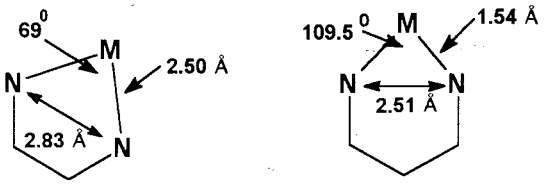


7 **8**

Molecular mechanics (MM) calculations on chelate rings of different sizes have led to an understanding of this effect.[22] For the five-membered ethylenediamine chelate ring **9**, calculations have shown that the lowest strain energy will occur for a metal ion giving a metal-N (M-N) bond-length of 2.50 Å and a metal chelate bond-angle (N-M-N) of 69^0 (Figure 4). However, for the six-membered chelate ring of diaminopropane **10**, a minimum strain energy will occur for a metal ion giving an M-N bond-length of 1.54 Å and a N-M-N bond-angle of

109.5^0, the six-membered chelate ring approximates to a low-energy cyclohexane chair conformation.[23] As metal ions increase in size their metal-ligand (M-L) bond-lengths and their coordination numbers also increase resulting in smaller L-M-L bond angles. Consequently, the smaller bond angles and longer bond lengths favoured by five membered chelate rings are more suited to larger metal ions while six-membered chelate rings favour smaller metal atoms with geometries close to the carbon atom.

Figure 4: Energy minimized data for diaminoethane and diaminopropane chelate rings. [22]

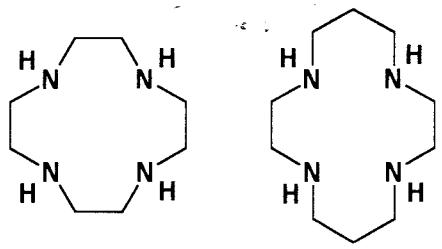


9 **10**

1.1.5 The selectivity of macrocyclic ligands

As shown earlier, metal complexes with macrocyclic ligands cannot be interpreted simply in terms of size-match selectivity. For example, while macrocycle **11** (Figure 5) complexes with large metal ions like Pb^{2+} forming complexes which are five log units more stable than the Pb^{2+} complex with macrocycle **12**, the macrocycle **12** forms a complex with the small Ni^{2+} ion which is 5 log units more stable than the corresponding complex of macrocycle **11**.[8] In order to understand this behaviour it is necessary to consider the conformers of these macrocyclic complexes.

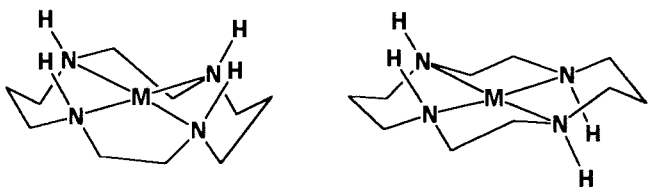
Figure 5: The tetra-aza macrocycles 12-aneN$_4$ and 14-aneN$_4$.



11 **12**

Using MM calculations, best-fit M-N bond lengths have been obtained for the different tetraazamacrocycle conformers, and the strain energies of the complexes at these best-fit sizes have been calculated.[24, 25] Two of the conformers of 14-aneN$_4$ are shown in Figure 6. The calculations revealed that for 12-aneN$_4$ the *trans*-III conformer is much more strained than the *trans*-I conformer, which has a preference for large metal ions. As one proceeds from 12-aneN$_4$ through 13-aneN$_4$ to 14-aneN$_4$ the *trans*-III conformer increases in stability relative to the *trans*-I conformer. The *trans*-III conformers, being more rigid than the *trans*-I conformers, do not complex very well to large metal ions. Thus, the selectivity of macrocycles for metal ions appears to depend on the stability and different metal ion size-preferences of the relevant ligand conformers. However, it should be noted that a metal ion which is too large to fit into the plane of the donor atoms can still be accommodated by coordination out of the plane.

Figure 6: The *trans*-I (13) and the *trans*-III (14) conformers of a 14-aneN$_4$ macrocyclic complex. [25]



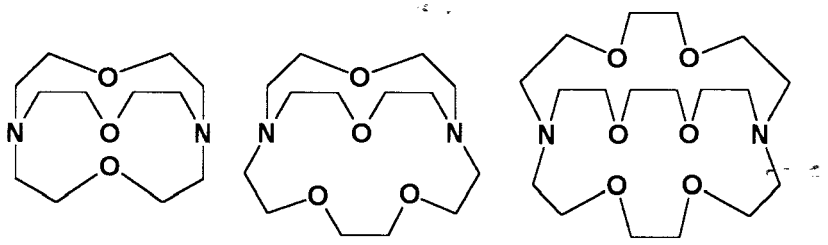
13 **14**

Furthermore, as a result of the ability of macrocycles to adopt various conformers, thus presenting the metal ion with a range of best-fit M-L bond-lengths, their size-selectivities are not very different from those of their open chain analogues.[8] Selectivity can often be enhanced by adding pendant donors or by synthesising more rigid ligands such as cryptands. Adding hydroxyethyl pendant groups to macrocycles appears to have the same effect as adding neutral oxygen donors to ligands, as described earlier, *i.e.* a decrease in complex stability for small metal ions. *N*-Acetate substituted tetraazamacrocycles show selectivity for large metal ions that can achieve a coordination number of eight, particularly Ca^{2+} and other metal ions such as the lanthanides, that have ionic M-L bonds.[26]

1.1.6 Highly preorganised ligands

Highly preorganised ligands include the cryptands, exemplified by compounds **15** to **17**. The effect of preorganisation in cryptand-111 **15** can be seen by comparing its first protonation constant (pK_{a1} = 17.8) with those of triethanolamine [(protonation constant (pK_a) = 7.8)] and other, larger cryptands.[27] MM Calculations show that cryptand-111 has only one stable conformer in which the lone pair on both amines is positioned inside the cavity.[28] The high protonation constant is due to hydrogen bonding between the proton and the second amino nitrogen. The significant drop in pK_{a1} for cryptand-211 **16** (pK_{a1} = 10.6) and cryptand-222 **17** (pK_{a1} = 9.60) reflects the importance of the dimensions of the cavity.

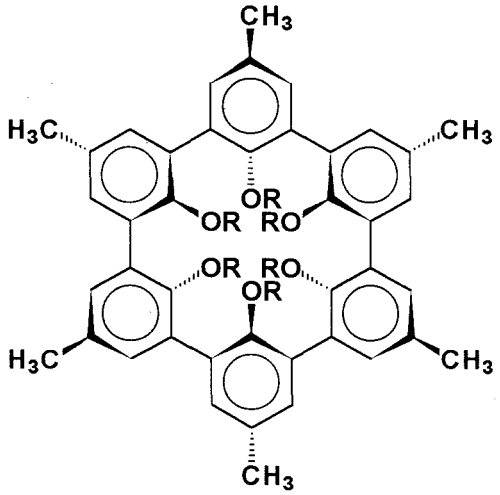
Figure 7: The cryptands mentioned in the text.



15 **16** **17**

The spherands developed by Cram are amongst the most highly preorganised ligands known.[29] Size-selectivity in these systems can be quite dramatic; spherand **18**, for example, can extract traces of Li^+ and Na^+ from reagent grade KOH. Crystallography shows that the cavity of this spherand is void of solvent molecules, resulting in substantial energy savings since desolvation of the donor atoms prior to complexation is not required.

Figure 8: A typical spherand developed by Cram. [29]

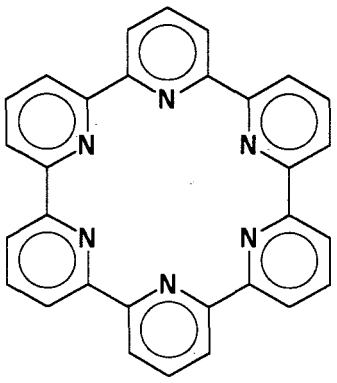


R = Me

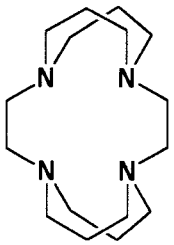
18

Creating rigid preorganised ligands with larger cavities is problematic as they tend to collapse to form lower energy conformers. More rigid groups, connecting the donor atoms, have been used to obviate this problem, an example being sexipyridine **19**.[30] A different approach to enhance rigidity involves reinforcement with bridges between donor atoms, as in the macrocycle **20**.[31] A problem encountered with highly preorganised ligands is that the rate of complexation decreases as the level of preorganisation increases, and kinetic studies have shown that ligand flexibility is necessary to allow the metal ion to enter or leave the cavity.[29] So the level of preorganisation that is useful is determined by the intended application of the ligand; ligands that remove metals from the environment or the human body or those used as extractants in hydrometallurgy require fairly rapid extraction kinetics, whereas inertness is advantageous in ligands that are merely required to hold the metal ion, *e.g.* NMR imaging agents.

Figure 9: Sexipyridine [30] and a reinforced macrocyclic ligand.[31]



19



20

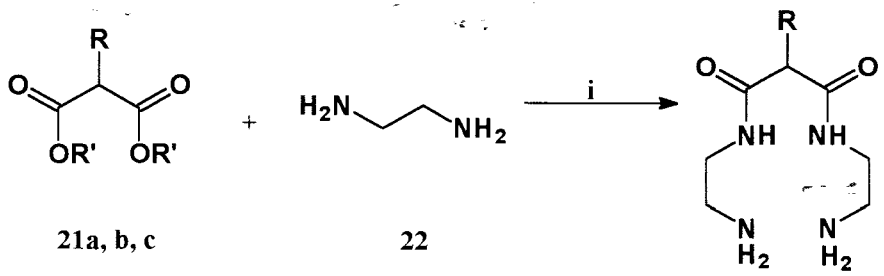
1.2 LIGANDS CONTAINING THE PROPANEDIAMIDE BACKBONE

The propanediamide backbone is a versatile functionality in that it can be easily derivatised allowing attachment of substituents which could have a variety of roles. These include making the ligand and its metal complex more organic soluble,[32, 33] providing a means of attachment to a substrate (protein or polymer) or providing an axial coordinating group. The deprotonated amides of suitable tetradentate propanediamide derivatives have been used to stabilise highly oxidised metal ions in rigid square planar systems.[32] These diamide ligands have also been used to model peptide-like ligands and have been used to help elucidate the bonding geometry of metal ions in biological systems.[34a,b] Suitably derivatised propanediamides have been used in solvent extraction systems, for example, 2,2'- dibutyl- *N,N'*-bis(8-quinolyl)malonamide has been found to be a highly selective extractant for copper,[33] while *N,N,N',N'*-tetraalkyl-propanediamides are the extractants of choice for removing actinides and lanthanides from nuclear waste waters.[35] Propanediamide ligands have also been studied as metal ion carriers for the transport of metal ions through membranes.[36]

1.2.1 Synthesis of propanediamide ligands

The well known propanediamide ligand, *N,N'*-bis(2-aminoethyl)propanediamide (BAEP) **23a**, has been synthesised by reacting dimethyl malonate **21a** with a large excess of ethylenediamine **22** at room temperature (Scheme 1).[37a,b] Removal of the excess ethylenediamine and methanol under vacuum gave a pink solid which was washed with cold ethanol but was not purified further. This mild aminolysis of malonate esters with diamines seems, where possible, to be the synthesis of choice and has been used in recent syntheses of propanediamides. For example, diethyl 2-cetylmalonate **21b**[38a] and diethyl 2-benzylmalonate **21c**[38b] have been reacted with ethylenediamine by this method to yield the diamides **23b** and **23c** in good yield.

Scheme 1: The synthesis of propanediamides by mild aminolysis of malonate esters.[37, 38]



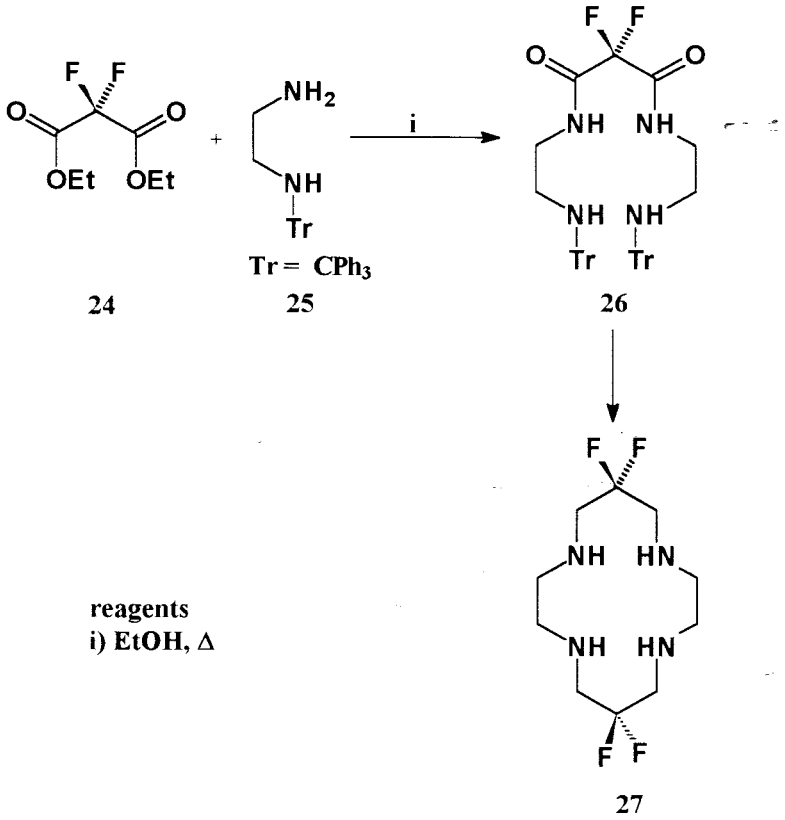
21a, b, c 22 23a, b, c

reagents
i) r.t., 2 days

	R	R'
a	H	Me
b	$C_{16}H_{33}$	Et
c	$PhCH_2$	Et

When the malonate backbone is substituted at the 2-position with bulky and/or deactivating substituents, it is necessary to use the more reactive acid chloride route for the synthesis of propanediamides. For example, 2,2-dibutyl-*N,N'*-bis(8-quinolyl)malonamide was synthesised by reacting dibutylmalonyl dichloride with 8-aminoquinoline.[33] The activating effect of substituents in the 2-position can be seen in the synthesis of the tetrafluorinated cyclam **27** (Scheme 2).[39] Condensation of diethyl malonate with 1,9-diamino-3,7-diazanonane in refluxing ethanol affords the parent dioxocyclam, but introduction of fluorines at the 2-position of diethyl malonate increases the rate of cyclisation, the more fluorines the faster the rate. This influence of fluorination on the malonate ester can also be seen in the infrared carbonyl stretching frequencies; [*V* (CO) 1730cm^{-1} (diethyl malonate), 1745 and 1770 cm^{-1} (monofluorinated) and 1780cm^{-1} (difluorinated)]. For the synthesis of tetrafluorinated cyclams, ethylenediamine was initially reacted with diethyl difluoromalonate **24**, but the reaction did not proceed as planned and monoprotected ethylenediamine had to be used.[39] Thus, *N*-tritylethylenediamine **25** was refluxed with diethyl difluoromalonate **24** in ethanol to give the diamide **26** (Scheme 2), which was reacted further to afford the tetrafluorocyclam **27**.[39]

Scheme 2: The use of mono-protected ethylenediamine for the synthesis of propanediamides.[39]



24 25 26 27

The synthesis of *N,N,N',N'*-tetraalkyl propanediamide derivatives typically requires the reaction of malonyl dichloride with secondary amines[35] but, in an alternative approach, diethyl malonate has been converted to *N,N,N',N'*-tetramethylpropanediamide in 81% yield by using three equivalents of lithium dimethylamide.[40] This convenient one pot reaction appears to be limited by steric hindrance, since no reaction occurs using aminodiisopropyllithium.

1.2.2 Complexation of propanediamide ligands

N,N'-Bis(2-aminoethyl)propanediamide (H_2L) has been complexed with copper, nickel and cobalt,[37] metals which are known to deprotonate the amide group making the ligand suitable for tetradentate square-planar coordination. In the synthesis of these complexes the base

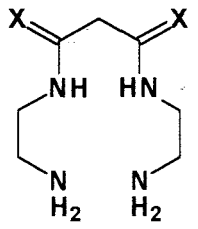
necessary to assist in the removal of the amide protons is provided by an excess of the ligand. Copper(II) and nickel(II) form neutral complexes (ML) with the ligand adopting a square planar arrangement around the metal, while cobalt(III) forms the ionic complex $[CoL(NH_3)_2]Cl.2H_2O$. From a consideration of models and the NMR spectra of this complex in D_2O it appears that the ligand donors occupy the equatorial positions with the ammonia ligands axial. Palladium(II) also forms square planar PdL complexes in a similar manner to copper and nickel.[37a] Evidence for the loss of the amide hydrogens was obtained by titrating the complexes with acid. In the case of the copper, nickel and palladium complexes four equivalents of acid were consumed in the titration. The infrared spectra of the complexes also provide evidence for deprotonation of the amide nitrogens, since there are no bands above $3000cm^{-1}$ (*i.e.* attributable to an N-H stretching mode). Furthermore, the carbonyl stretching frequency (amide I band) is decreased by 50 cm^{-1} and the amide II band, which involves the vibration of the N-H bond, is absent.

In order to investigate the binding between metals and peptides a crystal structure of [*N,N'*-bis(2-aminoethyl)malondiamidato]nickel(II) trihydrate, which had been synthesised under basic conditions, was undertaken.[34a] This confirmed that the nickel was coordinated by two amine nitrogens and two deprotonated amide nitrogens. The crystal consists of layers of molecules, the molecules in the layers being held together by hydrogen bonds with the water of hydration and van der Waals forces between the molecules; no hydrogen bonds exist between the layers. The nickel-to-amide nitrogen distances (1.869Å) are significantly shorter than the nickel-to-amine nitrogen distances (1.921Å).

Kimura determined the protonation constants and copper(II) stability constants with bis(2-aminoethyl)propanediamide **28a** (H_2L) at 25^0C and 0.2 M ionic strength ($NaClO_4$).[41] These constants were determined by potentiometric titration, and the amine protonation constants were found to be 9.08 ±0.05 and 8.82 ±0.05. Potentiometric titrations of the dioxo-ligands **28a**

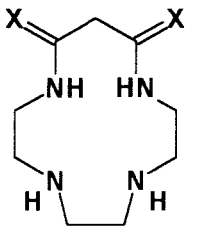
and **29a**, in the presence of divalent metal ions, showed that of the metal ions studied the most successful at deprotonating the amide nitrogens was copper(II). With zinc(II), cadmium(II) and lead(II) the dioxo ligands underwent no deprotonation at pH < 7 and at pH > 7 precipitation of hydrolysed metal ions occurred. The titration data indicates formation of doubly deprotonated complexes, represented as [CuL]. Equations were derived for the simultaneous or separate formation of $[CuH_2L]^{2+}$ and $[CuHL]^{+}$. However, the derived equations failed to fit the experimental data and it was concluded that neither of these complexes are formed in the buffer region. The copper(II)-ligand **28a** stability constant was calculated to be -5.1, a result comparable to the value of -6.5 found for the tripeptide, glycylglycylglycine, but lower than the value obtained for the analogous macrocycle 1,4,7,10-tetraazacyclotridecane-11,13-dione **29a**. As can be seen in Figure 10, both these dioxo ligands have much lower copper(II) stability constants than their oxo-free counterparts.

Figure 10: Copper(II) stability constants of diamide ligands and their oxo-free analogues.[41]



28a, b

	X	Log K Cu
28a	O	-5.1
28b	H_2	23.9



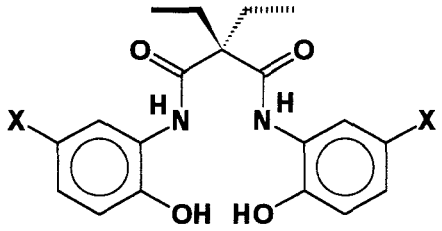
29a, b

	X	Log K Cu
29a	O	-2.2
29b	H_2	29.1

Ligand displacement studies of the *N,N'*-bis(2-aminoethyl)propanediamide (BAEP)-copper complex [CuL] with linear and cyclic tetraamine ligands show that, as the pH decreases so the rate of ligand exchange increases.[42] Ligand exchange reactions of the (BAEP)-nickel complex [NiL] and the *N,N'*-bis(2-aminoethyl)oxalamide (ODEN)-nickel complex with triethylenetetramine show that the NiH_{-2}BAEP complex reacts 550 times more rapidly than the NiH_{-2}ODEN complex.[43] Complexes of *N,N'*-bis(2-aminoethyl)propanediamide (BAEP) are similar to those of ODEN, both having five-membered side chelate rings with terminal amine donors, but differing in the size of their central chelate ring. The six-membered chelate ring of BAEP causes marked "orientation stress" resulting in an increase in the nickel-amide bond length; this bond lengthening is balanced by an increase in the tetrahedral bond angle of the propanediamide methylene group. The lengthening of the nickel-amide nitrogen bond permits more planar orientation of the coordinated amide groups. Jackson measured the stability constants of copper(II) with BAEP and ODEN and found that the 5,5,5 chelate complex formed by ODEN is more stable than the 5,6,5 chelate complex of BAEP.[44] Normally, copper(II) 5,6,5 membered chelate systems are more stable than 5,5,5 membered chelate systems and Jackson was the first to provide evidence for an exception to this trend.

The diamide di-*ortho*-phenolate ligand **30**, which contains the propanediamide backbone and phenolate pendant arms, was synthesised with the aim of developing ligands for selective complexation and stabilization of metal oxo cations *e.g.* VO_2^{2+} (Figure 11).[45] The propanediamide backbone was chosen as it has two amide nitrogens and can easily be derivatised in the 2-position. The substituent in the 2-position can be such that it can interact with an oxo oxygen through an intramolecular hydrogen bond, while also increasing the resistance of the ligand to oxidation. The X group on the aryl rings can be varied to tune the physical properties of the metal complexes.

Figure 11: An *ortho*-phenolate propanediamide ligand developed for the stabilization of oxo cations. [45]



30

In contrast to other oxovanadium(IV) (VO^{2+}) complexes, which tend to be oxygen or water sensitive, the VO_2^{2+} complexes of these ligands were found to be stable indefinitely in the solid state and for weeks in solution, with no precautions being taken to preclude oxygen or water. The stability of these complexes is undoubtedly a consequence of the strong donor stability of the *N*-amidate-*ortho*-phenolate binding pocket and the resistance of these ligands to oxidation.

1.2.3 Applications of propanediamide ligands

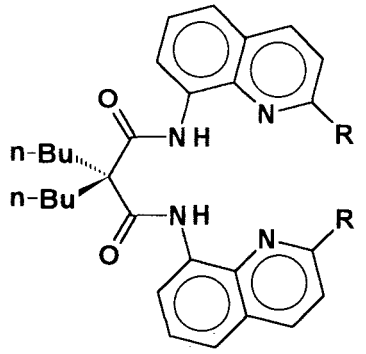
1.2.3.1 Solvent extraction

2,2-Dibutyl-*N,N'*-bis(8-quinolyl)malonamide (BQM) **31a** has been used for the highly selective solvent extraction of copper(II) from nickel(II), cobalt(II) and zinc(II) (Figure 12).[33] With chloroform as the organic phase and at a pH of 6.2, the ligand extracted more than 96% of the copper but no nickel, cobalt or zinc from the aqueous phase. Even with solutions 10^{-2} mM in copper ion and 1 mM each in nickel, cobalt and zinc, only copper was extracted.

UV absorbance measurements and analysis of the pH dependant extraction data suggest the formation of a 1:1 ligand-copper complex with the release of two amide protons. Substituting methyl groups at the 2 position of the quinoline rings (as in **31b**) had a remarkable effect, with

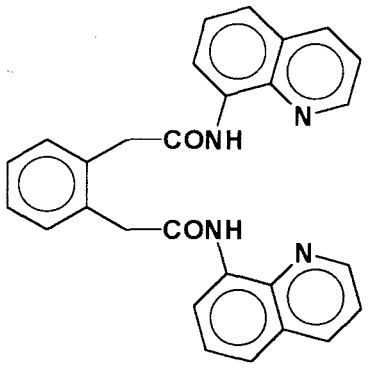
only 6% of the copper being selectively extracted. Models suggest that these methyl groups could interfere with the square-planar coordination geometry favoured by the copper(II) ion. Diamide **32** and monoamide **33** failed to extract any metal ions at all, indicating that appropriate arrangement of two amide groups is one of the most important factors for copper(II)-selective extraction. Infrared spectroscopy has been used to determine the bonding mode in BQM complexes of various divalent transition metal ions and has afforded evidence of deprotonated amides in the nickel, palladium, zinc, cadmium and copper complexes.[32]

Figure 12: Amide containing ligands which have been studied as extractants in the solvent extraction of copper.[33]

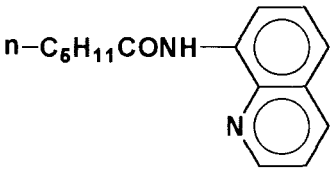


31a, b

	R
a	H
b	Me



32



33

The effect of substituents at the 2-position of the malonate backbone of BQM on the solvent extraction properties of the ligand have been examined.[46] Derivatives of BQM were synthesised by disubstitution at the 2-position with the following substituents; n-butyl, cyclohexylmethyl, benzyl, *para*-methylbenzyl, 2-phenylmethyl, 3-phenylpropyl and a mixed cyclohexylmethyl-

benzyl derivative. The proton NMR spectral data for corresponding nuclei in the derivatised ligands are very similar, chemical shift differences for amide and quinolyl protons varying within 0.03 ppm. In the solvent extraction of a mixture of metals these derivatives were found to be highly selective for copper and it was found that those derivatives with benzyl or *p*-methylbenzyl groups extracted copper(II) at *ca.* one pH unit lower than the other malonamides. The hydrophobicity of both groups of ligands is similar and steric reasons for the observed pH effect were investigated. Molecular modelling indicated that in the benzyl and *para*-methylbenzyl-substituted ligands, which have a short CH_2 "spacer" between C-2 and the aromatic ring, rotation of the 2-substituents is restricted, a situation which does not arise in the phenylethyl or phenylpropyl derivatives. However, the bis(cyclohexylmethyl) derivative which also has a CH_2 spacer shows the lowest extractability and slowest attainment of equilibrium.

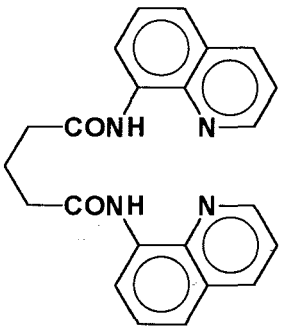
To investigate this effect further the change in proton NMR chemical shift of the quinolyl hydrogens upon complexation with nickel(II) was studied.[46] The change in chemical shift ($\Delta\delta$) was found to be substituent dependent, the $\Delta\delta$ values for the malonamide complexes having benzyl or *para*-methylbenzyl substituents being larger and indicating an interaction of the benzyl group with the remainder of the complex. Close examination of the individual shifts of the quinolyl protons suggests an interaction between the π electrons of the benzyl substituent and the metal (π-back donation). Reduced mobility of the benzyl groups around the α carbon could well stabilize this kind of interaction.

1.2.3.2 Metal ion carriers

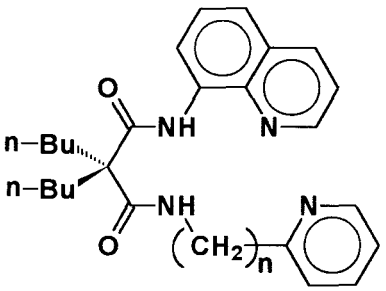
Selective transport of metal ions through liquid membranes, *i.e.* carrier-mediated continuous solvent extraction is an attractive method for separation and recovery. Because BQM **31a** shows selectivity for copper(II) ions near neutral pH it was investigated as a ligand for the

transport of copper(II) through liquid membranes;[36] however, its ability to transport copper(II) through liquid membranes was found to be low. *N,N'*-Di(8-quinolyl)glutaramide **34** (Figure 13), on the other hand, which hardly extracts any metal ions near neutral pH, transports copper(II) with high selectivity through liquid membranes (Figure 13). It was thus decided to synthesise carriers which had a malonamide structure (like BQM) for the rapid and selective extraction of ions from the aqueous phase into the organic phase, but which also had comparatively low complex stability (like glutaramide) to enable the release of ions from a liquid membrane phase into an aqueous phase. To this end the malonamide derivatives **35** and **36** were synthesised. To investigate the effect of the substituent at the 2-position on transport ability the 2-benzyl derivative **37** was also prepared.

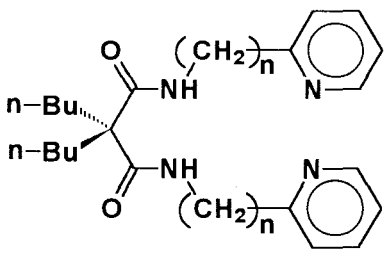
Figure 13: Propanediamide ligands which have been studied as metal ion carriers.[36]



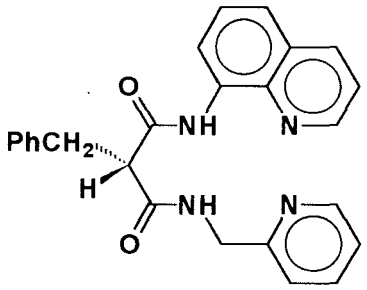
34



35 a, b, c



36 a, b, c



37

	n
a	0
b	1
c	2

Carrier **35b** exhibited the greatest capacity for copper(II) transport among the carriers shown in Figure 13, being distinctly superior to glutaramide. It was shown that carrier **35b** can efficiently transport copper(II) against its concentration gradient under the mild conditions where the source phase is at pH 6.2 and the receiving phase is at pH 1.4. The single ion transport of nickel(II), cobalt(II) and zinc(II) by carrier **35b** was attempted but, even after two days, none of these ions was transported. The transport ability of the 2-benzyl derivative **37** was comparable to that of the carrier **35b**.

1.3 LIGANDS CONTAINING BOTH THIA AND AMIDE FUNCTIONS

Although there is an abundance of thia-amine ligands, relatively few thia-amide analogs have been reported, the most common being the mercaptoacetamides. A couple of sulfur-containing amide macrocycles were reported in 1976[47] and, more recently, Kimura has synthesised novel sulfur-containing amide macrocycles with high selectivity for the noble metals.[48, 49, 50] The need for chelating agents which form stable complexes with the radionuclides, technetium(99m) and rhenium(186), has also led to the synthesis of novel sulfur-amide ligands.[51] Naturally occurring ligands, which fall into this class, include sulfur-containing peptides, enzymes and proteins.[52]

1.3.1 Mercaptoacetanilides

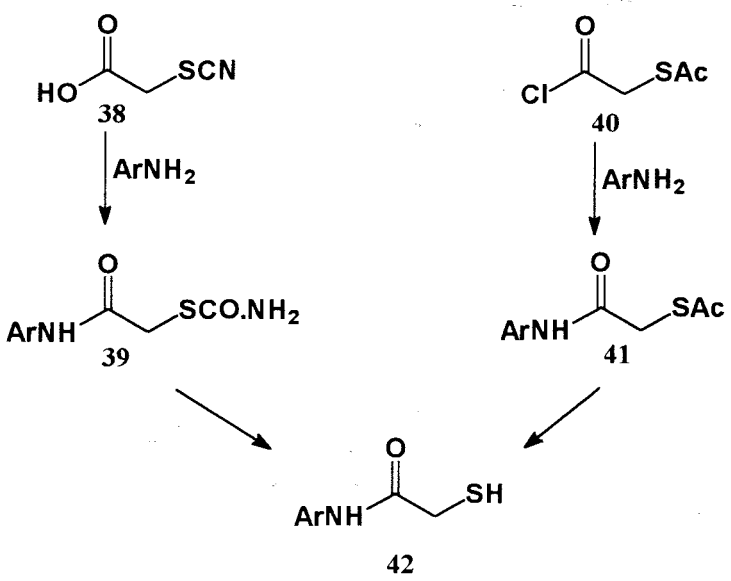
Mercaptoacetanilides complex with a large number of metal ions[53] and have found applications in the qualitative analysis of certain metal ions.[54] Stability constant studies have shown that mercaptoacetanilides form their most stable complexes with the soft metals palladium and lead.[55] Recently, antiviral properties exhibited by sulfur-nitrogen-oxygen transition metal complexes has renewed interest in mercaptoacetanilides and has led to the synthesis of mercaptoacetanilide complexes with hard metals.[56]

1.3.1.1 Synthesis of mercaptoacetanilides

An early synthesis[57] of substituted mercaptoacetanilides **42** involves interaction of an aromatic amine with thiocyanoacetic acid **38** (formed from chloroacetic acid and an alkali thiocyanate) to yield the carbamyl thioacetanilide **39**, which is hydrolysed to give the desired mercaptoacetanilide (Scheme 3). Weiss[58] used this carbamyl route with success to synthesise a number of ring substituted mercaptoacetanilides, obtaining the carbamyl compound **39** in 80-

90% yield by reacting the aromatic amine and sodium thiocyanoacetate at room temperature; subsequent hydrolysis of the carbamyl compound **39** yielded the mercaptoacetanilides in equally high yields. Certain amines, including *o*-nitroaniline, diphenylamine and sulfanilic acid, failed to react under these conditions. The *meta*-nitro and *para*-nitro derivatives were less reactive resulting in lower yields of the carbamyl derivative **39**. In many instances, purification of the mercaptoacetanilides was only achieved with difficulty owing to the ease of oxidation to the disulfide.

Scheme 3: Early syntheses of mercaptoacetanilides. [57, 59]



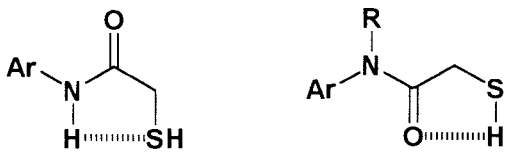
In an alternative synthesis, the acetylthioacetanilide **41,** which is obtained from the acid chloride **40** and an aromatic amine, is hydrolysed to yield the free mercaptoacetanilide. The disadvantages of this route are that the acid chloride is difficult to obtain and again the synthesis involves several steps.[59]

In 1947, Van Allan found that mercaptoacetanilides could be obtained in excellent yield and high purity without protecting the thiol group.[60] The process consists of refluxing an equimolar mixture of aniline and mercaptoacetic acid in benzene and removing the water that is formed; the benzene atmosphere minimises the formation of disulfide resulting in a crude product which has a higher degree of purity than those obtained by other processes. Misra and Sircar [54] adapted this method and synthesised a number of substituted mercaptoacetanilides by heating an equimolar mixture of aromatic amine and mercaptoacetic acid in a slow current of carbon dioxide. The synthesis of both 2- mercapto-3'-nitroacetanilide and 2-mercapto-4'-nitroacetanilide by this method have been reported, but no yields were given.

1.3.1.2 Spectroscopic studies of mercaptoacetanilides

West and Duff (1956) [61] suggested that mercaptoacetanilides exhibit tautomerism and may exist in keto and enol forms. However, more recent NMR and infrared studies (1972) [62] have provided no evidence of a hydroxy group, and thus support the keto structure of mercaptoacetanilides.

Figure 14: Intramolecular hydrogen-bonding in mercaptoacetanilides, proposed on the basis of infrared spectroscopy. [62]



43 **44**

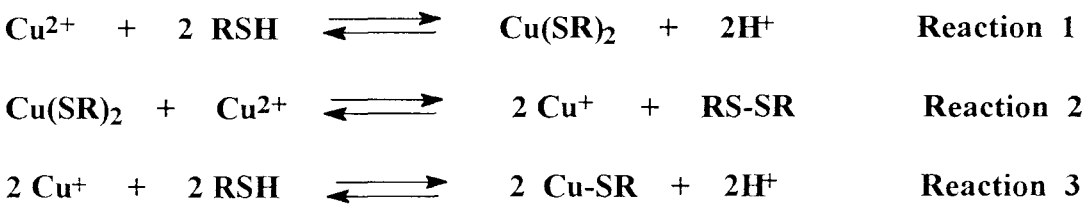
Substituents in the *para*-position of the mercaptoacetanilide benzene ring have been found to influence the amide carbonyl infrared stretching frequency. Strongly electron-withdrawing groups, such as chloro or carbonyl functions increase the carbonyl stretching frequency,

whereas electron-donating *para*-substituents (methyl and methoxy) lower the carbonyl absorption frequency. [62] Intramolecular hydrogen bonding causes shifts in the position of the NH and SH stretching frequencies and, consequently, the hydrogen bonded structures **43** and **44** have been proposed.[62] The hydrogen-bonded structure **43** dominates in secondary mercaptoacetanilides while structure **44** dominates in *N*-substituted derivatives, *i.e.* tertiary mercaptoacetanilides.

1.3.1.3 Qualitative complexation studies

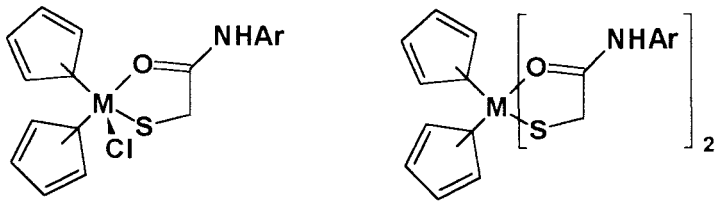
Mercaptoacetanilides complex readily with soft metals and were often precipitated with gold or lead as a means of characterising the mercaptoacetanilide.[63] Mercaptoacetanilides also complex with common metal ions of intermediate hard-soft character such as divalent copper, nickel and cobalt; [64] for example, cobalt(II) forms a 1:3 complex with mercaptoacetanilide with coordination taking place through the nitrogen and sulfur atoms.

Copper(II) ions oxidise mercaptoacetanilides, initially forming a blue black copper(II) intermediate (reaction 1); this intermediate then reacts with a second copper(II) ion to produce copper(I) ions and the disulfide of mercaptoacetanilide (reaction 2).[65] Finally a light yellow diamagnetic copper(I)-mercaptoacetanilide complex is formed (reaction 3).



The reported carcinostatic and antiviral activity of transition metal complexes with nitrogen-oxygen-sulfur chelating agents[56] resulted in mercaptoacetanilide complexes with harder metals being synthesised. Stannous chloride ($SnCl_2$),[66] dialkyltin dichloride,[67] dichlorobis(methylcyclopentadienyl)titanium(IV),[68] dichlorobis(cyclopentadienyl) zirconium(IV),[69] and dichlorobis(cyclopentadienyl)hafnium(IV)[70] have been reacted with mercaptoacetanilide. For the latter three metals, synthesis of the complexes took place under anhydrous conditions using tetrahydrofuran as a solvent and triethylamine as a base. Complexes with a ligand to metal ratio of 1:1 and 1:2 were synthesised and characterised by infrared and NMR spectroscopy. In the complexes the infrared NH and amide bands (excluding the carbonyl stretching band) appear in almost the same position as in the free ligand, indicating that the amide nitrogen is not coordinating to the metal. The amide carbonyl stretch is lowered from 1645-1640cm^{-1} (free ligand) to 1620cm^{-1} (complexed ligand), the decrease in carbonyl bond energy indicating coordination of the carbonyl oxygen to the metal. The disappearance of the SH band in the infrared spectrum of the complex indicates deprotonation of the thiol, suggesting formation of a metal-sulfur bond. The proton NMR data support this mode of coordination and the authors have tentatively assigned structures **45** and **46** (Figure 15) to the complexes.

Figure 15: Sulfur-oxygen chelates of mercaptoacetanilide with the hard metals titanium(IV),[68] zirconium(IV)[69] and hafnium(IV).[70]

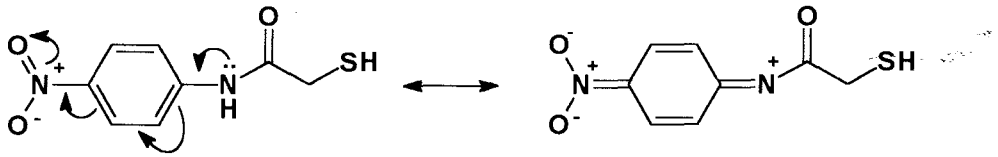


45 **46**

M = Ti, Zr, Hf

West and Duff[61] studied the effect of *para-* and *meta-* nitro substituents on the formation of mercaptoacetanilide complexes. Both nitro derivatives were less reactive toward metal ions than mercaptoacetanilide, with the *para*-nitro derivative being less reactive than the *meta*-nitro analogue. The decreased complexation ability was attributed to inductive effects for the *meta*-nitro derivative and resonance effects for the *para*-nitro derivative (Figure 16). These observations support the proposal that complexation takes place through the amide nitrogen and not the carbonyl oxygen, which is less affected by the electron-withdrawing aromatic substituents.

Figure 16: Canonical forms for *para*-nitroacetanilide showing the reduction in nucleophilicity of the amide nitrogen. [61]



47 48

Mercaptoacetanilides have also been used as diagnostic reagents for the determination of a wide variety of metals including cobalt,[63, 71, 72] copper,[73] cadmium,[74] platinum,[75] palladium,[76] gold and silver,[77] and molybdenum.[78]

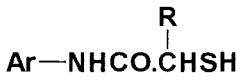
1.3.1.4 Quantitative complexation studies

1.3.1.4.1 Acid dissociation constants

Martin appears to have been the first researcher to carry out quantitative studies on mercaptoacetanilides.[79] Acid dissociation constants for the mercapto hydrogen (pK_{SH}) and metal formation constants (stability constants) were determined in dioxane-water mixtures, and

a linear relationship was found to exist between pK_{SH} and the mole fraction of dioxane (x) for several substituted mercaptoacetanilides (Table 2).

Table 2: Acid dissociation constants (pK_{SH}) of substituted mercaptoacetanilides expressed as a function of the mole fraction of dioxane. [79]



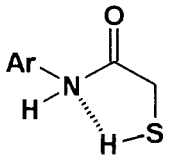
Compound	Ar	R	a	b	pK_{SH} (X = 0.38)
49	C_6H_5	H	8.08	10.53	12.08
50	4- $CH_3C_6H_4$	H	8.06	10.65	12.11
51	2,5-$(CH_3O)_2C_6H_3$	H	7.93	10.93	12.08
52	2,6-$(CH_3)_2C_6H_3$	H	8.35	10.38	12.29
53	2,6-$(C_2H_5)_2C_6H_3$	H	8.08	11.12	12.31
54	C_6H_5	C_2H_5	8.44	12.22	13.08

x is mole fraction of dioxane
x range: 0.137 - 0.380

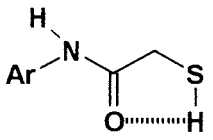
$$pK_{SH} = a + bx$$

The ethyl substituent adjacent to the mercapto group in compound **54** produces a marked increase in the pK_{SH} value, as a result of its electron-releasing inductive effect. Substituents at positions 2, 4 and 5 (as in compounds **50** and **51**) have little effect on the pK_{SH} value, whereas alkyl groups in the 2 and 6 positions effect a marked increase in pK_{SH}. To explain these phenomena Martin[78] suggested that the intramolecularly hydrogen bonded structure **55** was insignificant as the substituents in compounds **50** and **51** would surely increase the electron density at the nitrogen atom (Figure 17). *ortho*-Substituents would, however, favour the hydrogen bonding shown in structure **56** as steric effects would force the carbonyl oxygen closer to the mercapto group.

Figure 17: Intramolecularly hydrogen-bonded structures of mercaptoacetanilide as proposed by Martin.[79]



55

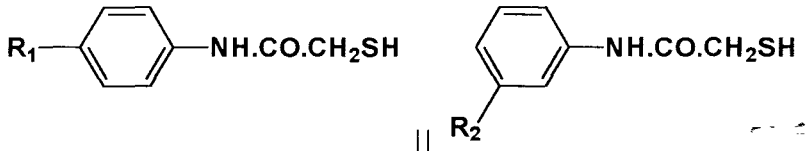


56

Other values determined for the pK_{SH} of mercaptoacetanilides [9.29 in 50% (v/v) dioxane at 30 °C[80] and 9.25 in 75% (v/v) ethanol at 25 °C[81]] do not compare well with the value of 12.08 obtained by Martin for a 75% (v/v) dioxane mixture.[79] The discrepancy may result from whether or not the method of Van Uitert [82] was used to correct the pH readings to take into account the presence of dioxane.

In 1972 Bhandari and Sogani reported both the mercapto (pK_{SH}) and amide (pK_{NH}) dissociation constants for mercaptoacetanilide at 30 °C in 70% (v/v) dioxane at 0.1 M ionic strength (KCl).[55] The pK_{NH} was estimated by noting the pH of a solution obtained by adding 1.5 equivalents of standard alkali to one equivalent of the ligand solution; an average of three measurements were taken and an "alkali" glass electrode was used. The dissociation constants for mercaptoacetanilide were reported as 9.95 (pK_{SH}) and 12.63 (pK_{NH}). Later this study was extended to include a range of *para*- and *meta*-substituted mercaptoacetanilides;[83] the acid dissociation constants obtained are shown in Table 3. Perusal of the data in Table 3 reveals, not unexpectedly, that electron-withdrawing groups such as Cl, Br, I, COOH, and NO_2 decrease the pK_{SH} value whereas electron-releasing groups such as CH_3, OCH_3 and OC_2H_5 increase the pK_{SH} value relative to the parent compound. The effect of substituents on pK_{NH} is similar but less pronounced.

Table 3: Mercapto and amide acid dissociation constants for *para*- and *meta*-substituted mercaptoacetanilides.[83]



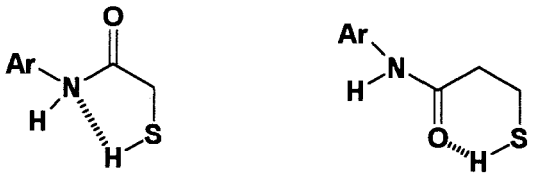
R_1	pK_{SH}	pK_{NH}	R_2	pK_{SH}	pK_{NH}
H	9.97	12.63	F	9.53	
NO_2	9.45	12.52	Cl	9.55	12.54
CF_3	9.57		Br	9.51	
COOH	9.71	12.56	I	9.54	
Cl	9.76	12.57	COOH	9.63	12.60
OH	9.90		OH	9.43	
OMe	10.05	12.63	Me	10.09	12.71
Me	10.07	12.69	OMe	10.10	12.64
			OEt	10.14	12.70

Bachlas and Agarwal [67] measured the mercapto dissociation constant of eleven *N*-aryl and *N*-cyclohexyl-2-mercaptoacetamides in 75% (v/v) dioxane at 30 °C and confirmed the trends reported by Bhandari and Sogani.[83] The relatively higher pK_{SH} value measured for the 2,6-dimethyl derivative (10.03) [compared to the 2,5-dimethyl derivative (9.83)], supports Martin's theory that *ortho*-substituents force the carbonyl oxygen closer to the mercapto hydrogen (**56**, Figure 17) and hence increases pK_{SH} values. However, the theory does not explain why the 3,5-dimethyl derivative has a similar pK_{SH} (10.01) to the 2,6-dimethyl derivative. Of the compounds examined, *N*-cyclohexyl-2-mercaptoacetamide was found to have the lowest pK_{SH} (9.49).

Gupta and Bachlas[84] determined the mercapto acid dissociation constants for 2-mercaptoacetanilide and 3-mercaptopropionanilide to be 9.82 and 11.60 respectively, and explained the large difference in pK_{SH} on the basis of the different ring structures formed by intramolecular hydrogen-bonding (Figure 18). They proposed that the five-membered hydrogen-bonded chelate **55** of mercaptoacetanilide is more strained than the six-membered chelate **57** of mercaptopropionanilide, the stronger hydrogen-bonding in the latter compound

(**57**) decreases its acidity. The proposals by Gupta and Bachlas, however, fail to consider the influence of inductive effects on the acidity of mercaptopropionanilide.

Figure 18: Intramolecular hydrogen-bonding in mercaptoacetanilide and mercapto-propionanilide, proposed on the basis of mercapto acid dissociation constants. [84]



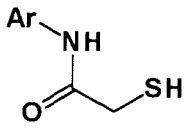
55 57

1.3.1.4.2 Metal stability constants

Martin [79] also determined the stability constants of complexes of divalent metal ions with several mercaptoacetanilides at 30 °C in 75% (v/v) dioxane, the stability of the metal complexes decreasing in the order UO_2 > Be > Ni > Mn. Although the poor solubility of the copper and cobalt chelates prevented measurement of stability constant data, the copper complex appeared to be more stable than the uranyl complex.

The stability constants of complexes of *ortho*-, *meta*- and *para*-chloromercaptoacetanilide with cobalt(II) have also been investigated.[85] These complexes are insoluble in water and were extracted into chloroform, the stability constants being determined in the latter solvent by the spectrophotometric method of Turner and Anderson. [86] Cobalt-ligand complexes of molar ratio 1:3 were formed and their stability constants are shown in Table 4.

Table 4: Stability constants of chloro-substituted mercaptoacetanilide-cobalt complexes.[85]



Ar	Log K_{Co}
C_6H_5	4.477
2-Cl-C_6H_4	4.92
3-Cl-C_6H_4	4.98
4-Cl-C_6H_4	3.845

The first indication that a combination of thia and amide functions may be selective for palladium came in 1973 when Bhandari and Sogani [55] determined the stability constants of lead, cadmium, zinc, nickel and palladium chelates with mercaptoacetanilide at 30 °C in 70% (v/v) dioxane at 0.1 **M** ionic strength (KCl). The relative stabilities of the divalent metal chelates were found to follow the order Pd > Pb > Cd > Zn > Ni; the values of these constants are given in Table 5.

Table 5: Stability constants for the bis-chelates of mercaptoacetanilide with divalent metal ions. [55]

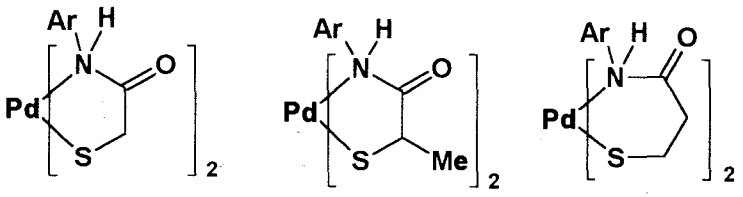
Divalent Metal Ion	Stability Constant (Log K)
Nickel	16.08
Zinc	16.80
Cadmium	18.18
Lead	21.72
Palladium	24.34

Table 5 shows that mercaptoacetanilide gives excellent selectivity for Pd^{2+} over Ni^{2+}, Zn^{2+} and Cd^{2+} and more remarkably, significant selectivity for Pd^{2+} over Pb^{2+}. The titrations show that only one proton is liberated per ligand molecule and the authors proposed that the amide proton and not the mercapto proton is liberated on complex formation, a nitrogen-sulfur chelate ring being formed. In the same year, the stability of chelates of mercaptoacetanilide with zinc(II) and nickel(II) in aqueous ethanol were measured by Kakkar and Khadikar,[81] the zinc chelate being

found to be marginally more stable than the nickel chelate. These researchers, however, suggested that the mercapto proton is liberated on complexation.

The effect of substituents and ring-size on chelate stability has been investigated for complexes of palladium(II) with 2-mercaptoacetanilide, 3-mercaptopropionanilide and 2-methyl -2-mercaptoacetanilide.[75] The molar ratio of ligand to palladium was 2:1in all three cases and the proposed chelate structures and their stability constants, which were determined spectrophotometrically, are shown in Figure 19. As can be seen from structures **58**, **59** and **60**, coordination is considered to involve a neutral nitrogen donor and a mercaptide donor, and increasing the size of the chelate ring from five to six leads to a significant drop in chelate stability.

Figure 19: Stability constants of 5-membered and 6-membered sulfur-nitrogen chelates with palladium.[75]



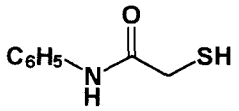
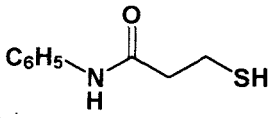
58 **59** **60**

Log K : **5.27** **5.36** **4.58**

The stability constants of 1:1 and 2:1 complexes of dialkyl tin(IV) cations with 2-mercaptoacetanilide and 3-mercaptopropionanilide have been determined in 75% (v/v) dioxane using the Irving-Rossotti method.[84] As can be seen in Table 6, changing the alkyl group (from methyl to ethyl to butyl) has very little effect on the first stability constant (log K_1), but the second stability constant decreases markedly with increasing size of the alkyl group. The decrease in log K_2 has been attributed to steric effects, since the alkyl groups attached to tin are

expected to hinder the entry of the second, incoming ligand more than the first.

Table 6: Stability constants of 1:1 and 2:1 complexes of mercaptoacetanilide and mercaptopropionanilide with dialkyltin(IV) cations.[84]

Ligand		$[Me_2Sn(IV)]^{+2}$	$[Et_2Sn(IV)]^{+2}$	$[nBu_2Sn(IV)]^{+2}$
	Log K_1	13.73	13.70	13.70
	Log K_2	8.08	7.94	7.81
	Log K_1K_2	21.81	21.64	21.51
	Log K_1	14.23	14.35	14.43
	Log K_2	9.69	9.44	9.23
	Log K_1K_2	23.92	23.79	23.66

Because equilibrium studies have revealed that the magnitude of formation constants for organotin-oxygen systems are 100 times greater than those of organotin-nitrogen systems, Gupta and Bachlas [84] proposed the formation of sulfur-oxygen rather than sulfur-nitrogen chelates. Interestingly, whereas the six-membered chelate of mercaptopropionanilide with dialkyl tin(IV) is more stable than the five-membered chelate of mercaptoacetanilide (see Table 6), the opposite stability order is observed with palladium. This is probably due to different modes of coordination and/or the size of the metal ion, six-membered chelate rings being more stable for small metal ions. The stability constants of complexes of dialkyltin(IV) cations with eleven *N*-aryl- and *N*-cyclohexyl-2-mercaptoacetamides have been determined,[67] and the results indicate that the smaller the dissociation constant of the ligand (*i.e.* the higher the pK_{SH}) the greater the magnitude of the formation constant. In the case of *N*-cyclohexyl-2-mercaptoacetamide, however, the steric bulk of the non-planar cyclohexyl moiety retards complex formation and, as a consequence, the formation constants are lower than expected.

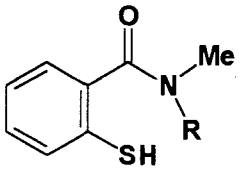
In conclusion, mercaptoacetanilides are versatile reagents for the analysis of a number of metal

ions, and quantitative studies by Bhandari and Sogani [55] as well as by Nacu [75] have shown these reagents to be highly selective for palladium. Two modes of coordination are possible:- i) hard metals [like tin(II),[66] tin(IV),[67] titanium(IV),[68] zirconium(IV)[69] and hafnium(IV)[70]] form oxygen-sulfur chelates with deprotonation of the mercapto group on complexation, while ii) softer metals [like divalent zinc, nickel, cobalt, platinum, palladium and other late transition metal cations] form sulfur-nitrogen chelates.[55, 81] One proton is liberated from the ligand upon formation of a sulfur-nitrogen chelate; Kakkar and Khadikar [81] propose deprotonation of the mercapto sulfur while Bhandari and Sogani [55] propose deprotonation of the amide moiety. Copper(II) oxidises the ligands to the corresponding disulfides.[65]

1.3.2 Sulfur-containing benzamide ligands

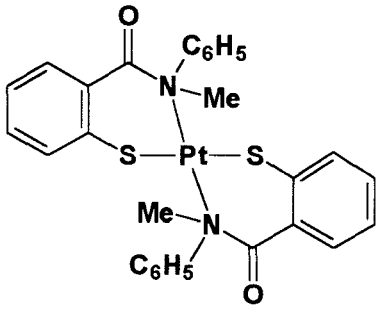
The benzamide derivatives **61** have been complexed with copper(I) and the divalent metals nickel, cobalt, zinc, cadmium, platinum and palladium.[87] Infrared and NMR studies (of the diamagnetic complexes) show that, with only one exception, coordination occurs through the

Figure 20: Sulfur-containing benzamide ligands.[87]



61 a, b

	R
a	Ph
b	CH_2Ph

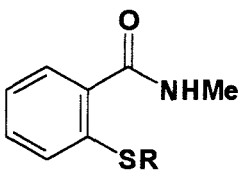


62

mercapto and amide oxygen groups, the exception being the benzanilide-platinum(II) complex **62**, which exhibits mercapto and amide nitrogen bonding. Deprotonation of the mercapto group occurs upon formation of all the chelates.

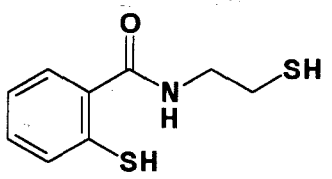
Other benzamide derived ligands include *o*-mercaptobenzamide which has been complexed with several metal ions [88] and the derivatives **63a**,[89] **63b**,[90] and **64** [91] which, although potential chelating agents, have not been studied as such (Figure 21).

Figure 21: Potential sulfur-containing benzamide ligands.



63 a, b

	R
a	H
b	Me

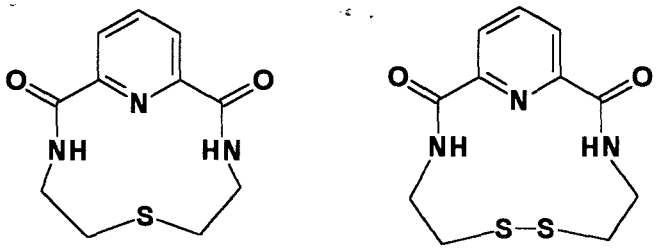


64

1.3.3 Amido-thioether macrocycles

The extensive review of the macrocycle literature by Izatt *et al.*[92] shows that several amido-polyether macrocycles have been synthesised but, prior to 1984, no quantitative complexation studies had been done on amido-thioether macrocycles. In 1976, the macrocyclic ligands **65** and **66** were synthesised by Vögtle, but were not complexed with metal ions (Figure 22).[47]

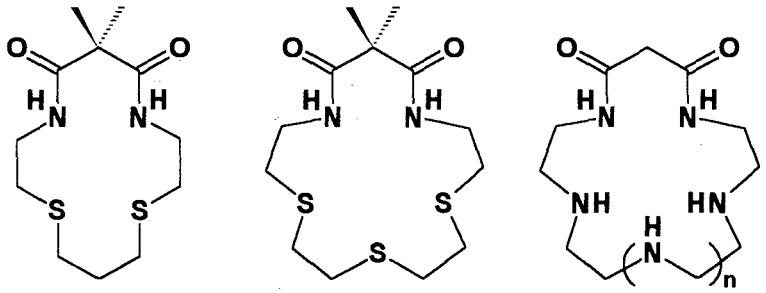
Figure 22: Amido-thioether macrocycles synthesised by Vögtle. [47]



65 **66**

In 1989, Kimura reported the synthesis of the tetradentate macrocyclic ligand **67** containing two amide and two sulfide units.[48] Complexation studies showed this macrocycle to be highly selective for divalent platinum and palladium over the divalent metals copper, nickel and cobalt. Later, the larger macrocycle **68** containing three sulfide units was synthesised and complexed with divalent platinum and palladium.(Figure 23).[49]

Figure 23: The diamide macrocycles developed by Kimura.[48, 49, 93]



67 **68** **69a (n = 0)**
69b (n = 1)

A long-term aim of Kimura's research was to design and synthesise ligands for the uptake of platinum from cisplatin {*cis*-$[Pt(NH_3)_2Cl_2]$}, and the macrocyclic polyamines **69** had been synthesised for this purpose. The dioxocyclams **69** were found to remove less than 1% of the platinum from cisplatin at low pH in the presence of sodium thiosulfate.[93] However, the sulfur-

containing macrocycles **67** and **68** were observed to remove platinum from cisplatin much more efficiently (*ca.* 40%) and rapidly than the dioxocyclams **69** and without any external additives.[49] The mode of complexation was found to involve initial attack on platinum by the sulfur donors, thus displacing the labile chloride ions in cisplatin, followed by displacement of the ammonia ligands by anionic amide nitrogen, the second process being much slower than the first.[49]

Even at elevated temperature (60 °C) and high pH (up to 11), these macrocycles fail to complex copper, nickel and cobalt. At room temperature and lower pH, the platinum(II) complexes are obtained in approximately 85% yield and the palladium(II) complexes in 90% (with macrocycle **67**) and 85% (with macrocycle **68**) yield. This selectivity is a result of the ligands having both sulfur and amide donors in the macrocyclic skeleton. The soft sulfur donors coordinate more readily with the soft platinum(II) and palladium(II) ions than the harder copper(II), nickel(II) and cobalt(II) ions. Moreover, platinum and palladium possess mixed properties of hard and soft acids and, towards amide ligands, their hard acidities are greater than those of copper(II) and nickel(II) enabling them to remove the amide protons to form metal-nitrogen bonds more readily. Thus, the amide functions, which are only effective after thia group coordination, play an important role in metal selectivity. Analogous amine thioether macrocycles do not show this platinum(II) and palladium(II) selectivity.[49]

1.3.4 Applications of ligands with thia and amide functions in medicine

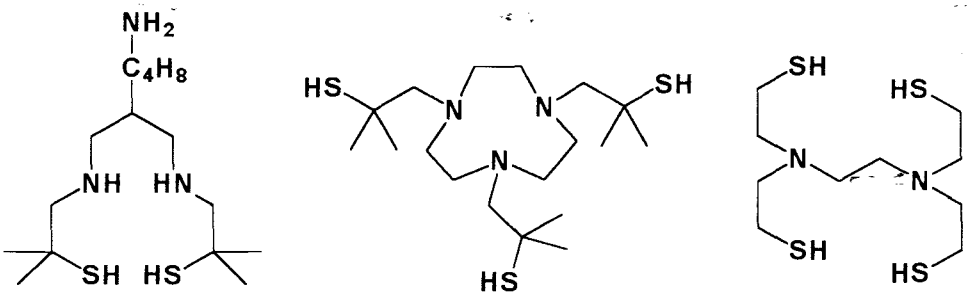
The majority of ligands used in radiopharmaceutical formulations are artificial complexing agents of synthetic origin. To be an effective diagnostic agent a ligand must form a complex, with the radioactive metal ion, which remains intact *in vivo*. This requires either that the metal ion exhibits kinetically inert behaviour, or that the complex has a very high stability constant. Furthermore, the complex should accumulate selectively in the target tissue, while any excess

complex should clear rapidly and completely from the blood stream.

Radionuclides of the group 7 elements possess useful physical characteristics for medical applications; the metastable isomer of technetium, ^{99m}Tc, is an ideal radionuclide for scintigraphic imaging while rhenium 186, ^{186}Re, has been judged appropriate for cancer radiotherapy.[94] The isotope ^{99m}Tc is by far the most widely used radionuclide for diagnostic imaging purposes,[94] accounting for some 85% of all nuclear medicine scans in the United States. The popularity of ^{99m}Tc in this field may be attributed both to the availability of $^{99m}TcO_4^-$ (pertechnetate) at low cost from generator systems and to its favourable decay properties. Technetium-99m decays with the emission of a 140keV γ-ray, suitable for detection but not strongly absorbed by living tissues, thus presenting low radiation doses to the patient. The decay product, ^{99}Tc, is a long half-life (2.12×10^5 years), low-energy β-emitter of low radiotoxicity.

The development of new generations of imaging agents presents a formidable challenge to synthetic inorganic chemists since, to be viable as an imaging agent, the technetium complex must be synthesised in better than 90% yield directly from pertechnetate in aqueous or semi - aqueous solution, preferably at room temperature and at a metal concentration of *ca.* 10^{-8} **M**.[95] Although few ligands meet all these criteria they are, nevertheless, of intrinsic interest in the context of the relatively unexplored chemistry of technetium. Many different chelating agents have been used to form stable complexes with technetium, many of which do not contain s and amide donors, for example, the bis(aminoethanethiol) (BAT) derivative **70** [96] an sulfur ligands **71** and **72** [97] (Figure 24). However, this section will focus on ch containing both thia and amide functions and their complexes with techn

Figure 24: Typical thiol-amine ligands used for complexing technetium. [96, 97]

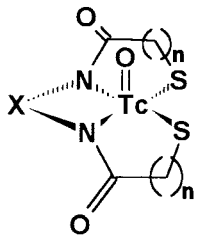


70 **71** **72**

1.3.4.1 Technetium complexes with thiol-amide ligands

Good stabilization of the Tc=O centre is obtained with dithioldiamide ligands. In order to prevent oxidation, and for convenience in characterisation and isolation of the ligands, they are prepared as their mercapto protected benzoyl esters. The technetium complexes are obtained by reduction of pertechnetate in the presence of an excess of the benzoyl protected ligands, and the oxotechnetate(V) chelates **73-77** (Figure 25) have been obtained in good yields.[98] The amide thiol ligands were chosen to span the basal positions of an expected square-pyramidal structure, deemed necessary to increase the kinetic stability of the low spin d^2 TcO core and to maximize *in vivo* stability. An evaluation of the optimum chelate ring sizes was necessary in order to maximise the yield prior to functionalization of the ligand backbone, this evaluation showed that chelate **73**, which contains three five-membered rings, was repeatedly obtained in quantitative yields.[98] The conditions of synthesis are dictated by kinetic rather than equilibrium control, and chelates **74** and **75** could not be obtained without some $TcO_2.xH_2O$ production. In the absence of thermodynamic stability data this suggests that the three five-membered ring configuration is most favoured. Chelate **77** could not be obtained in yields greater than 74%, and this was attributed to steric constraints in the *ortho*-phenylene backbone.

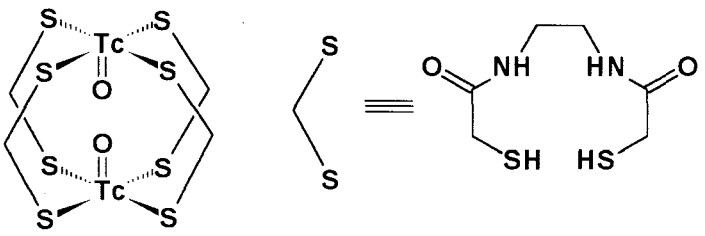
Figure 25: Technetium complexes with dithiol-diamide ligands. [98]



Complex	X	n
73	$(CH_2)_2$	1
74	$(CH_2)_3$	1
75	$(CH_2)_2$	2
76	$(CH_2)_3$	2
77	*o*-C_6H_4	1

The amidothiolate ligand used in the formation of chelate **73** was observed to form a deep blue intermediate with pertechnetate and an x-ray crystal structure revealed the novel lantern-like structure **78** with each ligand coordinated to the metal by sulfur alone (Figure **26**).[95] The formation of such large chelate rings was unexpected and is attributed to the preference of the Tc(V)O centre for thiolato ligands and the inherent stability of the $TcOS_4$ core. This blue, dimeric complex decomposes immediately and quantitatively to the monomeric technetium(V) complex **73** in aqueous alkaline solution. Studies of biological samples established that complex **73** was excreted unchanged in both urine and bile and thus had high *in vivo* stability. A ^{99m}Tc derivative of chelate **73**, with a carboxyl function on the ethylene backbone, has been used extensively to study renal tubular function.[99]

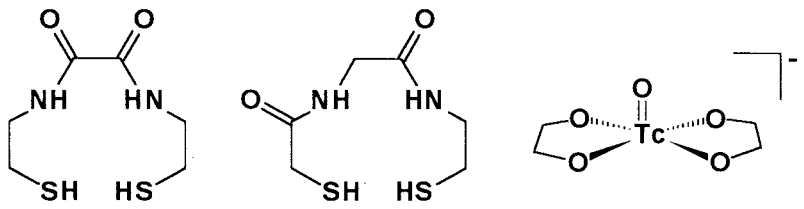
Figure 26: The novel lantern-like intermediate complex formed with pertechnetate. [95]



78

Davison [51] investigated the synthesis and stability of isomeric complexes that result from permutation of the amide functions in the ethylene backbone. The amidethiolates **79** and **80** were prepared from readily available synthons (Figure 27), the TcO complex with ligand **80** being obtained by dithionite reduction of pertechnetate in aqueous alkali in the presence of the ligand. However, due to its instability toward dithionite, the TcO complex with **79** could only be obtained in low yield using this synthetic method. The technetium complexes of both ligands can be synthesised by ligand-exchange procedures using the oxobis(ethanediolato)technetate(V) anion **81**, and these complexes, as well as complex **75**, are stable for extended periods in both acidic (pH~0) and basic (pH~14) solutions; they are kinetically robust and do not undergo substitution or ligand-exchange reactions with other thiols.

Figure 27: Ligands 79 and 80 illustrating permutation of the amide function and the common precursor 81.

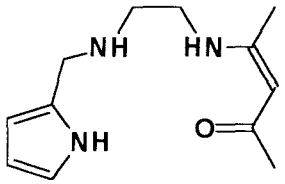


79 **80** **81**

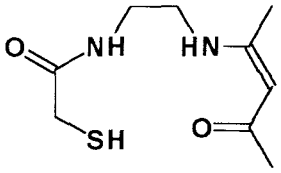
In the search for neutral and lipophilic technetium complexes, which are capable of crossing the blood brain barrier, the potentially quadridentate ligand **82** has been developed (Figure 28). The ligand is capable of losing three protons to stabilize $[Tc=O]^{3+}$ and yield neutral and lipophilic complexes. As part of a study to identify the chemical nature of the *in vivo* trapping mechanism, the functionality was altered to give the mercaptoacetamide ligand **83**,[100] and distribution studies showed that the structural changes did not have a negative effect on the ability of the technetium complex to cross the blood brain barrier. Retention of the technetium chelate of **83** in the brain suggested that oxidation of the pyrrole group in **82** does not play a role in the *in*

vivo trapping mechanism.

Figure 28: Ligands which form neutral, lipophilic technetium complexes.[100]



82



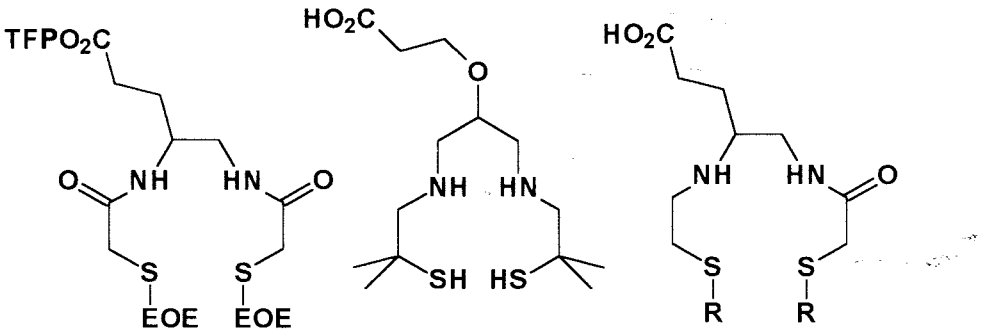
83

1.3.4.2 The attachment of radionuclides to antibodies

An important field in radioimmunotherapy is the attachment of radionuclides to antibodies. There are presently three approaches to the radiolabelling of antibodies, *viz.*, direct radiolabelling of the antibody, radiolabelling of a chelating agent conjugated to an antibody, and radiolabelling of a chelating agent before conjugation to an antibody.[101] The first approach [direct labelling of monoclonal antibodies (MoAb)] is possible, nonspecific binding of radiometals to proteins has been shown to be unstable *in vivo* and thus may not afford an ideal radiopharmaceutical. The latter two approaches require the use of bifunctional chelating agents to achieve stable attachment of the radiometal to MoAb. For optimal results, the chelating agent should coordinate the radiometal strongly and should also be attached through a stable covalent bond to the MoAb. Ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA) have been used for the purpose of labelling MoAbs with ^{111}In and ^{67}Cu; these chelates couple to protein *via* a stable amide bond and have acceptable formation constants for these radiometals.[102] A drawback with the use of these ligands is that they cannot be used for the superior and more readily available radionuclide ^{99m}Tc due to their low formation constants with this metal. Fritzberg has overcome this problem by introducing an ester group to the

backbone of ligand **74** for attachment to the antibody.[103] In his approach, the ligand is either conjugated to the antibody and then labelled with technetium or pre-labelled with technetium prior to attachment to the antibody. However, the prelabelled ligand forms the most stable bond with the antibody. This indirect approach of Fritzberg has several advantages, *viz.*, i) the metal chelate is formed under controlled conditions and is characterisable and ii) the complexes are highly stable both *in vitro* and *in vivo*.[101, 103]

Figure 29: Bifunctional chelating agents used for the radiolabelling of antibodies.[104]



84 **85** **86**

EOE = 1-ethoxyethyl
TFP = 2,3,5,6-tetrafluorophenyl

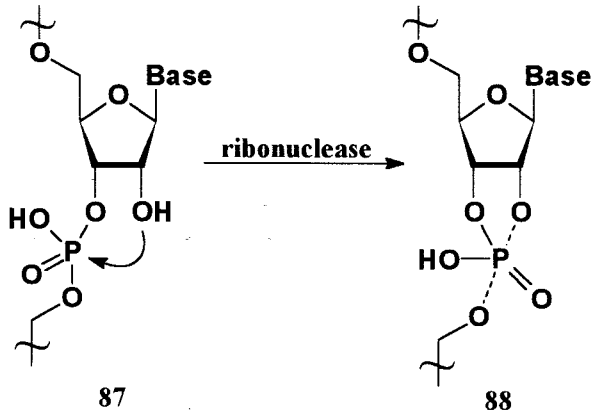
The *S*-protected diamidodithiolate ligand (DADS) **84** forms a highly stable complex with technetium at elevated temperatures (75-100°C) and low pH (2-3) (Figure 29).[104] Since diaminodithiolate (DADT) ligands (*e.g.* **85**) form technetium complexes at ambient temperature, these ligands show promise for the direct labelling of antibody-ligand conjugates. By substituting one of the amide nitrogens of DADS with an amine, it was hoped that the kinetics of technetium chelation would be enhanced while maintaining the high stability of the Tc-DADS antibody conjugates. For this reason a new class of chelating agents, the monoaminomonoamido (MAMA) **86** bifunctional ligands were synthesised.[104] These MAMA ligands showed a threefold increase in radiochemical yield of technetium complex over the DADS ligand.

Protection of the sulfur atoms minimizes the potential for aggregation of the antibody by free thiols, but the protecting groups are such that they are cleaved under mild technetium labelling conditions.

1.3.4.3 Janda's mimic

Janda used a derivative of a diamidodithiolato technetium complex as a ribonuclease inhibitor.[105] Hydrolysis of RNA is mediated by ribonuclease enzymes and is thought to proceed *via* a transition state in which the 2'-hydroxyl of one nucleobase fragment, and the 5'-hydroxyl of another, occupy axial positions of a phosphorus centred trigonal bipyramid **88** (Scheme 4).

Scheme 4: Formation of the transition state for ribonulease-mediated hydrolysis of RNA.[105]

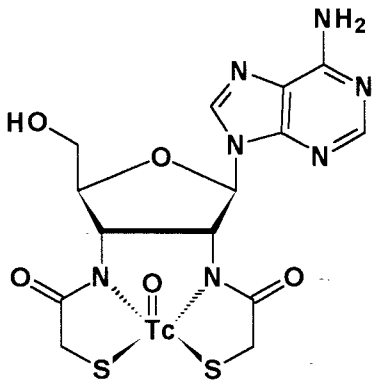


87 **88**

Since phosphorus does not form a stable penta-coordinate complex, vanadium has been used to model this postulated transition state for RNA hydrolysis. Although vanadium forms a trigonal-bipyramidal vanadate ribonucleoside complex, it is unstable in aqueous solution and, thus, no water-soluble vanadium-based pentacoordinate analogues that are potent inhibitors of ribonucleases exist. Janda's mimic **89** (Figure 30), however, is stable in aqueous solution, and a series of control experiments demonstrated that it is a potent inhibitor of ribonucleases by

transition state mimicry and not *via* other factors such as coordination of technetium to the enzyme.[105] Such complexes have potential as general inhibitors of ribonucleases in preparative RNA isolation or as inhibitors of other enzymes that catalyse phosphoryl-transfer reactions.

Figure 30: Janda's mimic.[105]



89

1.3.5 Sulfur-containing biomolecules

Sulfur-containing peptides, enzymes and proteins are an important class of compounds which contain sulfur and amide functions. Although many of these biomolecules complex with biological metal ions (*e.g.* metallothionein with zinc) as part of their normal mode of operation, they also complex with platinum which has been introduced into the body in the form of platinum based antitumor complexes. This has led to studies of the reactions of platinum antitumor complexes with sulfur containing biomolecules.

Many platinum complexes show antitumor activity, the first metal antitumor compound and the largest selling antitumor drug being cisplatin.[52] The therapeutic value of cisplatin is limited by its toxicity to several organs, especially the kidney. This toxicity is often dose limiting and has

been ascribed to the complexation of platinum with the sulfur-rich enzymes and proteins found in the kidney.[106] To remove platinum from these biomolecules many sulfur-containing ligands have been studied as possible rescue agents, some of which also contain the amide function.[107]

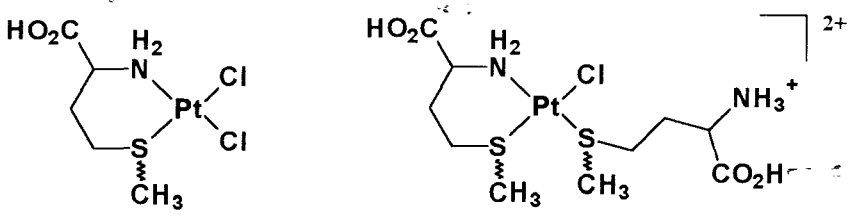
1.3.5.1 Reactions of platinum with sulfur-containing biomolecules

Platinum antitumor reagents can react with sulfur containing biomolecules in the blood plasma (albumin and methionine), in cells (glutathione) or at organs which have a high concentration of sulfur-containing enzymes and proteins. Typical sulfur-containing biomolecules which can react with platinum are cysteine, methionine, S-adenosyl-L-methionine, glutathione, metallothionein, and other proteins.[52] These platinum-sulfur interactions are considered to have a negative effect on antitumor activity and can be responsible for inactivation of the platinum species, for the development of resistance and for toxic side-effects such as nephrotoxicity.[52] Consequently, attention has recently been given to biologically important platinum-sulfur interactions.

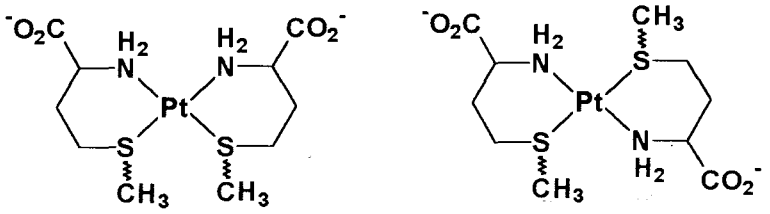
1.3.5.1.1 Reactions of platinum with sulfur-containing amino acids

Complexes of the amino acid L-methionine (L-MetH) and platinum(II) have been identified in the urine of patients receiving cisplatin therapy, and Pt(II)-methionine complexes form in blood plasma upon injection of cisplatin into rats.[108] Prior to 1992 very little research had been done on Pt(II)-methionine complexes, but NMR data has recently been presented which is consistent with either S,N or S,O coordination in a $[Pt(L\text{-}Met)(NH_3)_2]$ complex.[109] The reactions of L-methionine with tetrachloroplatinate $(PtCl_4)^{2-}$ at pH 7 have been studied using ^{1}H, ^{13}C, ^{15}N, and ^{195}Pt NMR spectroscopy[110] and, in all the adducts, S,N chelate rings have been shown to form, as illustrated in Figure 31.

Figure 31: Platinum L-methionine complexes.[110]



90 **91**



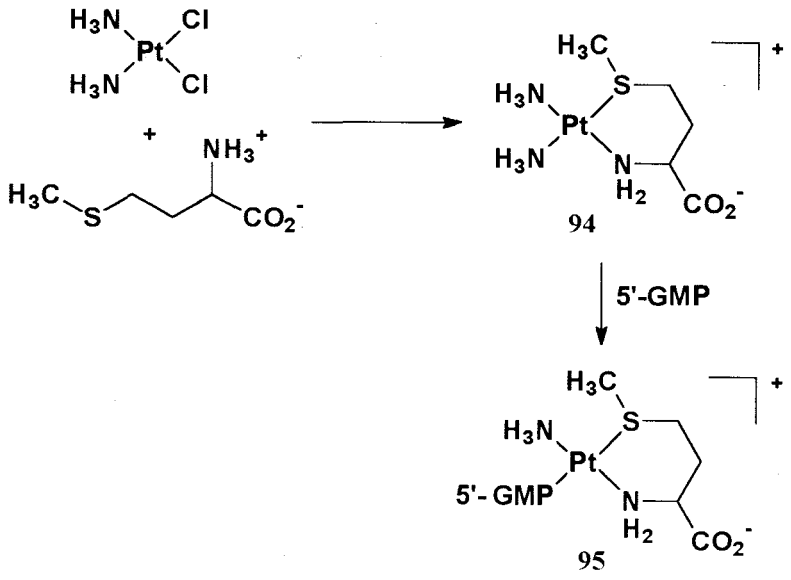
92 **93**

The 1:1 adduct **90** exists in two diastereomeric forms depending on the configuration of the coordinated thioether (Figure 31), and interconversion of the complexes (dynamic inversion at sulfur) was confirmed by variable temperature NMR studies.[110]

A variety of 1:2 Pt(II)-L-methionine adducts are known.[110] The adduct **91** exists as four diastereomers, which are present in equal proportions, while both the bischelate **92** and the less favoured *trans*-analogue **93** each occur in three diastereomeric forms. Equilibrium between the adduct **91** and the bischelate complexes is dependent on pH. At pH 7.2 the bischelate **92** predominates, while at low pH (~2) one chelate ring opens and product **91** is the predominant species. Methionine also reacts with cisplatin or hydrated cisplatin giving the bischelates **92** and **93** as well as platinum diammine and monoammine complexes. The *cis-trans* isomerism of the bischelates **92** and **93** has been studied,[111] and it has been found that the isomerization is slow and appears to be entropy driven, the solvent shell being more ordered in the *trans* isomer, which has partial charges more evenly distributed throughout the complex.

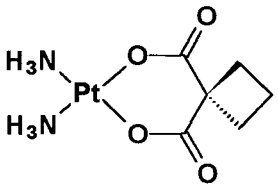
Due to the high affinity of platinum for sulfur-containing biomolecules there is speculation as to whether intracellular Pt-S complexes act as a reservoir for platination of DNA. Cisplatin-methionine products do not show antitumor properties,[52, 108] and this implies that the platinum is not passed on from methionine to DNA, even though the Pt-thioether methionine bond is more labile than the Pt-mercaptide cysteine bond. Recent studies have shown, however, that cisplatin, S,N-bound to methionine, reacts with guanosine 5'-monophosphate (5'-GMP) at a faster rate than free cisplatin.[112] (Platinum most commonly binds with the guanine bases of DNA, resulting in antitumor activity). The increased reaction rate is attributed to the *trans*-effect of the coordinated methionine sulfur in complex **94** (Scheme 5), which labilises the *trans*-ammine ligand, thus enhancing reaction with guanosine. Although S,N-chelation of methionine to platinum is irreversible at physiological pH, if the methionine is part of a peptide or other biological molecule the nitrogen may not be available for coordination to platinum, resulting in more labile, monodentate sulfur complexes.

Scheme 5: Reaction of methionine bound cisplatin with guanosine 5'-monophosphate. [112]

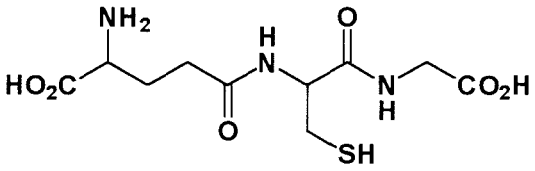


In contrast to cisplatin, the second generation anticancer drug carboplatin **96**, exhibits little nephrotoxicity, suggesting a difference in the interaction of carboplatin with thiol residues. To test this hypothesis the reaction of carboplatin with *N*-acetyl-L-methionine, *N*-acetyl-L-cysteine and glutathione **97** at pH 7 was followed by NMR spectroscopy.[113] The hypothesis was supported when, after ten hours, no reaction could be observed between carboplatin and either *N*-acetylcysteine or glutathione,[113] in contrast to the fairly rapid reaction of thiols with cisplatin. After standing for several weeks at room temperature, a yellow precipitate formed, which was shown to be the sulfur-bridged diplatinum complexes **98a** and **b** (Figure 32). Other biological molecules which also form dimers with diammine platinum compounds include cysteine and homocysteine (*e.g.* complexes **98c** and **d**).[116]

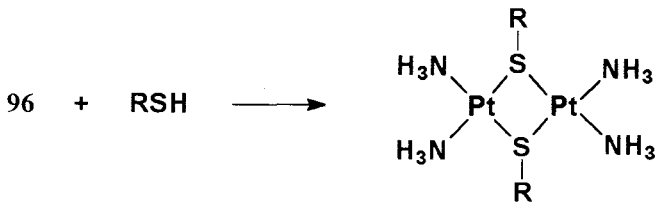
Figure 32: Carboplatin, glutathione and the sulfur bridged diplatinum complexes 98.[113]



96



97

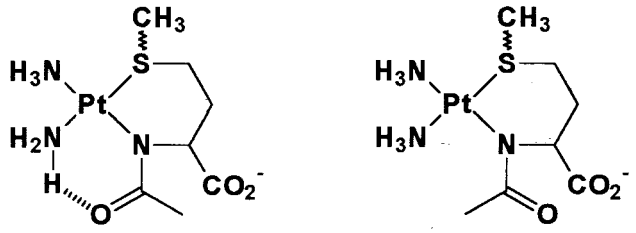


98

	RSH
a	N-acetylcysteine
b	glutathione
c	cysteine
d	homocysteine

Not surprisingly, *N*-acetyl-L-methionine does not coordinate with the platinum in carboplatin as readily as L-methionine. After eight hours, however, a significant amount of free cyclobutane-1,1-dicarboxylic acid (CBDCA) is formed, together with a thioamido chelate. This chelate exists as the *syn*- and *anti*-rotamers **99** and **100** (Figure 33), while slow inversion of the sulfur (on the NMR timescale) affords all four of the possible configurational isomers.

Figure 33: S,N-Platinum chelates of *N*-acetyl-L-methionine.[113]



99 **100**

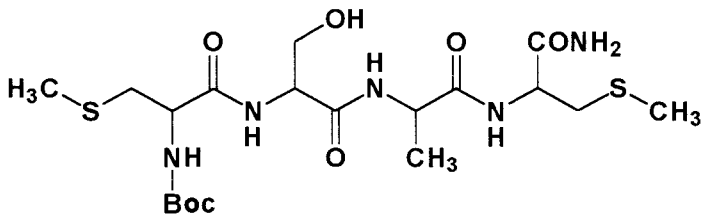
1.3.5.1.2 Reactions of platinum with peptides and proteins

Glutathione is the predominant intracellular thiol and is present in concentrations ranging from 0.5 to 10mM. A number of investigations into the reaction of cisplatin with glutathione have been published,[114, 115, 116] but, due to the complexity of the system, the reaction products have not been fully characterised. Wolf and Odenheimer[114] reacted glutathione and cisplatin in a 2:1 molar ratio and, mainly on the basis of infrared evidence, postulated that a bischelate complex is formed with coordination through sulfur and the deprotonated amide nitrogen. Dedon and Borch[115] also reacted glutathione (GSH) and cisplatin in a 2:1 ratio and obtained a high molecular weight polymeric compound with formula $[Pt(GS)_2]_n$, in which complexation to platinum occurs through the mercapto group. When glutathione and cisplatin were reacted in a 0.8:1 ratio a product analogous to the sulfur bridged dimeric complexes **98** (Figure 32) was formed but, after standing for several days, ammonia was lost from this complex and a

polymeric yellow solid deposited.[116]

Metallothionein, a low molecular weight protein with a high cysteine content, is known to bind with cisplatin both *in vivo* and *in vitro,* and the coordination is known to contain tetrathiolate (PtS_4) species.[117] The binding of cisplatin by metallothionein, which occurs mainly in the liver and kidneys, could be a major factor causing the nephrotoxicity of the drug. The cys-x-cys and cys-x-y-cys sequences (x and y being residues other than cysteine) are important species in metallothionein. To model these species the tetrapeptide, Boc-Cys^1(SCH_3)-Ser^2-Ala^3-Cys^4(SCH_3)-$CONH_2$ (CSAC) **101**, was synthesised and its complexation with cisplatin and other bifunctional platinum compounds studied (Figure 34).[118]

Figure 34: A tetrapeptide model of the cysteine residues in metallothionein.[118]



101

The platinum compounds were reacted in 1:1 and 2:1 metal to CSAC ratios and the pH was kept between 5.5 and 6.5. With cisplatin, a very complicated ^{1}H NMR spectrum resulted with broad and featureless signals, which were attributed to exchange processes between the different diastereomers (sulfur inversion) and/or to the presence of polymeric species. The chemical shift of the S-CH_3 resonance indicated bonding through the sulfur and ^{195}Pt NMR spectroscopy showed a broad signal which can be ascribed to a PtN_2S_2 complex. The complexity of the spectra precluded further identification. The reaction of *cis*-Pt(en)$(ONO_2)_2$ with CSAC resulted in products which gave three sets of ^{1}H NMR signals, again indicating complexation through the sulfur donors.[118]

From the research summarised above it can be seen that reactions of platinum with sulfur containing biomolecules have important medical consequences and that, under biological conditions, platinum mainly reacts with the sulfur of cysteinyl and methionine residues and with terminal amino groups.

1.3.5.2 Sulfur-containing rescue agents

Platinum-specific ligands have been used to reduce the dose limiting nephrotoxicity of platinum,[52] the most effective rescue agents proving to be thiol chelating agents. The dosage, duration and time of commencement of chelation therapy are factors which affect the excretion of platinum from biological systems and complicate the comparison of rescue agents. For example, treating cells *in vitro* with methionine prior to cisplatin dosage increases the cell toxicity of cisplatin, whereas simultaneous treatment with methionine and cisplatin reduces the cell toxicity of cisplatin.[119] An explanation for this phenomenon is that increasing the cellular concentration of methionine prior to cisplatin dosage could result in the formation of cell toxic intracellular methionine-Pt complexes, whereas administration of methionine with cisplatin, although decreasing the cell toxicity of cisplatin, enhances the cisplatin-induced nephrotoxicity.[120] This is in contrast to other rescue agents and could be due to the displacement of plasma-bound platinum by methionine, resulting in complexes which are available and toxic to the kidney.

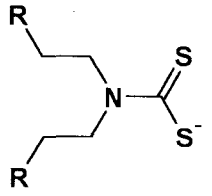
Ligands containing sulfur and amide functions which have been studied as rescue agents include *N*-acetylcysteine,[121] glutathione and the monoisopropyl ester of glutathione.[122] *N*-Acetyl cysteine, which readily penetrates various cell types, does not afford significant protection against cisplatin toxicity. The monoisopropyl ester of glutathione is more effective than glutathione in protecting against cisplatin toxicity, and is also capable of protecting against

lethal poisoning by lead and mercury (which glutathione is not). Glutathione monoisopropyl ester is effectively transported into cells where it is hydrolysed to glutathione, suggesting that intracellular glutathione is important for protection against heavy metal ions.[122]

Typical thiol-containing heavy metal chelators which have been investigated to determine their effect on renal platinum concentration include 2,3-dimercaptopropanol and 2,3-dimercaptosuccinic acid (DMS).[107] The latter ligand reduces the renal concentration of platinum by half but is unable to prevent cisplatin induced nephrotoxicity.

Sodium diethyldithiocarbamate [Na(ddtc)] **102a** is one of the more effective inhibitors of cisplatin-induced nephrotoxicity, and does not interfere with the antitumor properties of cisplatin (Figure 35).[106] However, the severe side-effects of this ligand have resulted in its replacement by di(hydroxyethyl)dithiocarbamate **102b**, which forms more soluble complexes with less toxic side-effects.[52]

Figure 35: Functionalised dithiocarbamates, effective platinum rescue agents.[106]



102a, R = H
102b, R = OH

To elucidate its mode of action, Na(ddtc) was reacted with the adducts from the reactions of chlorodiethylenetriamine platinum(II) {$[Pt(dien)Cl]^+$} with glutathione and with *S*-methylglutathione.[123] These sulfur containing peptides react with $[Pt(dien)Cl]^+$ by nucleophilic attack of the sulfur atom which displaces the labile chloro ligand. These adducts can be

considered as models for Pt-cysteine protein binding and Pt-methionine protein binding. The Na(ddtc) ligand was capable of removing $Pt(dien)^{2+}$ from the Pt-methionine models within two minutes, but the Pt-cysteine adducts of glutathione were stable to attack by Na(ddtc), suggesting that reduction of nephrotoxicity by Na(ddtc) is due to removal of platinum from methionine type sulfurs only.[123]

1.4 AIMS OF THE PRESENT INVESTIGATION

Many naturally occurring compounds, for example, metallothioneins, strongly bind a variety of metal ions, especially divalent cadmium, mercury and zinc.[124, 125] Others, however, complex very selectively; for example, siderophores are very selective for iron(III).[126] Many of these naturally occurring chelators are expensive to synthesise and cannot be used commercially. Consequently, much work has been directed at developing synthetic models. One of the methods for modelling large and complex molecules, like enzymes, is to attach smaller coenzymes to a polymeric substrate, which will provide the correct dielectric environment and mimic the enzyme's compact structure.[127] Polystyrene fulfills most of the requirements of such a substrate and is a widely used support structure.[128] Earlier work[129] in our research group investigated the attachment of the styrene monomer, or a similar aromatic group, to amino acids and other amine containing ligands, as models for polystyrene-supported complexing agents.

In nature, the platinum group metals (pgm) usually occur together with silver, gold and the major base metals, iron, copper, nickel and cobalt.[130] Commercial considerations require the pgm to be separated from these other metals and from each other in high yield and high purity.[130] Traditionally, these separations have been achieved by precipitation and filtration,[131] but problems associated with these methods, such as coprecipitation, have led to their replacement by solvent extraction processes. These solvent extraction methods require the use of metal-specific ligands to permit the separation of the pgm from the base metals. Platinum-specific ligands are also used in chelation therapy for patients who have been receiving chemotherapy with platinum-based anti-cancer drugs.[52] The toxic effects resulting from platinum interactions with sulfur-containing peptides and proteins are often dose limiting.[106]

These observations have provided the context for this research, specific objectives of which

have included the following.

1. The development of aryl-containing amine and amino acid type ligands, as models for polymer-linked chelating agents.

2. The design and synthesis of a series of novel ligands, containing both sulfur and amide functions, which are expected to have good selectivity for platinum and palladium.

3. An evaluation of the metal specificity and complexation properties of these sulfur-amide ligands, with particular reference to:

    i) the solvent extraction of platinum and palladium from the base metals.

    ii) the complexation of platinum and cisplatin at neutral pH.

2 DISCUSSION

In the discussion which follows attention is given to factors influencing the design of :- amino-amide ligands (Section 2.1.1); tetraacetate systems (Section 2.1.2); and ligands which contain sulfur and amide functions (Sections 2.1.3 and 2.1.4). This is followed by an overview of the synthesis and characterisation of:- the amino-amide ligands (Sections 2.2.1); the tetraacetate ligands (Section2.2.2); and the sulfur-containing amide ligands (Sections 2.2.3 and 2.2.4). Spectroscopic features which help elucidate the conformations of the uncoordinated sulfur-amide ligands in organic solvents are considered in Section 2.3. Finally, the results of the solvent extraction studies and the complexation reactions of the ligands with platinum and palladium are discussed in Sections 2.4.2 and 2.4.3 respectively.

2.1 LIGAND DESIGN

Most of the ligands prepared in this study contain the secondary amide function in conjunction with nitrogen or sulfur donor atoms. The ligands were designed so that metal ions, which are capable of deprotonating and complexing with the amide nitrogen, will form chelate rings and, consequently, stable complexes. Examples of such metals are divalent platinum, palladium, copper, nickel, cobalt, cadmium and lead. Hard metals, including divalent copper, nickel and cobalt, are known to bond with the amide oxygen,[68, 69, 70] but such metal-oxygen bonds tend to be weaker than the metal-amide nitrogen bonds. Furthermore, should metals bind with the amide oxygen of certain ligands in this study, geometric constraints will prevent coordination with the other donor atoms of the ligand.

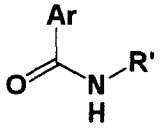
Although nitrogen and sulfur donors are capable of coordinating metals over a relatively wide pH range, the ability of metals to deprotonate and complex with the amide nitrogen is more

dependent on pH. The secondary amide function thus provides a form of pH control over chelation. For example, potentiometric titrations of divalent metal ion-dipeptide systems have revealed the following pH preferences for metal-peptide nitrogen coordination:- platinum(II), pH < 2.5;[132] palladium(II), pH 2.5 - 3.5;[133, 134] copper(II), pH 5 - 6[135, 136] and nickel(II), pH 8 - 9.[137, 138]

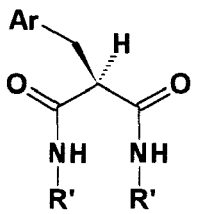
2.1.1 The design of amino-amide ligands

Since the development of Merrifield's solid phase peptide synthesis,[139] polymers have found increasing use as passive supports, the most widely-used being polystyrene.[128] Earlier attempts to attach the styrene monomer to various amino acid and amine ligands proved problematic as the styrene monomer readily polymerised during attachment to the ligand.[129] To overcome these problems the styrene vinyl group was replaced by a methyl group, the tolyl system being expected to model the effects of the polystyrene support on ligand complexation. As a continuation of this earlier study, we have investigated the attachment of aromatic substituents to various ligands, and have targeted systems such as **103** and **104** for synthesis (Figure 36), the R' group being an alkylamino chain of variable length.

Figure 36: The amide and amine containing ligands targeted for synthesis.



103



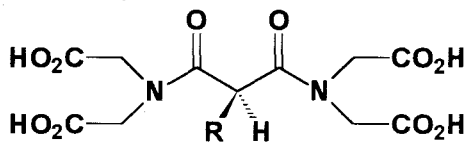
104

Previous studies have addressed the effect of *N*-alkylation on the complexing properties of diethylenetriamine,[140] triethylenetetramine[140] and ethylenediamine,[141, 142, 143, 144] and the influence of *C*-alkylation[144, 145] on the complexing properties of ethylenediamine. The methylene group of the propanediamide backbone in ligands of type **104** provides a useful point for attachment to a polymer or, as is the case in this study, an aromatic substituent. Interestingly, benzyl substituents in the 2-position of propanediamide ligands have been reported to stabilise the resulting metal complex.[46]

2.1.2 The design of tetraacetic acid analogues

In an earlier study,[129] use was made of iminodiacetic acid as a means of attaching a dicarboxylic acid system to an aromatic group. In the present investigation, this idea has been extended to the attachment of carboxylic acid groups to the propanediamide backbone which, in turn, can be linked to a polymer. Consequently, ligands of type **105** were targeted for synthesis (Figure 37).

Figure 37: The EDTA analogues synthesised in this study.



105

These ligands are somewhat analogous to the widely-used complexing agents, ethylene-diaminetetraacetic acid (EDTA) and trimethylenediaminetetraacetic acid (TMDTA), which form stable complexes with a wide range of metals and which have often been functionalised on their ethylene or trimethylene "spacers". However, amide analogues of type **105** do not appear to have been synthesised previously. In the metal complexes of EDTA and TMDTA, the amine

nitrogens coordinate with the metal ion but, in the amide derivatives **105**, it is expected that delocalisation of the amide nitrogen lone pair will considerably reduce or prevent nitrogen coordination. Thus, complexation should take place through the negatively charged carboxylate oxygens, resulting in increased specificity for hard metal ions such as iron(III).

2.1.3 The design of sulfur-containing monoamide ligands

Research has shown that ligands containing both sulfur and amide functions are specific for platinum and palladium.[49, 55] Basic conditions are required to synthesise platinum(II) and palladium(II) complexes of macrocycles **67** and **68** (p. 41), the high pH being necessary to assist deprotonation of the secondary amide. Macrocycles **67** and **68** are also capable of removing platinum from cisplatin;[49, 50] the first step in this process, involving displacement of the labile chloride ligands of cisplatin by the sulfur donors, is fast and quantitative. The second step, involving deprotonation and complexation with the amide nitrogens, is much slower and gradual rupture of the platinum-sulfur bonds occurs concurrently, resulting in reduced yields (*ca.* 40%) of the final complexes. Consequently, certain ligands targeted in this study contain only one amide function and up to three sulfur donors, which include thiol functions which bind platinum more strongly than thioethers. This strategy of replacing one of two amide functions in a chelating agent by a kinetically more reactive donor has also been used in the synthesis of technetium complexes, and resulted in significantly higher yields of the final complex.[104] These considerations were taken into account in designing the sulfur-containing monoamide ligands (**106**) targeted in this study, and the following design features (I-V) are summarised in Figure 38.

I) *ortho-N,S*-Disubstitution to permit 5-membered chelates.

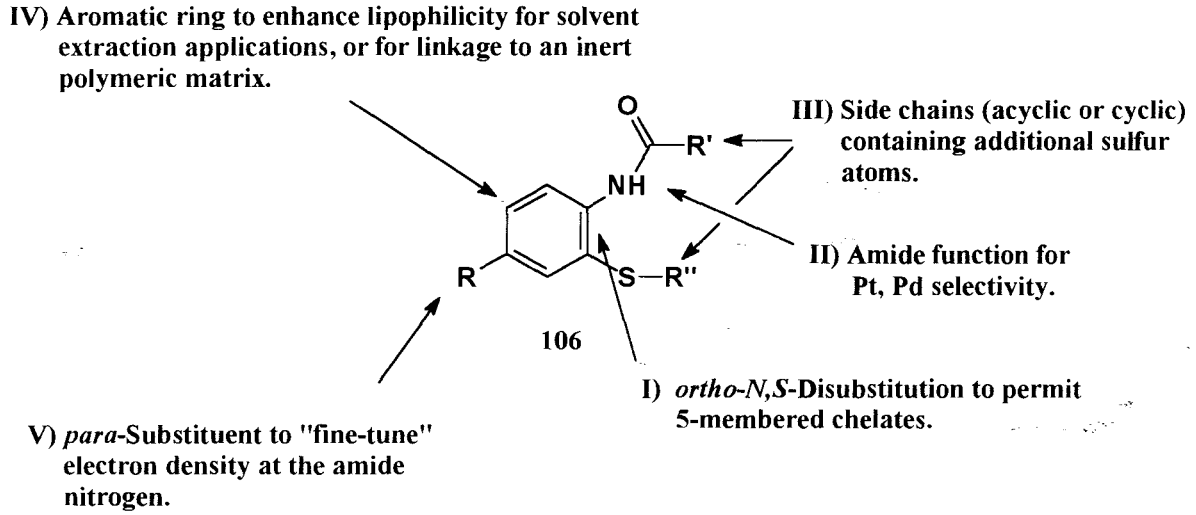
II) Amide function for Pt, Pd selectivity.

III) Side chains (acyclic or cyclic) containing additional sulfur atoms.

IV) Aromatic ring to enhance lipophilicity for solvent extraction applications, or for linkage to an inert polymeric matrix.

V) *para*-Substituent to "fine-tune" electron density at the amide nitrogen.

Figure 38: The design features of the novel, sulfur-containing monoamide ligands targeted in this study.

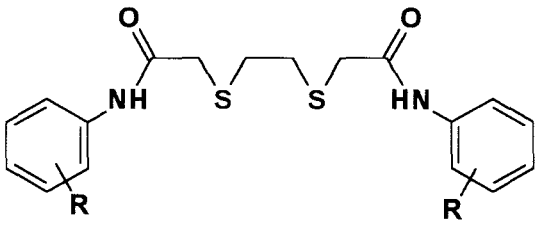


2.1.4 The design of sulfur-containing diamide ligands

Ligands which are used commercially as extractants for the solvent extraction of metal ions are required to be inexpensive and easy to synthesise, and must form organic-soluble metal complexes. In an attempt to fulfil these requirements, the novel diamide ligands **107** were developed (Figure 39). These ligands are readily synthesised, and coordination of the deprotonated amide nitrogens with divalent metals will result in neutral complexes. The aromatic groups are substituted so as to permit "tuning" of the pKa's of the secondary amide functions. Certain *ortho*-substituents are capable of hydrogen-bonding with the amide hydrogen,[146, 147, 148] and, consequently, a range of *ortho*-derivatised ligands of type **107** were

targeted to study the effect of such hydrogen-bonding on complexation.

Figure 39: The sulfur-containing diamide ligands targeted in this study.



107

2.2 LIGAND SYNTHESIS

While initial work was directed at the preparation of amino-amide ligands (Section 2.2.1) and tetraacetic acid derivatives (Section 2.2.2), the major focus has been the synthesis of sulfur-containing monoamide ligands (Section 2.2.3).

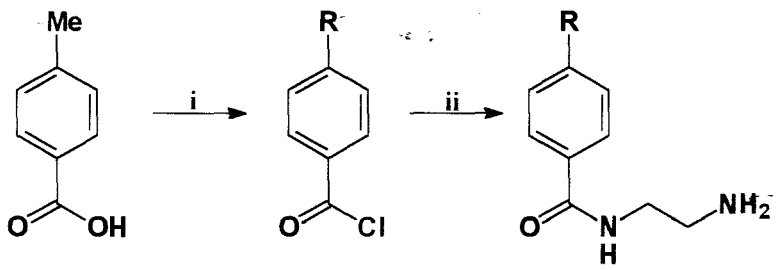
2.2.1 Ligands containing amine and amide functions

Research on these ligands constitutes an extension of earlier work[129] which was concerned with the attachment of ligands to a polymeric matrix. In the present study, as well as the earlier one,[129] *p*-toluoyl chloride, α-chloro-*p*-xylene, benzoyl chloride or benzyl chloride were used to mimic activated linking groups in, for example, a polystyrene matrix. The synthesis of these ligands, although superficially straight-forward, presented numerous difficulties.

2.2.1.1 Monobenzoylation of ethylenediamine

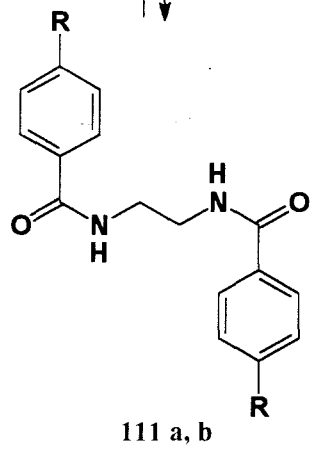
p-Toluoyl chloride **109b** was synthesised from *p*-toluic acid **108** using the method described by Nganie (Scheme 6),[149] but the acylation step (**109-110**) proved surprisingly difficult. When previously reported methods[129] were used for the synthesis of the benzamide derivatives **110a,b**, the main product, in each case, was a white, insoluble, crystalline derivative, which formed immediately upon addition of the acid chloride to ethylenediamine. In the case of the toluoyl system, the white precipitate has been reported to be the mono *N*-acylated product **110b**. However, titration of this product with acid and base revealed that it was a neutral compound, and the ^{1}H NMR spectrum showed it to be the diamide **111b**.

Scheme 6: The acylation of ethylenediamine.



108 **109 a, b** **110 a, b**

	R
a	H
b	Me



reagents
i) $SOCl_2$
ii) $NH_2CH_2CH_2NH_2$, Et_3N, $CHCl_3$

111 a, b

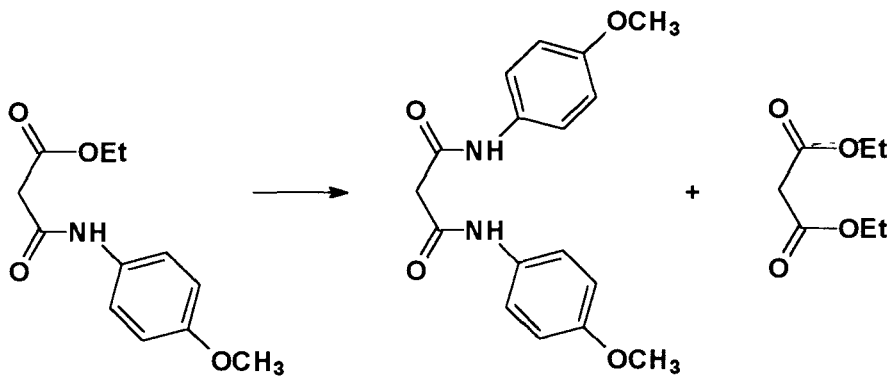
A literature search revealed that the problem of monobenzoylation of ethylenediamines dates back to 1938, when it was reported that treatment of ethylenediamine hydrochloride with benzoyl chloride, in the presence of sodium hydroxide, yielded dibenzoylethylenediamine (mp 245-6^{0}C) as the only product.[150] Monobenzoylethylenediamine has been synthesised by aminolysis of ethyl benzoate with ethylenediamine; this gives a 50% yield if the monobenzoylethylenediamine is extracted into toluene, whereas distillation results in dehydration to 2-phenylimidazoline.[151] This dehydration is reversible and monobenzoyl-ethylenediamine has been isolated as the picrate, following hydrolysis of 2-phenylimidazoline.[152] Two alternative syntheses for monobenzoylethylenediamine involve the hydrogenation of the corresponding nitrile with Raney nickel,[153] or treatment of cyanomethyl benzoate with

ethylenediamine.[154] Monobenzoylethylenediamine and mono(*p*-toluoyl)ethylenediamine have been obtained as liquids, and their hydrochloride salts as solids.[155, 156]

In this study, it was found that the reaction of ethylenediamine with benzoyl chloride is so rapid that, even with vigorous stirring, disubstitution is essentially complete before proper mixing of the benzoyl chloride takes place. The immediate formation of a white precipitate of the diamide was finally prevented by adding a dilute solution of benzoyl chloride dropwise to a solution containing an excess of ethylenediamine, which was at a higher concentration than the solution of acid chloride being added. However, when the reaction was allowed to stir for several hours, after addition of all the benzoyl chloride, the diamide precipitated in fair yield. The monoamide **110a** was separated from the diamide by extraction into aqueous hydrochloric acid, basification (pH > 11) with sodium hydroxide solution, and extraction into chloroform. Evaporation of the chloroform at low temperature gave the crude monoamide as a light green liquid, which was shown by titration with acid to be approximately 83% pure. Further purification was achieved by flash chromatography but, even though the difference in the R_F values of the diamide and monoamide is large, titration with acid showed this chromatographically purified product to be only 95% pure. The impurity was shown by TLC to be the diamide **111a** and it appears that the monoamide **110a** is readily equilibrated to the insoluble diamide **111a**.

Similar shifts in equilibrium for amides have been reported in the literature. Vacuum distillation of a mixture of excess ethyl benzoate and ethylenediamine gives the diamide quantitatively,[157] while vacuum distillation of monobenzoylethylenediamine affords a mixture of 2-phenylimidazoline and dibenzoylethylenediamine.[158, 159] Vacuum distillation of the monoamide **112** similarly affords the diamide **113** (Scheme 7), with loss of the more volatile diethyl malonate (Scheme 7).[160]

Scheme 7: Products formed during the vacuum distillation of a monoamide of diethyl malonate.[160]



112 113

Barrett *et al.*[161] have reported dramatic improvements in the monoacylation of diamines using "dynamic protection" with 18-crown-6 in the presence of a proton source (*p*-toluenesulfonic acid). Although their research was primarily concerned with selective acylation of a secondary amino function in the presence of primary amino functions, it was found, surprisingly, that selective monobenzoylation of ethylenediamine was also improved in the presence of 18-crown-6. Use of two equivalents of 18-crown-6 resulted in the formation of 76% monoamide and 3% diamide, while one equivalent of 18-crown-6 gave 56% monoamide and 17% diamide. In the absence of 18-crown-6 the yields were 8% and 27% for monoamide and diamide respectively. For ease of purification Barrett *et al.*[161] isolated the monoacylated products as their toluene-4-sulfonamides.

18-Crown-6 is known to complex with primary alkylammonium salts *via* three hydrogen bonds and pole-dipole interactions,[162] and selective complexation with primary alkylammonium salts explains the selective benzoylation of free secondary amines in the presence of primary amines. For primary diamines complexation of the crown ether with the primary amine salt of monobenzoylethylenediamine could inhibit equilibration to the diamide, giving the appearance

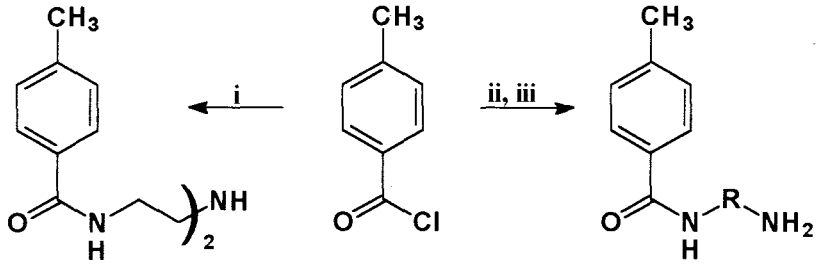
of selective complexation.

While it is clearly difficult to obtain free monobenzoylethylenediamine in high purity, good yields of reasonably pure monobenzoylethylenediamine were, in fact, obtained from benzoyl chloride and ethylenediamine by:- i) ensuring that the concentrations of the reactant solutions were correct; ii) working up soon after addition of the reactants; iii) keeping the temperature low during work-up; and iv) purifying by chromatography and not vacuum distillation.

2.2.1.2 Monobenzoylation of polyamines

Reaction of *p*-toluoyl chloride with an excess of diethylenetriamine (dien) in triethylamine (acting as solvent and base) gave, after work-up and flash chromatography, the diacylated product **116** as a colourless, brittle solid (Scheme 8). When the procedure was repeated in the absence of triethylamine the monoacylated product **114b** was obtained in low yield.

Scheme 8: The experimental conditions used for the acylation of dien and trien.



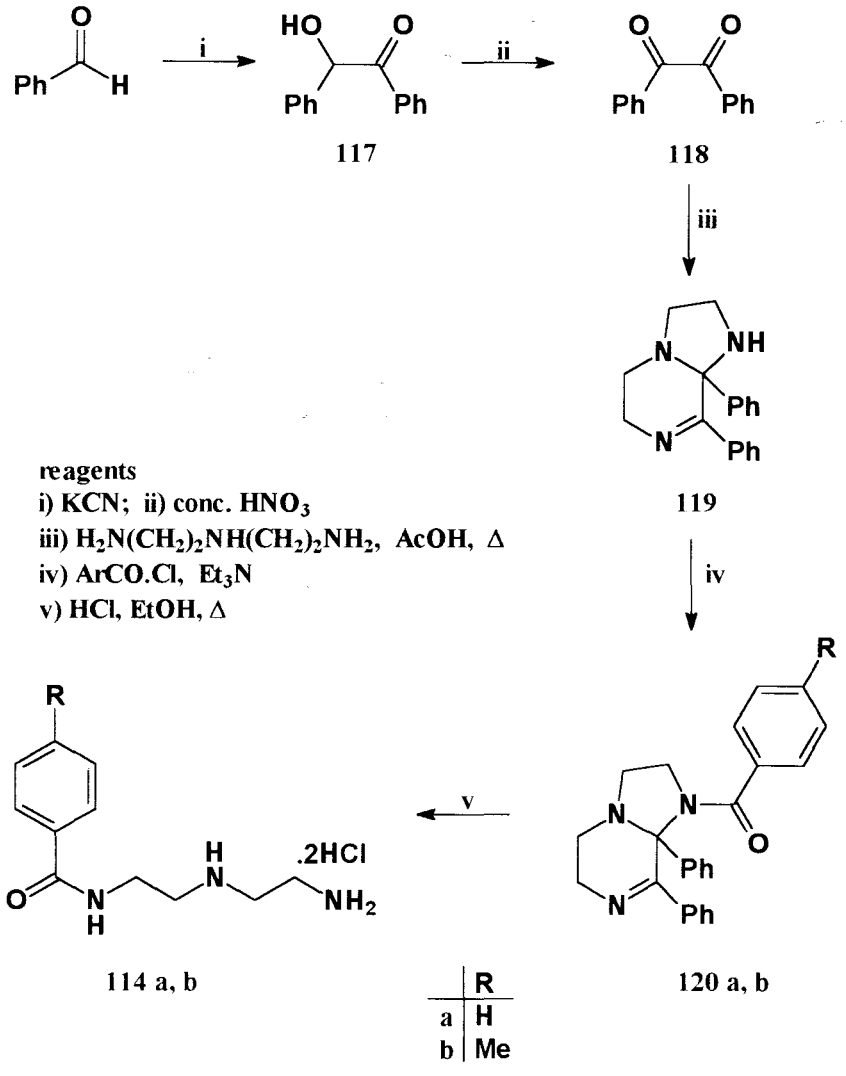
116 109 b

	R
114b	$(CH_2)_2NH(CH_2)_2$
115	$(CH_2)_2NH(CH_2)_2NH(CH_2)_2$

different experimental conditions
i) H_2NRNH_2, Et_3N
ii) H_2NRNH_2
iii) $H_2NRNH_2.(HNO_3)_2$ or $H_2NRNH_2.HCl$, Et_3N

The dien used in the initial reactions was purified by fractional distillation from sodium wire; an alternative method for purification involves formation of the hydrochloride salt (dien.HCl),[163] but reaction of this salt with *p*-toluoyl chloride, in the presence of triethylamine, failed to improve product yield or purity. The reaction of triethylenetetramine (trien) with *p*-toluoyl chloride resulted in the formation of complex mixtures, the components of which could not easily be separated. Use of the dinitric acid salt of trien (trien.2HNO_3)[163] resulted in a slower, cleaner reaction, but it was still not possible to obtain acylated derivative **115** as a pure compound.

Scheme 9: The fused piperazine route used for the synthesis of monoacylated dien.[167]



Chemoselective *N*-acylation of triamines has, in fact, been achieved,[164, 165, 166] but the methods used are known to effect *N,N'*-diacylation of the terminal primary amino groups. The fused piperazine route of Okawara[167] is, reportedly, the only known method for the effective preparation of selectively *N*-monoacylated triamines and, consequently, this synthetic route was investigated.

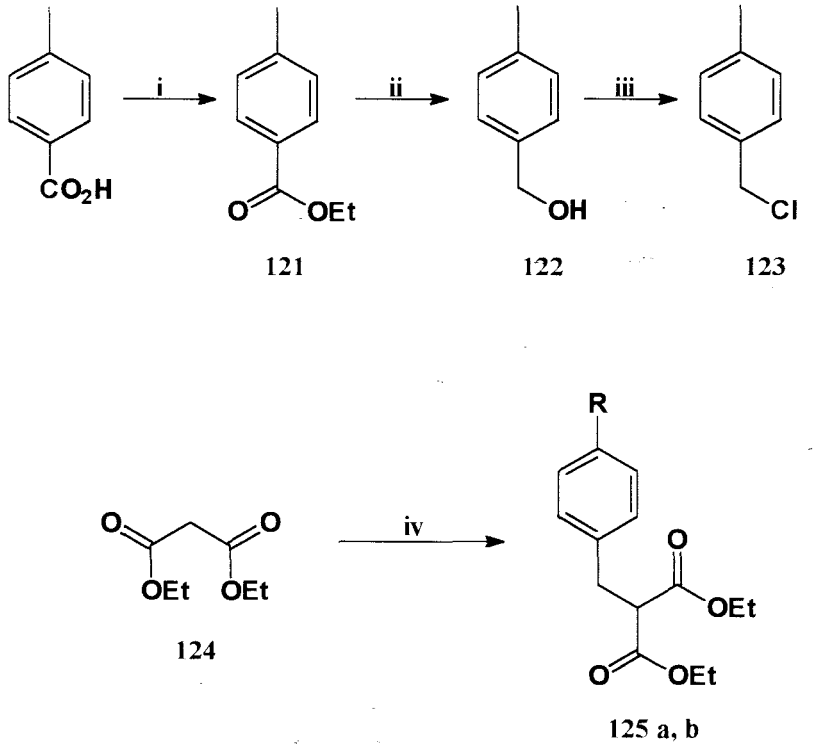
The synthesis involves the protection of two of the amino groups in dien by fusing dien with benzil **118** to give the fused piperazine derivative **119** (Scheme 9). Benzil was synthesised from benzoin **117**,[168a] which was obtained, in turn, from benzaldehyde using the Benzoin Condensation.[168b] The fused piperazine derivative **119** contains one secondary amino group, which was acylated with benzoyl chloride or *p*-toluoyl chloride, to give the amides **120a,b**. Heating the amides under reflux in a 1 **M**-hydrochloric acid-ethanol mixture yielded the terminal *N*-monoacylated triamines **114a,b** as the dihydrochloride salts. Heating for longer periods in dilute acid (0.1 **M**-HCl)-ethanol mixtures has been reported[169] to give the free amine, but gave low yields in our hands. Although this synthetic route gave moderate to good yields of intermediates **119** (91% yield) and **120** (59% yield for derivative **120a**), hydrolysis of the acylated pyrazines **120** could only be achieved in a maximum crude yield of 38%.

2.2.1.3 The synthesis of propanediamide-amine ligands

The approach followed for the synthesis of the propanediamide ligands **126**, **127** and **128** (Scheme 11, p. 78) was to attach the *p*-methylbenzyl or benzyl substituent to the malonate backbone prior to aminolysis (Scheme 10). Benzyl chloride was commercially available, while α-chloro-*p*-xylene **123** was synthesised from *p*-toluic acid. The sodio-malonic ester was obtained from diethyl malonate **124** using sodium ethoxide, and nucleophilic attack of this carbanion on benzyl chloride or α-chloro-*p*-xylene yielded the 2-substituted diethyl malonate

derivatives **125a,b**. Although equimolar quantities of reagents were used, significant amounts of the 2,2-disubstituted malonate derivatives were also produced. However, vacuum distillation with a fractionating column permitted efficient separation of the required products.

Scheme 10: Functionalisation of the malonate backbone.



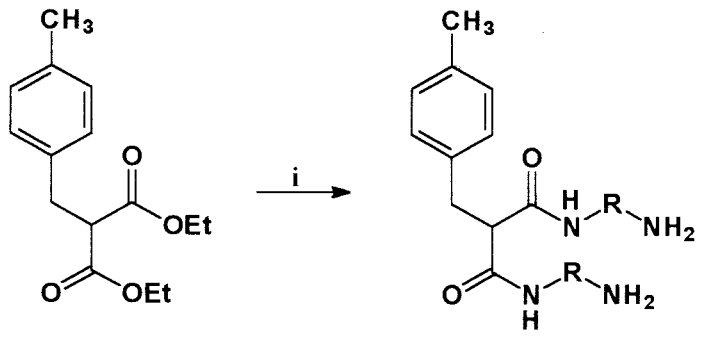
reagents
i) EtOH, H^+; ii) $LiAlH_4$
iii) $SOCl_2$
iv) NaOEt, $PhCH_2Cl$ or compd. 123

	R
a	H
b	Me

The first attempts at synthesising the "double strand" polyamines **126c**, **127** and **128** involved aminolysis of the malonate ester **125b** (Scheme 11). Heating the malonate ester **125b** with an excess of ethylenediamine for 12 hours afforded mainly the starting ester, but use of an autoclave permitted higher temperatures (160-200 °C) to be achieved and resulted in higher yields of the diamides. Work-up and purification were problematic in that the polyamines are

water soluble and too high-boiling for vacuum distillation. Preparative gas chromatography was attempted but resulted in charring of the products. Unreacted ester and excess polyamine were removed from the product mixture by vacuum distillation, but this resulted in substantial thickening of the product mixture. HPLC showed this remaining viscous residue to contain several components. Removal of the starting materials in this manner probably results in the formation of polyamides and this would account for the thickening of the product mixtures. Trituration of the product mixture with hexane was shown by preparative gas chromatography to effectively remove all the unreacted malonate ester.

Scheme 11: Aminolysis of the substituted malonate ester.



125 b

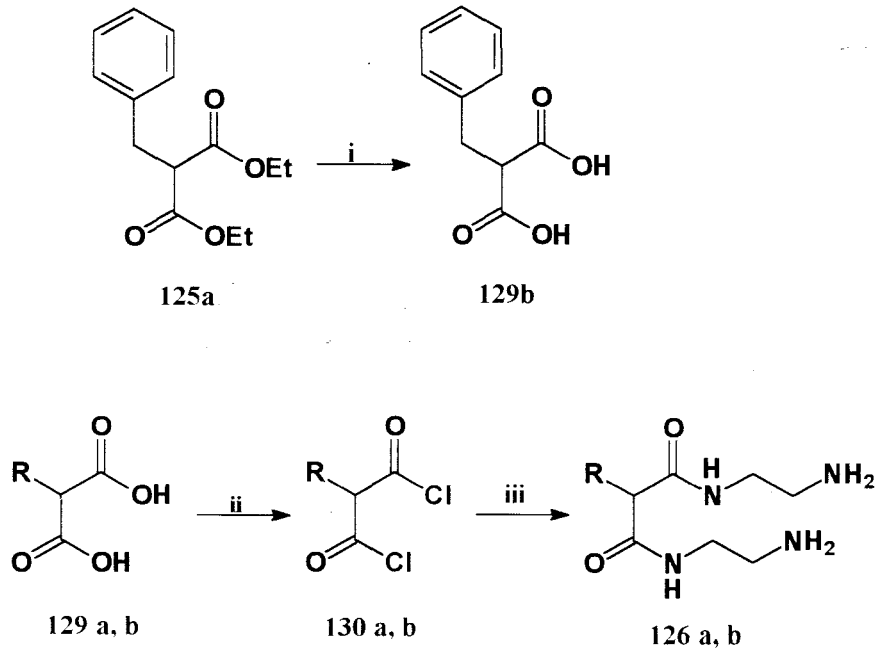
	R
126c	$(CH_2)_2$
127	$(CH_2)_2NH(CH_2)_2$
128	$(CH_2)_2NH(CH_2)_2NH(CH_2)_2$

reagents
i) H_2NRNH_2, Δ

The problems associated with the aminolysis of esters prompted the use of the more reactive acid chlorides (Scheme 12). 2-Benzylmalonic acid **129b** was obtained by alkaline hydrolysis of the ester derivative (acidic hydrolysis may cause decarboxylation of malonic acid systems),[168c] and then converted to 2-benzylmalonyl dichloride **130b** using thionyl chloride.[170] The malonyl dichloride was reacted with ethylenediamine in a number of different ways. The reported method[129] of adding ethylenediamine to malonyl dichloride and then partitioning the products

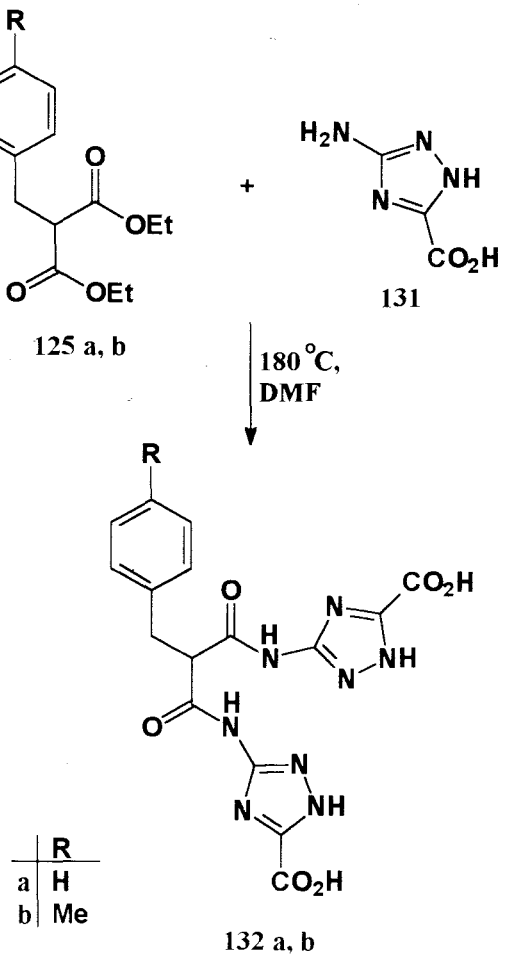
between aqueous and organic phases was not successful; the product could not be extracted from the aqueous phase and the order of addition of reactants would seem to encourage polymerisation. Inverse addition of the dichloride **130b** to a solution containing excess ethylenediamine also resulted in the formation of several products, although flash chromatography of this product mixture, using a polar eluent (MeOH-$CHCl_3$), yielded small amounts of the required diamide **126b**. The use of protected ethylenediamines was also investigated. Mono-*N*-tosylated ethylenediamine[169] was reacted with malonyl dichloride and the protecting groups were removed with hydrobromic acid; workup and purification, however, proved difficult.

Scheme 12: Synthesis of propanediamides using the reactive acid chloride route.



The most successful method for obtaining the diamide derivatives **126a,b** was eventually found to be mild aminolysis of the corresponding esters. The malonate ester was mixed with a large excess of ethylenediamine and allowed to stand at room temperature for a few days, during which time white crystals of product formed in the reaction mixture. Earlier researchers had used this method for the synthesis of the malonyl derivative **126a**,[37] and it was expected, initially, that the deactivating and steric effects of the benzyl group would preclude this method for the synthesis of the analogue **126b**. Subsequent to our preparation of this ligand, its synthesis (using a similar mild aminolysis procedure) was reported for the first time.[38b]

Scheme 13: Proposed products from the aminolysis of substituted malonate esters with an amino triazole.



Aminolysis of the 2-substituted diethyl malonate compounds **125** with 3-amino-1,2,4- triazole-5-carboxylic acid **131** in an autoclave at 180 °C yielded pure crystalline products (Scheme 13). The purity of the products was verified by HPLC, and infrared spectroscopy indicated the presence of amide carbonyl groups; however, the NMR and mass spectrometric data did not provide unequivocal confirmation of the structures **132a,b**.

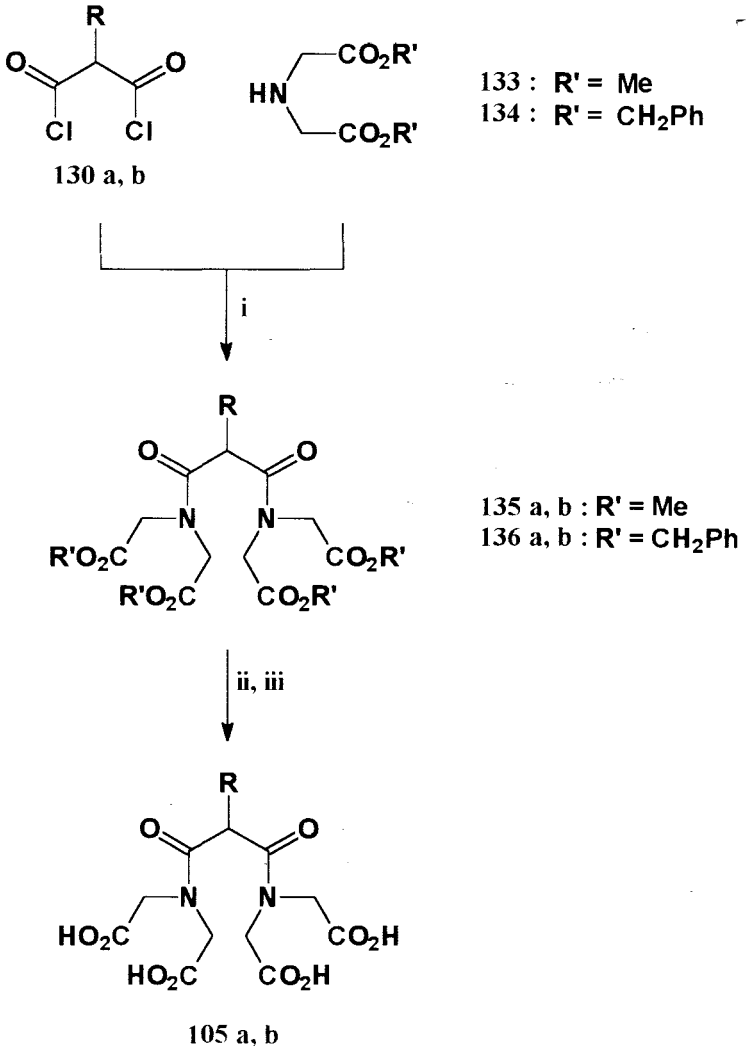
2.2.2 Tetraacetic acid derivatives

These ligands are also based on the propanediamide backbone, and the synthesis of the parent ligand **105a** and its 2-benzyl substituted derivative **105b** is outlined in Scheme 14. Initially, diethyl 2-benzylmalonate ester **125a** was treated directly with iminodiacetic acid (IDA) at 150 °C, but this proved unsuccessful and the acid chloride route was explored. Treatment of malonyl dichloride **130a**, synthesised from malonic acid,[170] or 2-benzylmalonyl dichloride **130b** with IDA (in the latter case with heating in both THF and in pyridine) was also unsuccessful. The failure of these reactions was attributed to the zwitterionic character of IDA, which reduces both the nucleophilicity of the amino group and the solubility of the compound in organic solvents, resulting in heterogeneous reaction mixtures.

In recent synthetic studies[171, 172] it has been noted that protection of the carboxyl groups in amino acids is advantageous, since it removes the problems associated with zwitterions and allows conventional chromatographic purification of the ligand prior to final deprotection. The carboxyl protecting groups must be chosen to ensure that deprotection does not introduce intractable impurities. In the present studies, the methyl ester function was initially chosen as a carboxyl protecting group, and dimethyl iminodiacetate **133** was prepared by refluxing IDA in methanol in the presence of thionyl chloride (Scheme 15, p. 85).[173] Depending on the work-up, either the hydrogen chloride salt of the dimethyl ester (white crystals) or the free amino

compound (clear liquid) was obtained.

Scheme 14: Synthesis of the tetraesters, and their subsequent hydrolysis to the tetracarboxylic acids.



reagents
i) Et_3N, THF or pyridine
ii) NaOH, H_2O, THF
iii) H^+

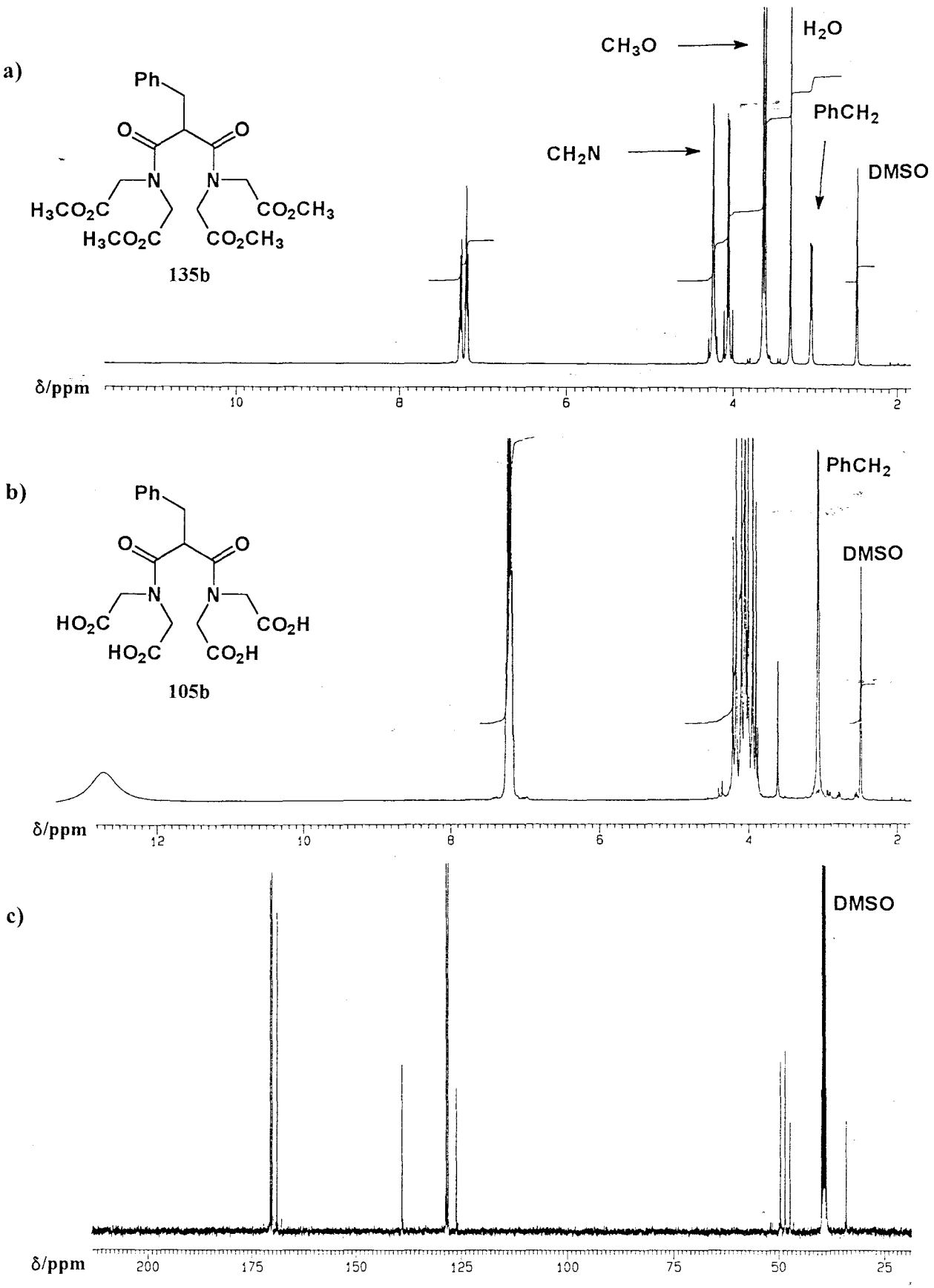
	R
a	H
b	CH_2Ph

Reaction of the hydrogen chloride salt of the diester **133** with the malonyl dichlorides **130a,b** (Scheme 14), in pyridine or in THF (containing triethylamine), gave low yields of the methyl esters **135**, whereas reaction of the free amine **133**, under similar conditions, gave reasonable yields of the tetramethyl esters **135a,b**.

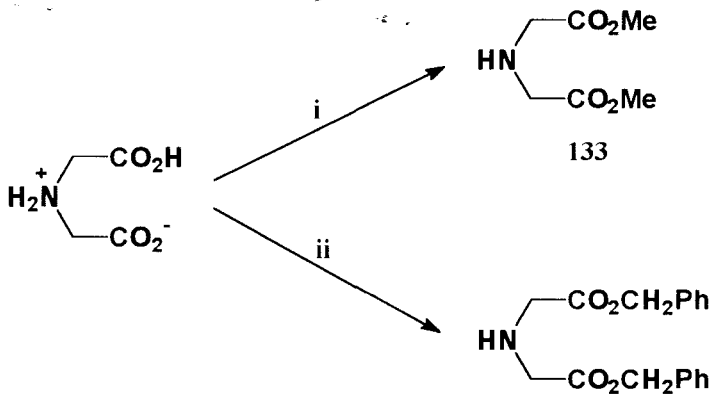
Acid-catalysed hydrolysis of the esters **135a,b** to the corresponding acids **105a,b** using hydrochloric acid seemed the simplest approach, as the hydrogen chloride can easily be removed under vacuum. Hydrochloric acid-dioxane mixtures were consequently used to ensure homogeneity of the reaction mixture but, under these conditions, total deprotection was difficult to achieve without concomitant hydrolysis of the amide functions. Several hydrolyses were attempted in which acid strength, heating times and temperatures, and dioxane content were varied; all resulted in partial hydrolysis of the amide functions. The best results were finally obtained by base-catalysed hydrolysis using an aqueous sodium hydroxide-THF mixture, followed by acidification (with HCl) and, then, ion exchange.

The ^{1}H NMR spectra of the tetramethyl ester **135b** and its base-catalysed hydrolysis product **105b** are shown in Figure 40. The absence of a MeO doublet at *ca.* 3.6 ppm in the spectrum of the tetraacid **105b** (Figure 40b) indicates complete hydrolysis of the ester functions. The small singlet at *ca.* 3.6 ppm has been tentatively assigned to the methylene protons of IDA, assuming a small amount of amide hydrolysis. The ^{13}C NMR spectrum of the tetraacid **105b** (Figure 40c), shows it to be reasonably pure; the doubling of the acid carbonyl signals (at 170.1 and 170.5 ppm) and the methylene signals (at 48.6 and 49.7 ppm) is attributed to hindered rotation around the amide N-C(O) bond as discussed below.

Figure 40: a) ^{1}H NMR spectrum of the tetramethyl ester 135b in DMSO-d_6.
b) ^{1}H - and c) ^{13}C NMR spectra of the tetraacid 105b in DMSO-d_6.



Scheme 15: The synthesis of dimethyl and dibenzyl esters of IDA.

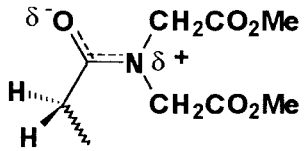


To overcome the problems associated with the hydrolysis of methyl esters, the synthesis of more readily hydrolysable esters was undertaken; such esters include phenyl,[174] *t*-butyl and benzyl esters.[172] Phenyl esters are easily cleaved with hydrogen peroxide,[174] but attempts to synthesise the diphenyl ester of IDA were unsuccessful. Synthesis of the *t*-butyl ester of IDA was also problematic. However, dibenzyl iminodiacetate **134**, a compound which does not appear to have been reported in the literature, was readily synthesised in high yield by refluxing IDA with benzyl alcohol and *p*-toluenesulfonic acid in benzene (Scheme 15).[172] Reaction of dibenzyl iminodiacetate **134** with the malonyl dichlorides **130a,b** yielded the tetrabenzyl esters **136a,b** (Scheme 14). Unfortunately acid-catalysed hydrolysis of these tetrabenzyl esters was also accompanied by cleavage of the amide functions.

Literature[175] on the stability of protecting groups indicates that benzyl esters are more stable than methyl esters at low pH, while the reverse is true at high pH. Amide functions, although generally more stable in basic than acidic media, are also susceptible to hydrolysis at a pH greater than 12.[175] The hydrolysis of the tetrabenzyl esters was therefore attempted in the

presence of excess sodium hydroxide, in solutions which were sufficiently dilute to ensure that the pH was less than 12. Under these conditions, the tetrabenzyl esters **136a,b** were readily hydrolysed at room temperature. Evaporation of the acidified aqueous phase, either under vacuum or by freeze drying, was, however, accompanied by considerable darkening of the products. Flash chromatography did not improve the appearance of these products. The benzyl substituted derivative **105b** was less prone to decomposition than the parent system **105a**, and was shown by ^{1}H and ^{13}C NMR spectroscopy to be the desired product. The spectra of acid **105b**, obtained by the hydrolysis of the benzyl ester, were the same as those shown in Figure 40, except that the ^{1}H NMR spectrum did not show a singlet at 3.6 ppm.

Figure 41: Partial structure of the tetramethyl ester 135a indicating the delocalisation responsible for hindered rotation about the N-(CO) bonds.

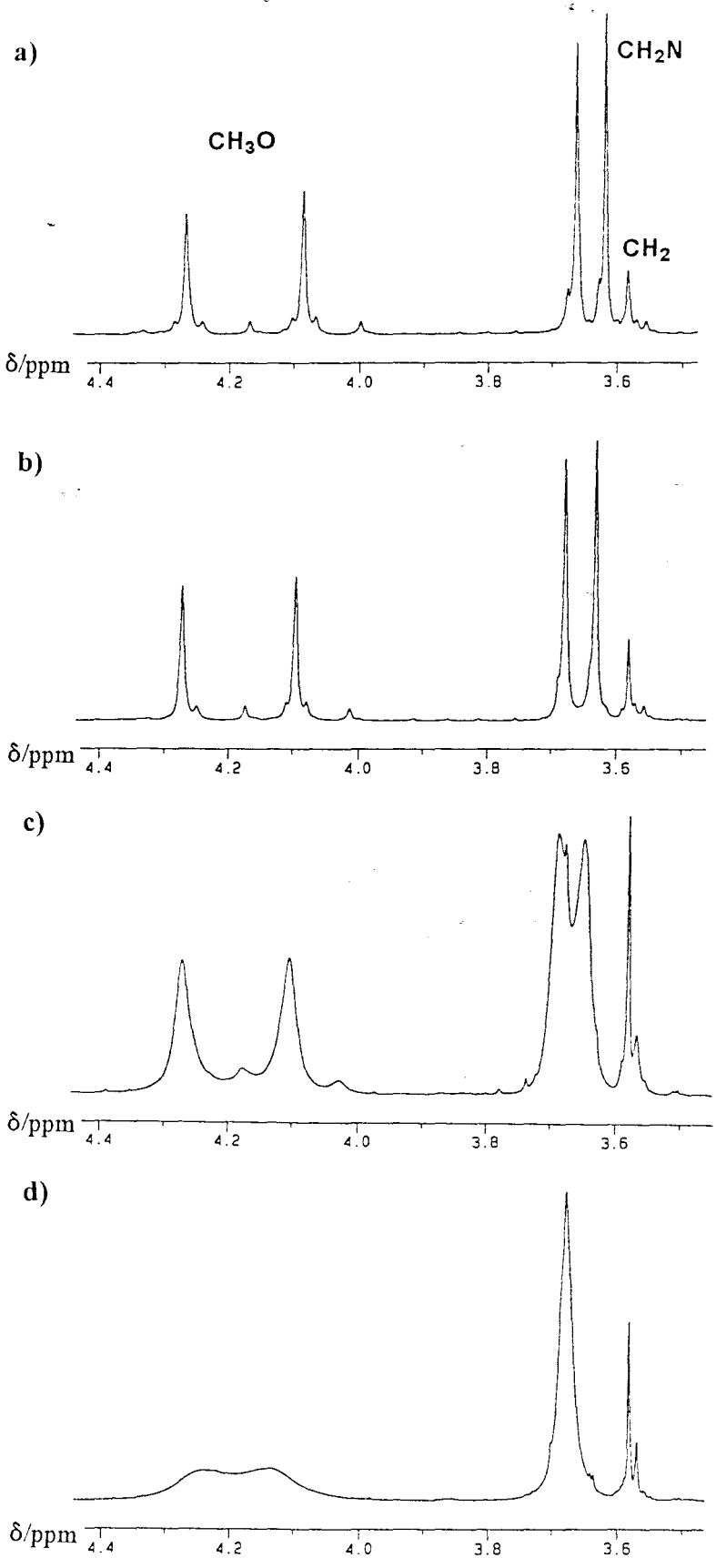


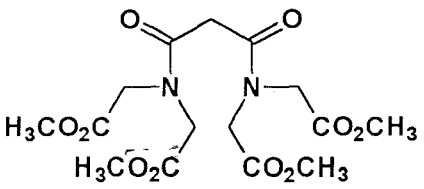
The ^{1}H and ^{13}C NMR spectra of the methyl esters **135a,b**, the benzyl esters **136a,b** and the carboxylic acid **105b** all show doubling of signals, which is attributed to hindered rotation around the amide N-(CO) bond (Figure 41). To confirm that these "extra signals", particularly the three carbonyl signals, were not the result of impurities, a variable temperature NMR study of the methyl ester **135a** in DMSO-d_6 was performed. The ^{1}H and ^{13}C NMR spectra from these studies are shown in Figures 42 and 43 respectively. The observed coalescence or partial coalescence of the *N*-methylene and methoxy ^{1}H NMR signals, respectively, confirm the presence of rotational isomers. Coalescence of the two downfield ^{13}C carbonyl signals permits assignment of the upfield carbonyl signal, in most cases, to the amide carbonyl carbon; in the case of the tetrabenzyl ester **136b**, however, the shifts appear to be reversed. The doubling of

other ^{13}C signals is similarly attributed to rotational isomerism.

The methyl ester **135a** was chosen for variable temperature studies because its ^{1}H NMR spectrum shows the expected doubling of the methoxy and *N*-methylene signals. As can be seen from the ^{1}H NMR spectrum of the 2-benzyl substituted analogue (Figure 40a), introduction of the benzyl substituent results in further splitting of these methylene signals. This effect is also seen in the ^{1}H NMR spectrum of the benzyl ester **136b**.

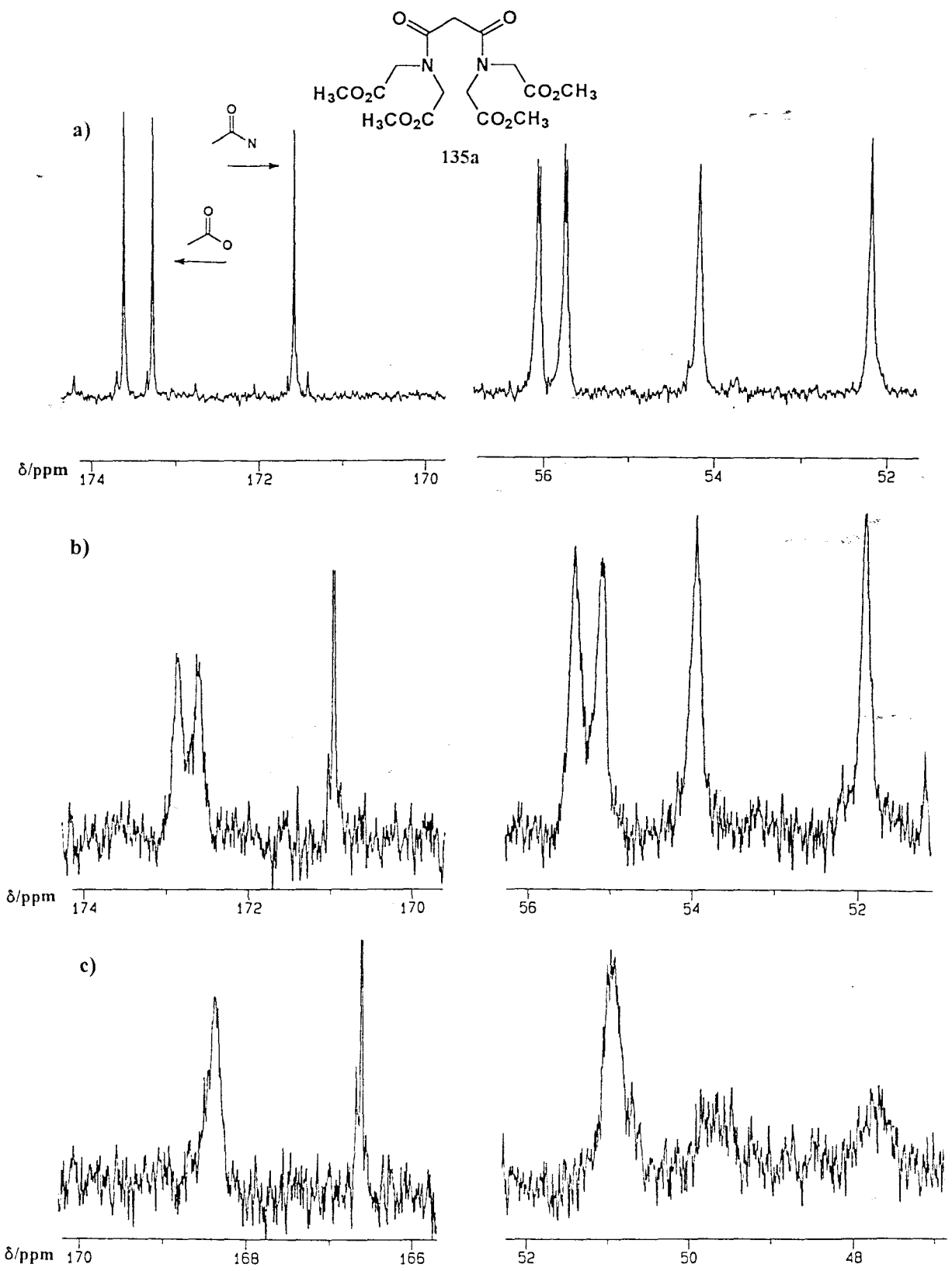
Figure 42: Partial 400 MHz ^{1}H NMR spectra of the tetramethyl ester 135a in DMSO-d_6 at a) 303K, b) 333K, c) 363K and d) 383K.





135a

Figure 43: Partial ^{13}C NMR spectra of the tetramethyl ester 135a in DMSO-d_6 at a) 303K, b) 363K and c) 383K.



2.2.3 The synthesis of sulfur-containing monoamide ligands

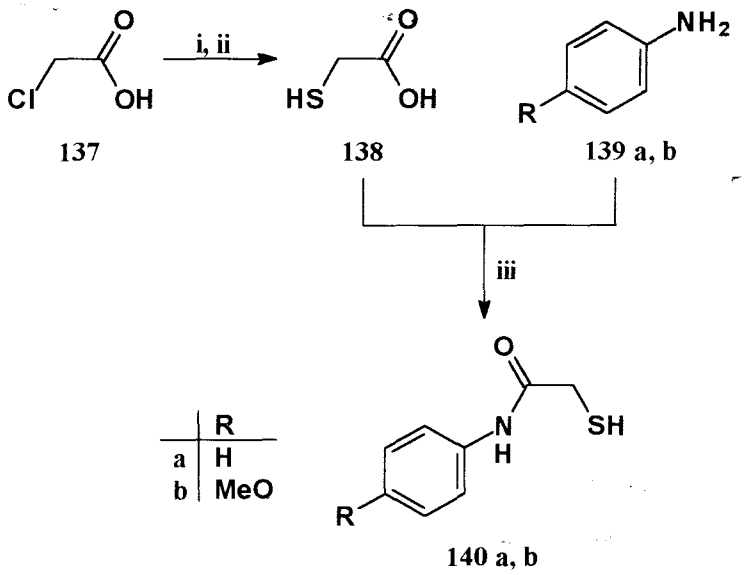
In this study, the synthetic efforts were focussed largely on obtaining a series of sulfur-containing monoamide ligands, which incorporate the design features established in section 2.1.3 (p. 67).

2.2.3.1 The synthesis of mercaptoacetanilides

Mercaptoacetic acid **138**, an important synthetic intermediate in the synthesis of mercaptoacetanilides, was initially synthesised from α-chloroacetic acid **137** and thiourea (Scheme 16)[176] *via* a thiuronium salt which was hydrolysed to the free mercaptan **138** with sodium hydroxide. This indirect method of thiol formation has the advantage of preventing formation of monosulfides.[177] Mercaptoacetic acid **138** was subsequently obtained from a commercial source.

The mercaptoacetanilides **140a,b** were synthesised by the method of Misra and Sircar,[54] which requires heating an equimolar mixture of mercaptoacetic **138** and aniline or *p*-methoxyaniline in a stream of dry nitrogen (Scheme 16). The stream of dry nitrogen removes the water that is formed and prevents oxidation of the mercapto function to the disulfide, a problem which is encountered when the carbamyl route is used for the synthesis of these compounds.[58] Loss of reactants in the stream of dry nitrogen can result in reduced yields of mercaptoacetanilide, but this difficulty can be minimised by keeping the temperature of the melt between 100 and 110 ^{0}C, and by ensuring that the nitrogen flow is not too rapid. In the event, this method resulted in good yields of the mercaptoacetanilides **140a,b** which were purified by recrystallisation from ethanol-water mixtures.

Scheme 16: The synthesis of mercaptoacetanilides.

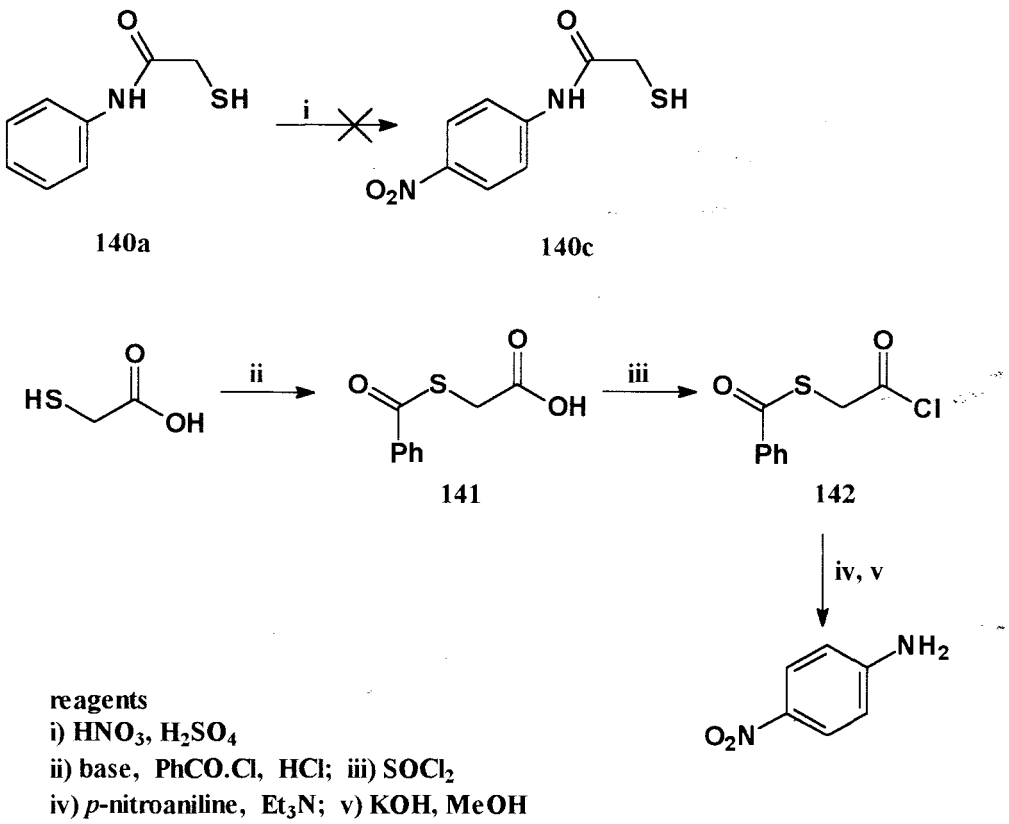


Extended heating of a melt containing *p*-nitroaniline and mercaptoacetic acid failed to produce the required *p*-nitromercaptoacetanilide, and a number of alternative routes were investigated for the synthesis of this compound. These are shown in Scheme 17. Nitration of the parent mercaptoacetanilide **140a** using the classical nitration reagents, concentrated sulfuric acid and concentrated nitric acid,[168d] produced a yellow precipitate. Flash chromatography of this precipitate yielded starting material (25%) and a uv-active component which, unlike the expected product, failed to move on silica.[168d]

A second approach to the synthesis of *p*-nitromercaptoacetanilide involved reacting *p*-nitroaniline with the benzoyl-protected acid chloride **142**. This acid chloride was synthesised by reacting benzoyl chloride with mercaptoacetic acid, following the method of Zervas *et al.*[178] The resulting benzoyl-protected carboxylic acid **141** was treated with thionyl chloride to give the acid chloride **142**, which was reacted with *p*-nitroaniline under anhydrous conditions using

triethylamine as a base. From TLC it was apparent that most, but not all, of the *p*-nitroaniline had been consumed in the reaction. Cleavage of the thiol ester with methanolic potassium hydroxide was unfortunately accompanied by hydrolysis of the amide function and, due to time constraints, this reaction was not repeated.

Scheme 17: Attempted syntheses of *p*-nitromercaptoacetanilide.



reagents
i) HNO_3, H_2SO_4
ii) base, PhCO.Cl, HCl; iii) $SOCl_2$
iv) *p*-nitroaniline, Et_3N; v) KOH, MeOH

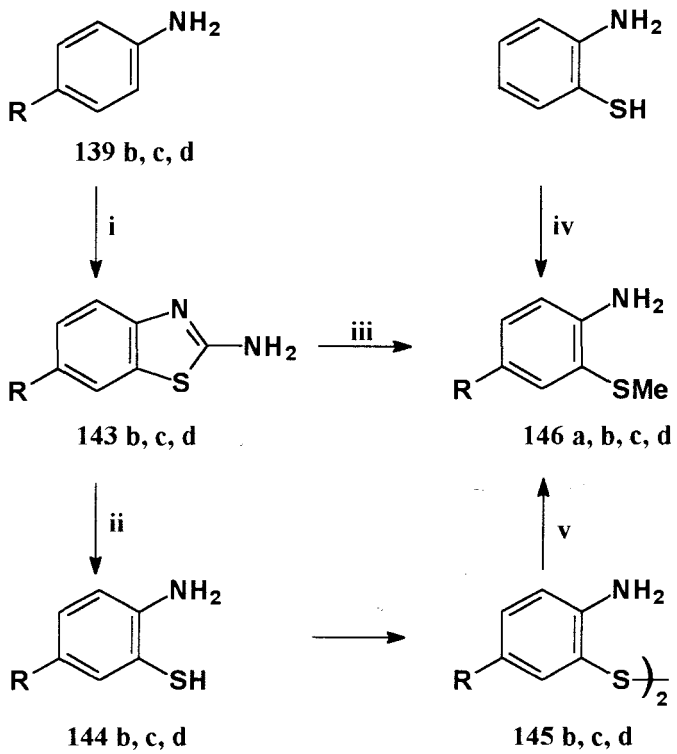
2.2.3.2 Synthesis of methyl sulfide ligands

The natural starting point for the synthesis of the sulfur-containing amide ligands based on structure **106** (p. 68) is the *ortho*-aminothiophenol backbone, onto which the side arms of the ligands can be added at a later stage. Introduction of the functional group *para* to the amide could take place after the parent ligands **106** (R = H) have been synthesised, provided that this

does not interfere with the other functional groups on the ligand and that the aromatic amide is sufficiently *para*-directing. After considering these factors, it seemed expedient to have the *para*-substituent in place early in the synthesis and, in the event, the synthetic procedure chosen for introducing the sulfur onto the benzene ring required a substituent *para* to the amino group. The synthesis of ligands of type **106** also requires the introduction of sulfur *ortho* to the aromatic amino group. *o*-Aminobenzenethiol was commercially available and was used as the starting point for the synthesis of the parent ligands. For the *para*-substituted derivatives, techniques for introducing sulfur *ortho* to the amino group of a *para*-substituted aniline were investigated.

Most of the methods reported for the preparation of the required 5-substituted-2-aminobenzenethiols involve the formation of an intermediate zinc mercaptide.[179, 180, 181] Decomposition of the zinc salt to afford the free mercaptan, however, requires prolonged boiling and extensive loss of the product results. In the Herz reaction,[182] a *para*-substituted aniline is condensed with sulfur chloride to form the Herz compound (a thiazathiolium chloride), which is cleaved with base to give the aromatic mercaptide. A second option involves the synthesis of benzothiazoles from the appropriate aniline; cleavage of the benzothiazole then yields the desired *ortho*-aminobenzenethiols. While benzothiazoles can be cleaved by various methods,[183, 184, 185] not all of them are suitable for 2-aminobenzothiazoles. A third general method for the introduction of an *ortho*-sulfur group, *ortho*-lithiation, was considered.[186, 187] This involves abstraction, with a strong base (BuLi), of the hydrogen *ortho* to the protected amino function; however, the *ortho*-directing methoxy group may lead to a number of regio-isomers forming and consequently this method was not considered further.[187] The synthetic route finally chosen for the introduction of sulfur *ortho* to the aromatic amino group was thiocyanation. This involves formation of a 6-substituted-2-amino-benzothiazole,[188, 189, 190] followed by hydrolytic cleavage to give the 5-substituted-2-aminobenzenethiols.[183, 191]

Scheme 18: Thiocyanation route to *ortho*-thio-substituted anilines.



reagents
i) NaNCS or NH_4NCS, Br_2, AcOH;
ii) KOH , AcOH;
iii) KOH, Δ , MeI ; iv) KOH, MeI ;
v) Ph_3P, MeI.

	R
a	H
b	MeO
c	Cl
d	Me

The initial thiocyanation reactions were performed using *p*-chloro- and *p*-methylaniline. In a typical reaction, the *para*-substituted aniline **139** (Scheme 18) and ammonium thiocyanate are dissolved in acetic acid and bromine, in acetic acid, is added to the cooled solution. The bromine oxidises the thiocyanate to thiocyanogen, which behaves as a pseudohalogen, and attaches to the benzene ring in the free *ortho*-position; this monothiocyanato-substituted

compound then cyclises to the 6-substituted-2-aminobenzothiazole **143**.† Thiocyanogen is extremely sensitive towards hydrolysis and is preferably produced *in situ* at low temperatures (*ca.* <10°C). The solvent used, acetic acid, freezes at these low temperatures forming a slurry which requires mechanical stirring. It was found, however, that addition of water or chloroform [5% (v/v)] lowered the freezing point, and made the cold slurry easier to handle.

Unfortunately, the above mentioned thiocyanation procedure afforded very little product with *p*-methoxyaniline. Repeating the reaction at lower temperatures in methanol saturated with sodium bromide (which provided more homogeneous reaction conditions at low temperature) failed to improve the yield of the methoxy-substituted benzothiazole **143b**. When copper(II) chloride was used as the oxidising agent (in place of bromine),[189] higher temperatures were required and a thick black oil formed. Acceptable yields of the 6-methoxy derivative **143b** were finally obtained when the reaction was performed as a two-pot synthesis; the thiocyanogen was generated separately, using bromine and an excess of sodium thiocyanate, and then added to the solution of *p*-methoxyaniline. This suggests that, in the one-pot synthesis, significant bromination of the highly activated methoxyaniline ring was occurring, while failure of the reaction in methanol could reflect the absence of an acidic medium, which aids cyclisation of the thiocyanato substituted intermediate to the benzothiazole.

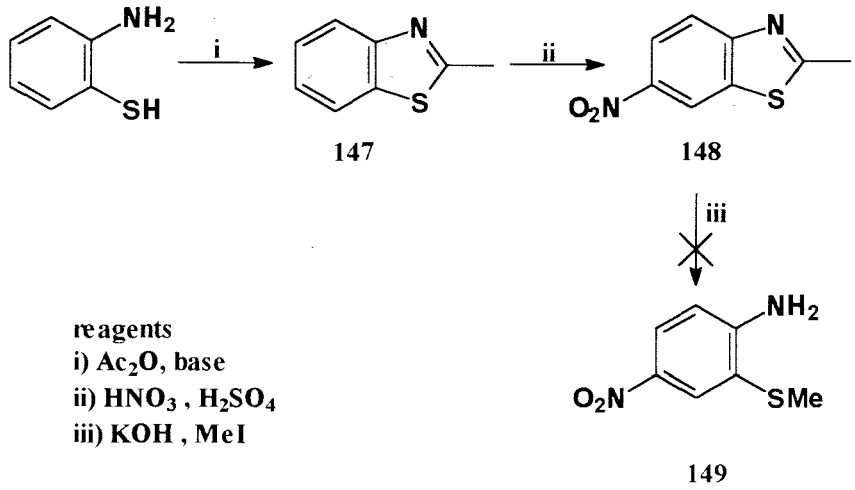
Base-catalysed hydrolysis of the benzothiazoles[183] **143** afforded the free mercaptans **144** together with significant amounts of the corresponding disulfide **145**. Although the 5-substituted-2-aminobenzenethiols **144** were not originally targeted, very few pKa studies have been done on 2-aminobenzenethiol systems. Moreover, as such studies would shed light on the effect of the substituent *para* to the amino group, attempts were made to obtain pure samples

† This reaction proceeds rapidly and, in most cases, ring substitution by bromine is negligible.

for pK_a determinations. However, various measures, such as conducting the reaction under nitrogen, keeping the temperature below 0 °C during acidification and recrystallising from absolute ethanol, in darkness, under nitrogen and/or in the presence of activated charcoal, all failed to produce samples which were free of disulfide.

Owing to the ease of oxidation of the aromatic mercapto group, it was decided to synthesise the methyl sulfides **146b,c** directly from the potassium mercaptide intermediate formed by base-catalysed hydrolysis of the benzothiazole precursors. The potassium mercaptides were, in fact, not isolated, but methyl iodide was added directly to the alkaline solution following hydrolysis. The parent system **146a** (R = H) was synthesised by adding one equivalent of base (KOH) to 2-aminobenzenethiol, followed by methyl iodide.[192, 193] Reduction of the disulfide **145d** using Ph_3P followed by addition of methyl iodide afforded the methyl sulfide **146d**. These syntheses afforded the methyl sulfides **146** in moderate to good yields.

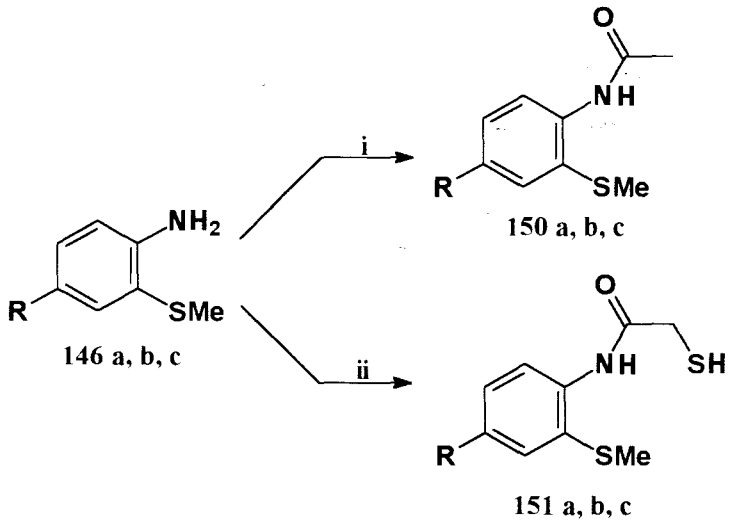
Scheme 19: Attempted approach to the nitro derivatives.



Attempts to effect thiocyanation of *p*-nitroaniline were unsuccessful, the reaction yielding the starting *p*-nitroaniline each time. To overcome this problem the synthetic strategy shown in Scheme 19 was explored. 2-Methylbenzothiazole **147** was obtained by acetylating

o-aminobenzenethiol in the presence of a weak base (*N,N*-dimethylaniline).[194] As expected,[195, 196] nitration of this benzothiazole yielded *ca.* 50% of the 6-nitro isomer **148**, with other isomers being formed in low yield. The 6-nitro product was separated from the other, less soluble, isomers by recrystallisation from ethanol but, unfortunately, cleavage of 6-nitrobenzothiazole **148** yielded a water-soluble, black residue which proved difficult to identify.

Scheme 20: Formation of the methyl sulfide ligands.



reagents
i) Ac_2O
ii) $HSCH_2CO_2H$, Δ, N_2

	R
a	H
b	MeO
c	Cl

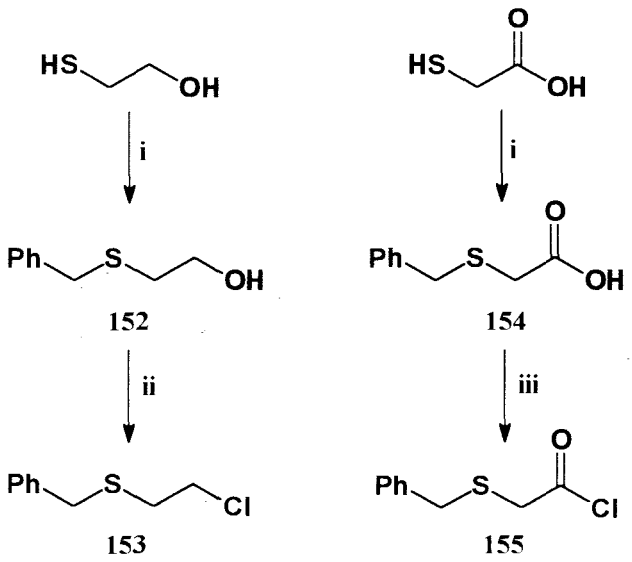
Acetylation of the methyl sulfide intermediates **146a-c** using hydrochloric acid and excess acetic anhydride afforded the corresponding bidentate target ligands **150a-c** (Scheme 20). Heating the methyl sulfides **146a-c** with mercaptoacetic acid in a stream of dry nitrogen yielded the tridentate ligands **151a-c**. The methyl sulfide function in ligands **150a-c** and **151a-c**, in place of an aromatic mercapto group, is essential to prevent cyclisation with consequent benzothiazole formation,[194] as well as to prevent oxidation of the aromatic mercapto function to the disulfide. Both processes take place readily at room temperature.

2.2.3.3 The use of protecting groups to extend the chelating "arms"

2.2.3.3.1 The benzyl protecting group

Further elaboration of the ligands to extend the chelating arms required protection of nucleophilic thiol groups. The protecting group used must not migrate to nitrogen during synthesis (as acyl protecting groups are known to do), must not be cleaved during synthesis of the target ligand and, after synthesis, must be cleaved without affecting the amide function. The benzyl protecting group, which is readily attached to the thiol function[197, 198] and has been used in the synthesis of sulfur-containing peptides,[199] appeared to satisfy these criteria.

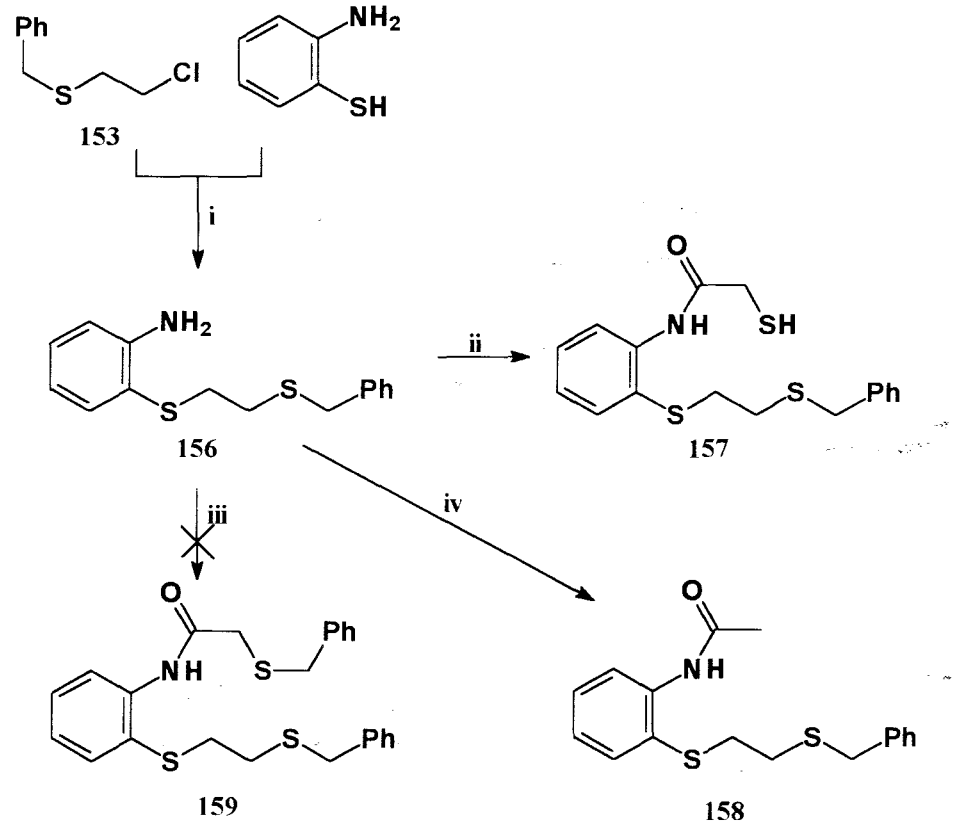
Scheme 21: The synthesis of benzyl-protected chloro compounds.



The benzyl sulfide **152** was readily formed by heating benzyl chloride with mercaptoethanol in the presence of base (Scheme 21). In an analogous reaction, benzyl chloride was reacted with

mercaptoacetic acid to give the benzyl-protected compound **154**. The benzyl-protected intermediates **152** and **154** were converted to the chloro compounds **153** and **155**, respectively, with thionyl chloride,[200] and both products were purified by vacuum distillation.

Scheme 22: Synthetic approaches to benzyl-protected ligands.



reagents
i) KOH, MeOH
ii) $HSCH_2CO_2H$, N_2, Δ
iii) $ClCH_2CO.Cl$, Et_3N, $PhCH_2SH$
iv) Ac_2O, H_2SO_4

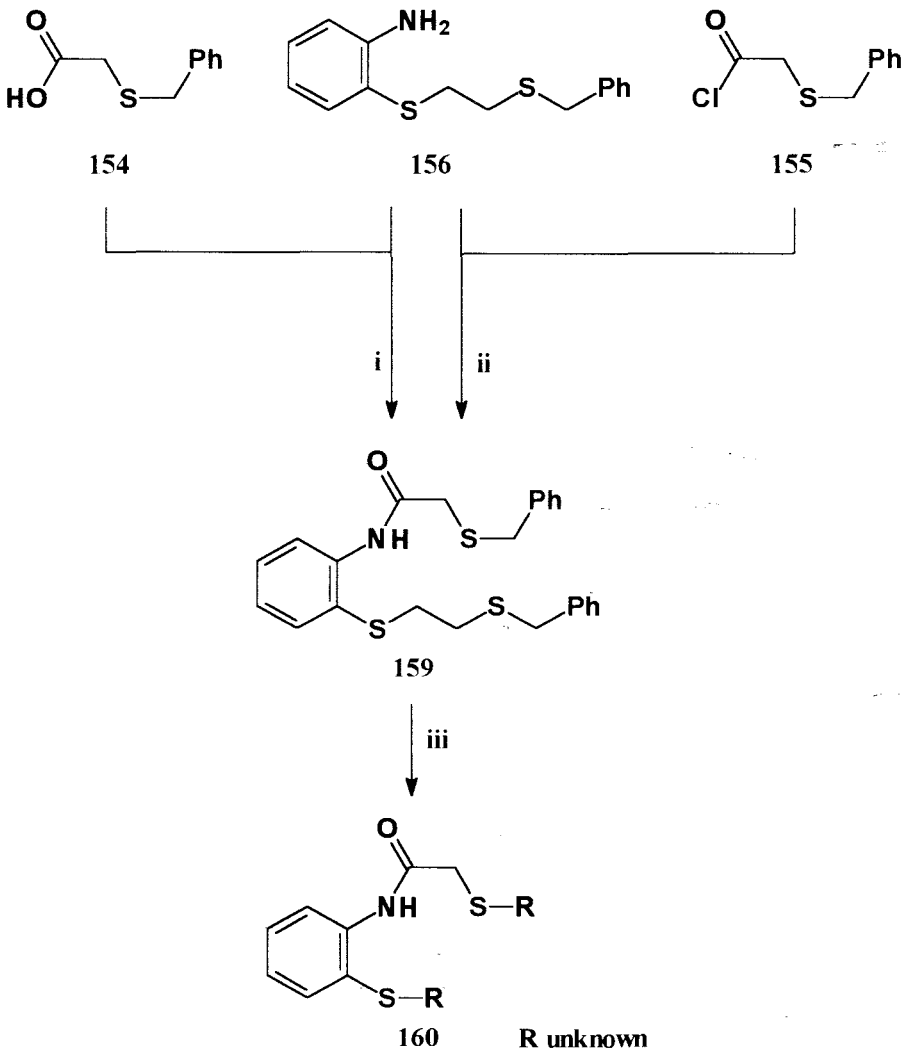
Benzyl 2-chloroethyl sulfide **153** was reacted with *o*-aminobenzenethiol in the presence of base to yield the benzyl-protected intermediate **156** (Scheme 22). Heating this intermediate with meracptoacetic acid, in a stream of dry nitrogen, over an extended period of time (*ca.* 8 h), resulted in negligible yields of the amide **157**. An unsuccessful attempt was then made to

synthesise the benzyl-protected dimercapto ligand **159** using chloroacetyl chloride and benzyl mercaptan (prepared from benzyl chloride); this lack of success coupled with the highly unpleasant odour of benzyl mercaptan prompted us to abandon this particular approach. The intermediate **156**, however, was successfully acetylated, using a large excess of acetic anhydride and a few drops of concentrated sulfuric acid,[168e] to give the benzyl-protected ligand **158**. This method of acetylation is normally used on sterically hindered amines and, in this case, was found to be superior to the conventional method of using acetic anhydride in acetic acid.

The synthesis of the tetradentate benzyl-protected ligand **159** was finally accomplished in two ways (Scheme 23). In the one approach, the benzyl-protected mercaptoacetic acid **154** was coupled with the aromatic amine **156** using the coupling agent carbonyldiimidazole (CDI). The second, and preferred route, involving reaction of the aromatic amine **156** with the acid chloride **155** in the presence of triethylamine, gave better yields of the ligand **159**. Moreover, the carbonyldiimidazole reaction did not go to completion, making it difficult to separate the resulting amide from the starting amine.

Benzyl protecting groups are normally removed by reductive cleavage of benzyl sulfides using sodium in liquid ammonia - a procedure which does not affect the amide function.[201, 202] The procedure used by Crenshaw and Field[91] was employed to cleave the benzyl protecting groups in the dibenzyl compound **159**. The substrate was added to liquid ammonia, followed by small pieces of freshly cut sodium metal until the first permanent blue colour remained. Ammonium chloride was added to destroy excess sodium and, after allowing the liquid ammonia to evaporate, a complex mixture of products was obtained, the main component being tentatively shown (by 60MHz ^{1}H NMR spectroscopy) to contain a functionality similar to compound **160**.

Scheme 23: The two methods used for the synthesis of the dibenzyl ligand 159.



reagents
i) CDI; ii) Et_3N; iii) Na, liquid NH_3

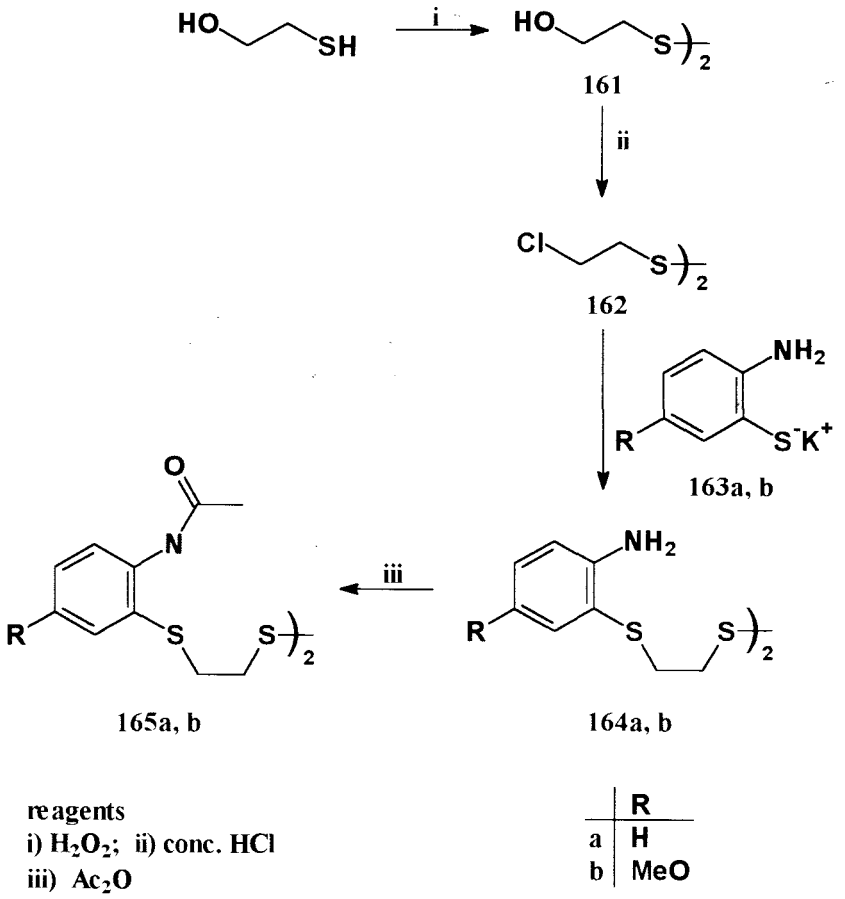
Reports in the literature reveal that the use of excess sodium often results in complete desulfurisation of a compound,[203, 204] and, moreover, the dibenzyl compound **159** is not soluble in liquid ammonia. Sodium in liquid ammonia has also been reported to reduce aliphatic sulfides to the corresponding mercaptides and hydrocarbons,[205] while aryl thioethers are cleaved by reaction with metals,[206, 207] albeit with much greater difficulty than benzyl and allyl systems. Due to these complications, and the fact that the disulfide linkage (Section 2.2.3.3.2) was showing

promise as a protecting function, the reductive fission was not repeated. The benzyl-protected ligands **158** and **159** were kept, however, to be tested in solvent extraction systems containing copper(II) ions, which are known to oxidise mercapto functions to disulfides.[65]

2.2.3.3.2 The disulfide protecting function

The application of the disulfide linkage as a protecting function was investigated, with the target ligand acting as its own protecting group. Thus, final fission of the disulfide linkage was expected to afford two equivalents of the required ligand. This approach is outlined in Scheme 24.

Scheme 24: The use of the disulfide linkage as a protecting function.

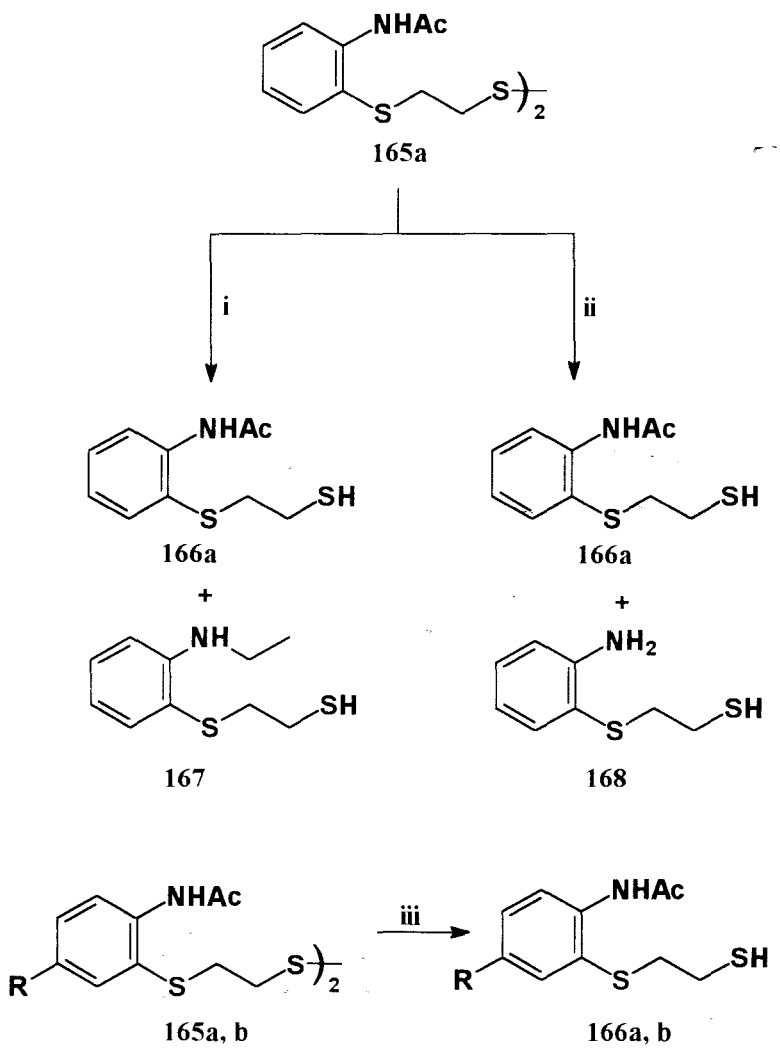


2-Mercaptoethanol was oxidised with hydrogen peroxide,[208] and the disulfide **161**, obtained as a viscous syrup after removal of water under vacuum,[††] was heated with concentrated hydrochloric acid to yield the crude bis(2-chloroethyl) disulfide **162**, which was purified by vacuum distillation.[209] The reactive sulfur mustard **162** was added to the aromatic *ortho*-aminomercaptides [the 4-methoxy analogue **163b** being obtained by base-catalysed hydrolysis of the benzothiazole **143b** (Scheme 18)]. In this manner the disulfide intermediates **164a,b** were formed in almost quantitative yield and in sufficiently pure form to allow further reaction without purification. The free amino function, in each case, was then acetylated with excess acetic anhydride[168e] to produce the crystalline amides **165a,b**.

The next, crucial step in this synthetic route was reduction of the disulfide function in the intermediates **165a,b** to obtain the free mercaptan without affecting the amide group. Sodium borohydride has been reported to cleave disulfides,[210] but this reagent gave low yields when used for the reduction of the disulfide **165a**. A more powerful reducing system, sodium borohydride-aluminium trichloride, has been reported to reduce disulfides quantitatively,[211] without reducing amide functions.[212] [A later report indicated that this reagent reduces tertiary amides (*eg. N,N*-diethylbenzamide) but does not reduce primary amides (*e.g.* benzamide).[213]] When this reagent was tested on the secondary amide **165a**, a significant amount of the amide function was, in fact, reduced and, after chromatography on silica gel, the mercaptoamine **167** and the mercaptoamide **166a** were obtained in 29% and 25% yield respectively (Scheme 25).

[††] During removal of water from the reaction mixture, on a rotary evaporator, the flask shattered due, presumably, to heating of the excess hydrogen peroxide. In subsequent preparations, the excess hydrogen peroxide was destroyed with potassium permanganate prior to the *in vacuo* removal of water.

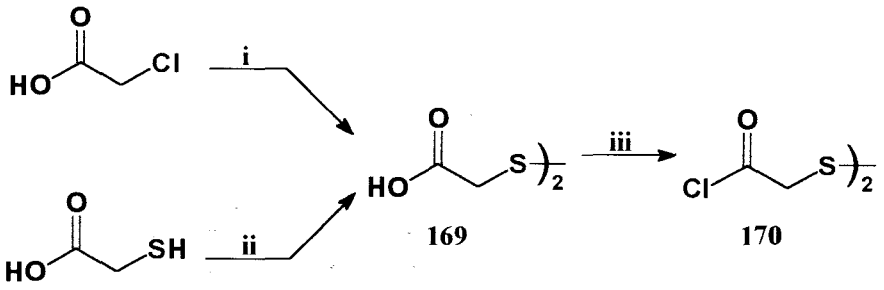
Scheme 25: Reduction of the disulfide function.



A third reagent, which has been used for the reduction of organic disulfides, is triphenylphosphine, reductions using this reagent having been performed in refluxing benzene[214] and aqueous methanol.[215, 216] Aromatic disulfides are rapidly and quantitatively reduced by this reagent at room temperature,[215, 216] whereas certain alkyl disulfides such as diethyl disulfide are

stable towards triphenylphosphine.[214] The reduction of the disulfide linkage in **165a**, using triphenylphosphine, was first attempted in methanol containing aqueous perchloric acid at reflux temperature; after separating the product mixture by flash chromatography, the target ligand **166a** was obtained in only 28% yield and the hydrolysed product **168** in 33% yield. Reduction of the disulfide function of compounds **165a,b** by triphenylphosphine was best achieved under nitrogen in 10% aqueous methanol. Exclusion of atmospheric oxygen minimizes the possibility of oxidation of the thiol back to the disulfide. The resulting mercaptans **166a,b** were separated from the triphenylphosphine oxide and excess triphenylphosphine by extraction into 10% aqueous sodium hydroxide, followed by acidification and re-extraction into an organic phase. This procedure resulted in greater than 60% yields of the target ligands **166a,b**.

Scheme 26: Synthesis of the disulfide protected acid chloride intermediate.

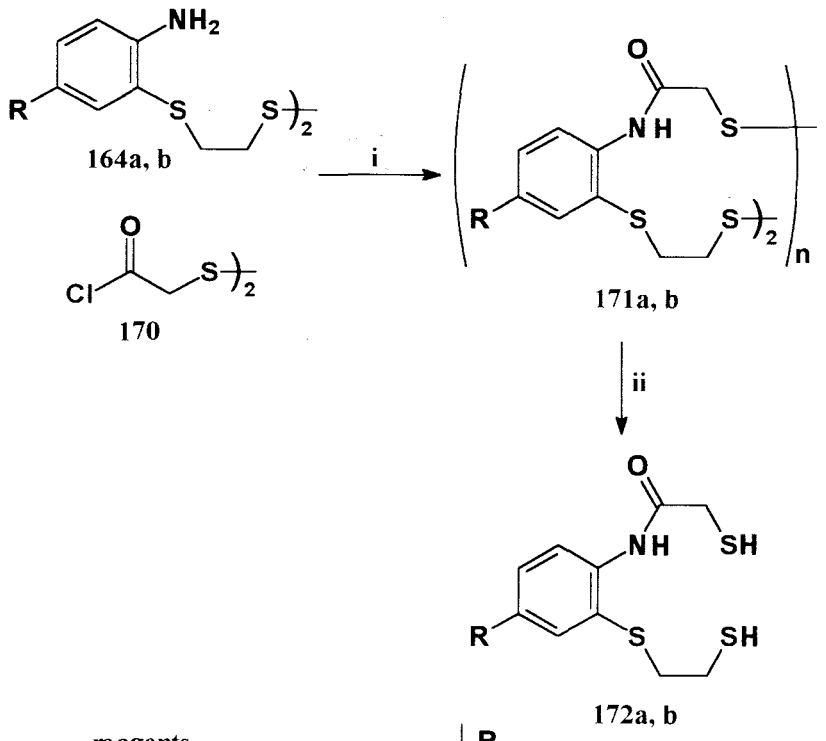


reagents
i) $Na_2S_2O_3$, Na_2CO_3, I_2; ii) I_2, KI; iii) $SOCl_2$

The idea of using a disulfide as a protecting function was extended to the synthesis of tetradentate ligands. Due to the dangers involved in oxidising organic compounds with hydrogen peroxide, and the possibility of over-oxidation,[217] other reagents for oxidising thiols to disulfides were investigated. When a thiol is dissolved in an excess of dimethyl sulfoxide (DMSO) and stirred for a maximum of eight hours with heating, the corresponding disulfides are obtained in excellent yield and purity,[218] and this procedure was applied to the synthesis of

disulfide **169**. Because this disulfide is water soluble, the DMSO had to be removed by vacuum distillation, leaving a black oil from which the product could not be induced to crystallise. The disulfide **169** was finally prepared by two methods, *viz.*, from chloroacetic acid using sodium thiosulfate[219] and the preferred procedure which involved the oxidation of mercaptoacetic acid (Scheme 26). This oxidation was accomplished using an aqueous solution of iodine and potassium iodide.[220] The iodine solution was added dropwise to mercaptoacetic acid until the brown colour remained, and the excess iodine was then quenched with sodium thiosulfate. The aqueous solution was extracted with several aliquots of ether, and evaporation of the combined extracts yielded crystals of the disulfide **169** in good yield. The bis(acid chloride) **170** was obtained by stirring the diacid **169** in thionyl chloride for two days. Vacuum distillation of the product was accompanied by decomposition and, consequently, the compound is better left undistilled.

Scheme 27: The disulfide route to the dimercapto ligands.



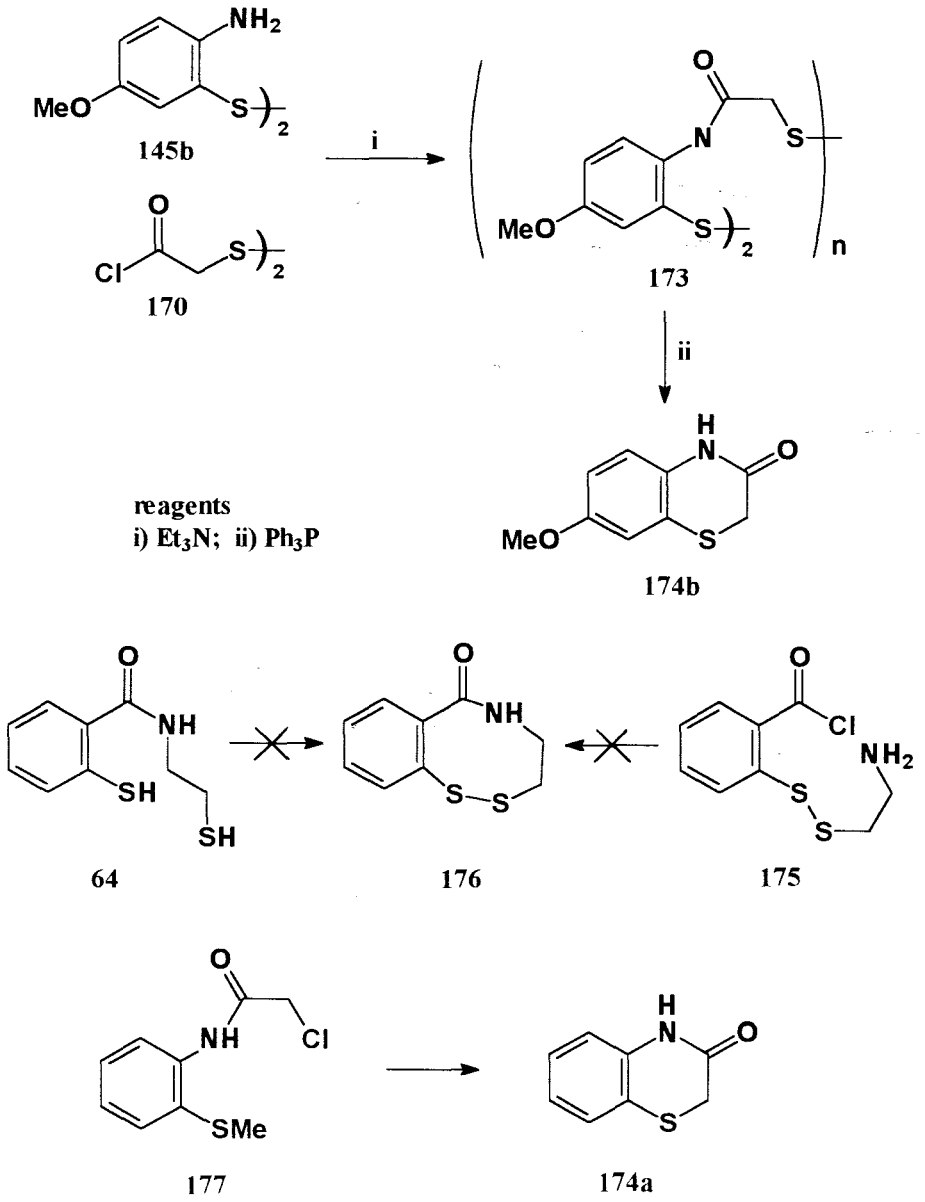
Reaction of the acid chloride **170** with the amino group of intermediates **164a,b**, using triethylamine as a base, gave the polymeric products **171** [a powder for compound **171a** (R = H) and a thick gum for compound **171b** (R = MeO)] (Scheme 27). The polymers were reduced with triphenylphosphine using the experimental conditions determined earlier. Although formation of the polymers **171a,b** occurred in high yield, the reduction step proved less efficient affording the crude ligands **172a** and **172b** in 60-70% and 5-10% yields respectively. The formation of the dimercapto ligands **172a,b** was readily confirmed by the presence of two mercapto proton triplets, at *ca.* 2.07 and 1.65 ppm, in their ^{1}H NMR spectra (illustrated for compound **172b** in Figure 44, p. 114).

The methoxy-substituted polymer **171b** was not very soluble in aqueous methanol, but even carrying out the reduction in dilute solutions failed to improve the yield. In some cases, the low yields from the reduction of polymer **171b** could be attributed, at least partially, to the presence of the aryl disulfide polymer **173** (Scheme 28). This particular contaminant **145b** appeared to be formed as a by-product when the free mercaptan **144b** (p. 94) was isolated prior to reaction with the sulfur mustard **162** (Scheme 24, p. 102). The diaryl disulfide impurity **145b** would have reacted with the bis(acid chloride) **170** and reduction of the resulting polymer **173** with triphenylphosphine afforded lactam **174b** as the major product, together with the required ligand **172b**. This compound was characterised by NMR, IR and MS techniques, and its unexpected isolation led to the realisation that significant amounts of the aryl disulfide polymer **173** were present. Consequently, subsequent syntheses of amine **164b** (Scheme 24, p. 102) did not involve isolation of the aromatic thiol **144b**.

Interestingly, attempts by Crenshaw and Field [91] at synthesising the 8-membered lactam **176** were unsuccessful. These researchers tried to synthesise lactam **176** by oxidation of the dimercapto compound **64**, and by ring closure of the acid chloride **175**, both attempts yielding

polymers. However, smaller cyclic sulfides appear to form readily, and attempted purification of the methyl sulfide **177** by distillation has been reported[192] to afforded lactam **174a** in up to 75% yield.

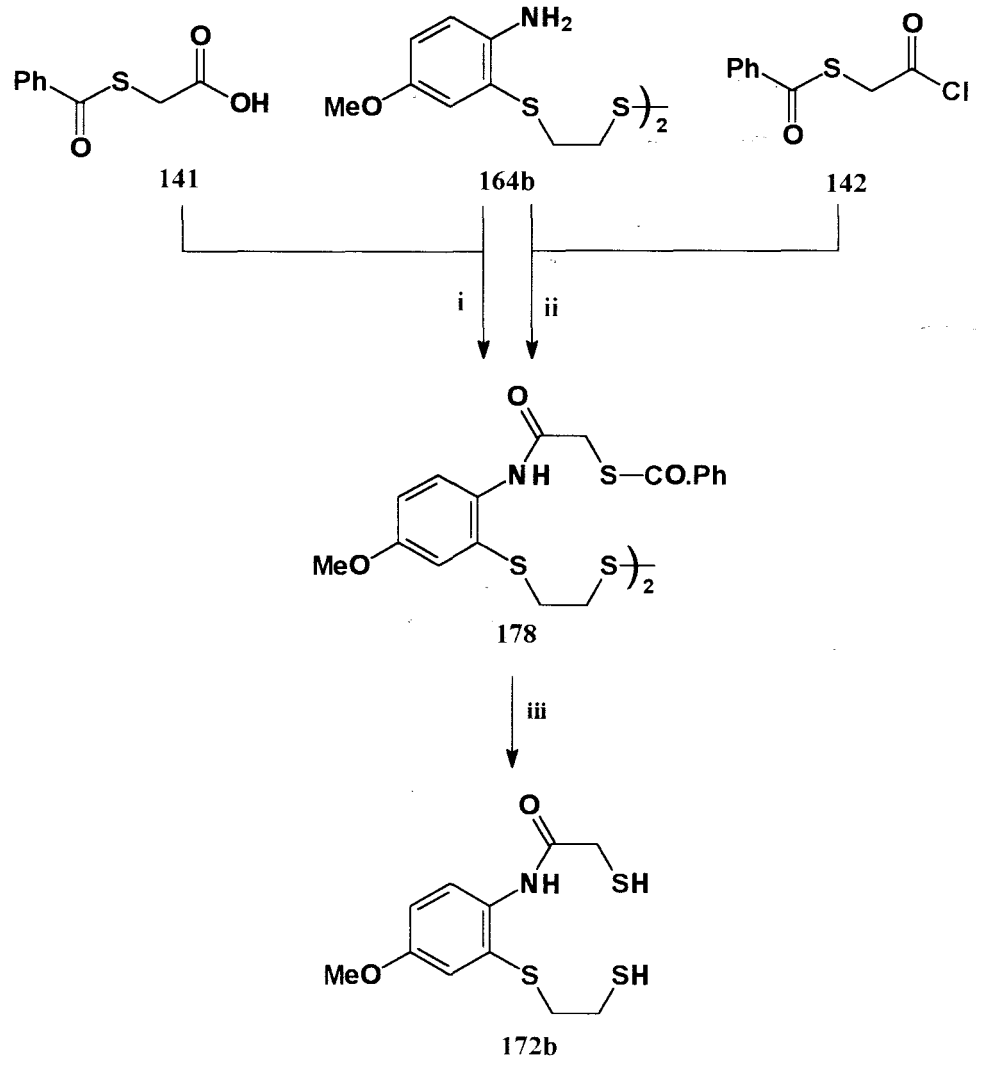
Scheme 28: Formation of the 6-membered lactam 174, and attempts by Crenshaw and Field[91] to synthesise a similar lactam.



2.2.3.3.3 The benzoyl protecting group

Due to problems encountered in reducing the methoxy-substituted polymer **171b**, it was decided to limit the size of the protected substrate, thus making it more soluble and, hopefully, easier to reduce. Consequently, a combination of the disulfide function and the

Scheme 29: Synthesis of dimercapto ligand 172b using a combination of benzoyl and disulfide protecting groups.



reagents
i) CDI; ii) Et_3N;
iii) Ph_3P, KOH.

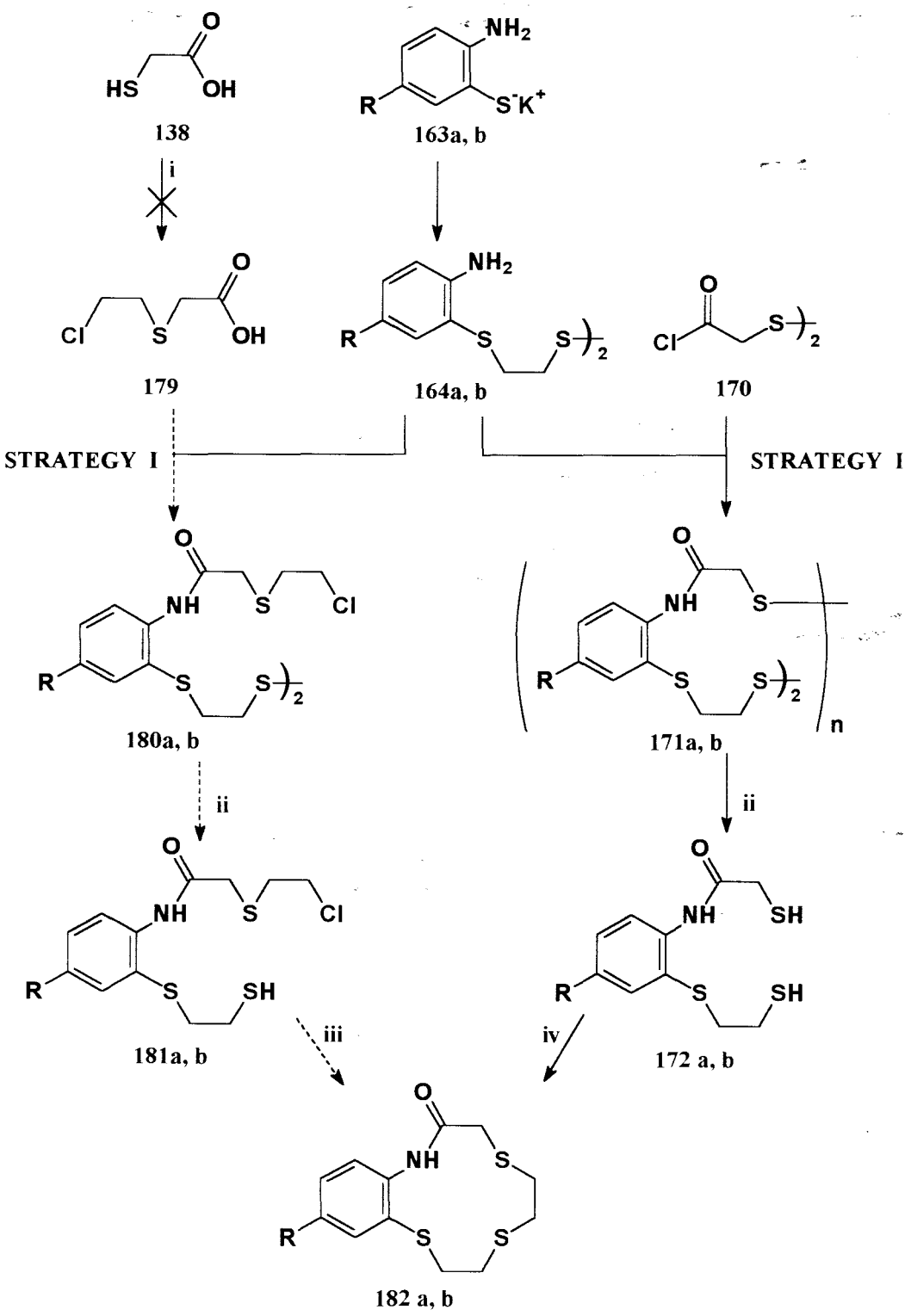
benzoyl protecting group was explored. The benzoyl protected acid chloride **142**, or the benzoyl protected acid **141**, was reacted with the amino group of intermediate **164b** to obtain the benzoyl- and disulfide-protected product **178** in good yield (almost 100% when the acid chloride route is used) (Scheme 29). The disulfide linkage was then reduced with triphenylphosphine, and aqueous base was used to hydrolyse the thiol ester and effect separation of the dimercapto ligand **172b** from triphenylphosphine. These deprotection and separation steps yielded the methoxy derivative **172b** in greater than 90% crude yield.

2.2.3.4 The synthesis of macrocyclic ligands

The two synthetic pathways considered for the synthesis of the macrocyclic ligands **182a,b** are shown in Scheme 30. Both involve the intermediate disulfide dimers **164a,b**, which are readily accessible in reasonable yield (see Scheme 24, p. 102). In the first pathway (Strategy I), however, the final step involves a single displacement ring-closure, which was expected to proceed with fewer side reactions than the final cyclisation step in Strategy II.

Attempts to synthesise compound **179** using 1,2-dichloroethane and mercaptoacetic acid were problematic; 2-chloroethyl sulfides are known to hydrolyse easily at the C-Cl bond,[221] and the resulting hydroxy acids polymerise rapidly.[222] Compound **179** has been prepared by ultraviolet irradiation of a mixture of mercaptoacetic acid and vinyl chloride,[223] but the lack of a readily available ultraviolet reactor precluded use of this procedure. Ono's method[224] for reacting dichloromethane with thiols was then explored but the results were not promising.

Scheme 30: Synthetic strategies for the synthesis of the macrocyclic ligands.



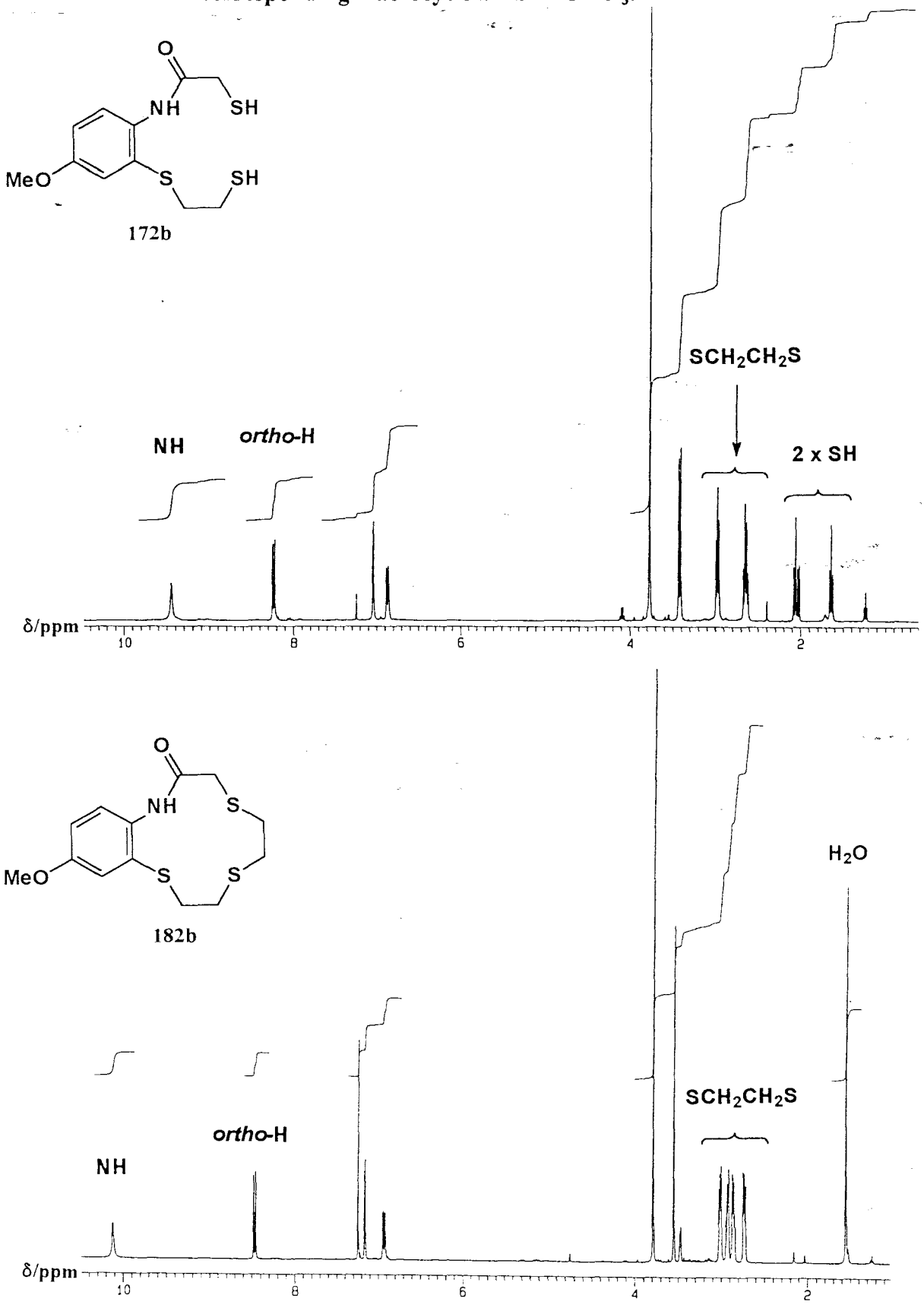
These difficulties, coupled with the availability of the dimercapto ligands **172a,b** (see Scheme 27, p. 106) prompted the adoption of the second strategy. The dimercapto ligands **172a,b** were cyclised using 1,2-dibromoethane in the presence of cesium carbonate. This particular base was chosen in order to exploit the so-called "cesium effect."[225, 226] Normally, cyclisations to form macrocycles require high dilution techniques and, in spite of this, often proceed in poor yield.[227] Thiols are readily deprotonated by cesium carbonate in DMF to form cesium thiolates which, under the correct conditions, readily undergo intramolecular S_N2 ring closure. Moreover, when cesium is used as the counter ion, the formation of even fairly large macrocycles takes place in good yield. This "Cesium effect" has been attributed to the solubility of cesium salts in polar aprotic solvents (*e.g.* DMF) and their resulting dissociation into solvated cations and free anions. These "naked anions" are very reactive in aprotic solvents and, when high dilution techniques are employed, intramolecular cyclisation is favoured.

Simulated high dilution techniques[225] were used to prepare macrocycles **182a,b**. Using this technique, solutions of 1,2-dibromoethane and the dimercapto compound **172** (both in dry DMF) were added *slowly* (during 12-15h) and *simultaneously* to a solution of cesium carbonate in dry DMF under dry nitrogen. Addition of the reagents from burettes at the same slow rate for a lengthy period was impossible to achieve and, consequently, portions of the reagents were added slowly and simultaneously, with approximately 40 minute pauses between additions, the whole addition procedure lasting over 12 hours. For the success of the cyclisation, reactant purity is very important[225] and, consequently, prior to use, the dibromide was purified by distillation and the dimercapto compounds by flash chromatography.

The ^{1}H NMR spectra of the resulting macrocycles **182a,b** show an absence of the mercapto signals characteristic of the dimercapto ligands **172**, and the presence of four methylene multiplets at *ca.* 3 ppm corresponding to the two ethylene bridges of the macrocycle (illustrated

for the methoxy-substituted analogue **182b** in Figure 44). The yields of macrocycles **182a** and **182b**, after flash chromatography, were 31% and 17% respectively. These yields are lower than expected, especially when one considers that the rigid, *ortho*-disubstituted phenyl group reduces the rotational degrees of freedom. A similarly sized macrocyclic thia crown ether, 1,4,7,10-tetrathiacyclodecane, is reported to have been synthesised in greater than 80% yield using this method.[225]

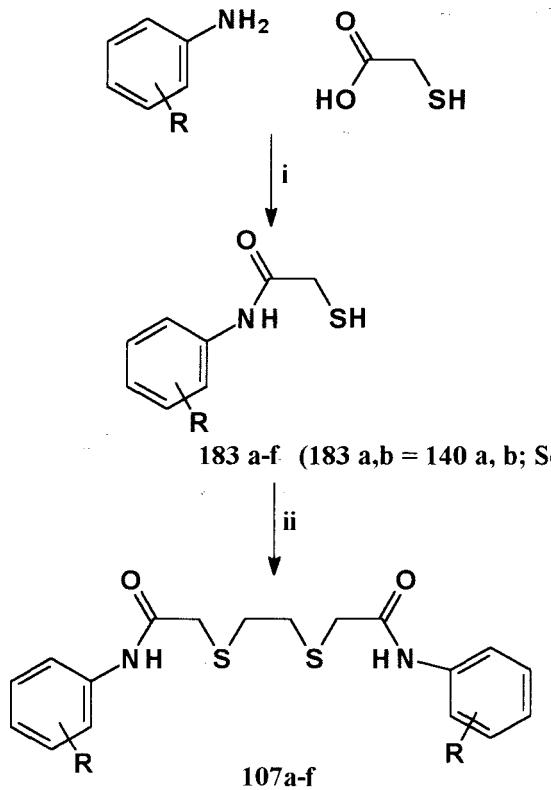
Figure 44: 400 MHz ^{1}H NMR spectra of the dimercapto ligand 172b and the corresponding macrocycle 182b in $CDCl_3$.



2.2.4 Synthesis of sulfur-containing diamide ligands

The synthesis of these ligands is outlined in Scheme 31 and proved relatively straight forward. The ring-substituted mercaptoacetanilides **183** were synthesised by the method of Misra and Sircar,[54] discussed earlier (p. 90). These mercaptoacetanilides were reacted with 1,2-dibromoethane in methanolic potassium hydroxide to yield the target diamide ligands **107a-f**. Purification was accomplished by recrystallisation from ethanol-water mixtures.

Scheme 31: Synthesis of the diamide ligands.



	R
a	H
b	4-MeO-
c	3-Cl-
d	2-Cl-
e	2-Me-
f	2-MeO-

reagents
i) N_2 , Δ
ii) $BrCH_2CH_2Br$, KOH

2.3 THE *ORTHO* SHIFT IN ACETANILIDE-DERIVED LIGANDS

Information on the conformations of the novel acetanilide-derived ligands synthesised in this study can be obtained from their ^{1}H NMR spectra, and particularly from the chemical shift of the aromatic hydrogen *ortho* to the amide function. Consequently, in this section, the factors influencing the chemical shift of the *ortho* proton are briefly reviewed and the calculated *"ortho* shifts" for the acetanilide derived ligands are discussed.

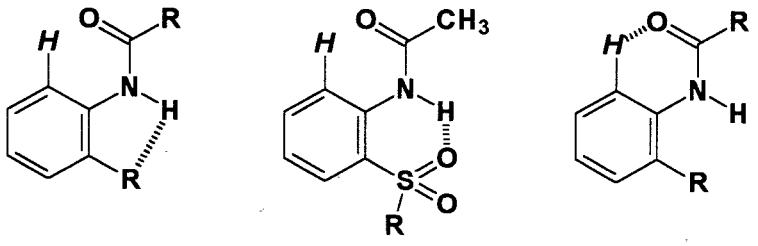
2.3.1 The *ortho* shift

The NMR shielding parameters of substituents on a benzene ring have been shown to be additive, except for *ortho*-protons on *ortho*-disubstituted benzenes, where small deviations (less than 0.5ppm) can occur.[228] For *ortho*-substituted acetanilides, however, large downfield shifts of the *ortho*-proton occur, which deviate substantially from the shifts predicted by the additive principle. This deshielding of the *ortho*-proton, which is minimal in unsubstituted and *para*- and *meta*-substituted acetanilides, has been referred to as the *"ortho* effect."[146] This term is also used to describe directing- as well as kinetic effects in aromatic substitution[229] and, consequently, the term *"ortho* shift" will be used in this work.

Studies[230] of the *ortho* shift in acetanilides have revealed that the nature of the *ortho*-substituent is important; *ortho*-substituents which can hydrogen-bond with the amide proton (*e.g.* structure **184**; Figure 45) cause larger downfield shifts of the *ortho*-proton than substituents which cannot participate in such bonding. These shifts have been attributed to long range deshielding by the amide carbonyl group.[231] When the amide proton is hydrogen-bonded to an *ortho*-substituent (structure **184**), the amide carbonyl group is approximately co-planar with the aromatic ring - a conformation in which the carbonyl group exerts its maximum deshielding effect. (The shielding

and deshielding zones associated with the magnetic anisotropy of the carbonyl group have been clarified by Karabatsos.[232]) Further evidence for hydrogen-bonding of the type illustrated in structure **184** is provided by significant deshielding of the amide proton. Studies[233] of acetanilides have also shown that the intramolecular hydrogen-bonding is relatively weak when the *ortho*, hydrogen-bonding entity is a sulfone or a sulfonamide as in structures **185a** and **185b** respectively. Generally, it has been found that the the 5-membered hydrogen-bonded ring structures **184,** formed by *ortho*-chloro and *ortho*-methoxy substituents, are more stable than 6-membered structures.[229, 233] In the absence of a hydrogen-bonding *ortho*-substituent, the deshielding (anisotropic) contribution to the *ortho* shift is reduced by more than 50% and it has been concluded that, in such cases, the amide group is slightly inclined to the plane of the aromatic ring.

Figure 45: Intramolecular hydrogen-bonded structures discussed in this work.



184 **185a R = CH_3** **186**
185b R = $N(CH_3)_2$

The extent of coplanarity of the aromatic ring and the amide group has been gauged by the "acylation shift technique."[229] The downfield shift of aromatic protons upon acylation of an aromatic amine is due to a combination of anisotropic and electronic effects. The magnitude of the electronic contributions may be gauged by the *para*-proton shifts, as anisotropic effects on *para*-protons are assumed to be negligible. The difference in the acylation shifts of the *para*- and *ortho*-proton is taken as the anisotropic contribution to the *ortho* shift in a particular

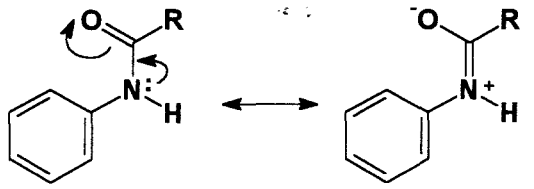
system. In a slightly different approach, Zanger *et al.*[146] used substituent shielding parameters to determine the anisotropic contribution to the *ortho* shift; the calculated chemical shift ($\delta_{calc.}$) for the *ortho*-proton, was subtracted from the observed chemical shift (δ_{obs}), the difference ($\Delta\delta$) being the anisotropic contribution (Table 7). Since the deshielding effect of the carbonyl group is so large, these researchers[146] proposed that hydrogen-bonding between the amide oxygen and the *ortho*-hydrogen (as in structure **186**) is probable.

Table 7: Observed and calculated chemical shifts (ppm) for the *ortho*-proton in *ortho*-substituted acetanilides.[146]

ortho-substituent	$\delta_{obs.}$	$\delta_{calc.}$	$\Delta\delta$
CH_3	7.48	7.33	0.15
F	8.20	7.43	0.77
OH	7.68	7.06	0.62
NO_2	8.74	7.73	1.01
COOH	8.50	7.53	0.97
Cl	8.33	7.43	0.90
OCH_3	8.32	7.20	1.12

Crystallographic, infrared, ^{1}H NMR and dipole moment studies have shown that *N*-monosubstituted amides, in which the acyl group is larger than formyl, exist solely or largely in the *syn*-conformation **187** (Figure 46) with respect to the N-(CO) partial double bond.[229] Although the *ortho* shift is not always attributed to intramolecular hydrogen-bonding between the amide proton and the *ortho*-substituent (as in structure **184**),[234, 235] Rae[147] has attributed the effect to such intramolecular hydrogen-bonding and the *syn*-conformation about the N-(CO) partial double bond. He further postulates that the magnitude of the acylation shift is a measure of the strength of the hydrogen-bonding interaction. Typical acylation shifts for various *ortho*-substituents are shown in Table 8.

Figure 46: The *syn* conformation with respect to the N-(CO) partial double bond.



R ≠ H

187 **188**

Table 8: Typical acylation shifts for various *ortho*-substituted acetanilides, determined in $CDCl_3$ or CCl_4. [147, 230]

Ortho-substituent	Acylation shift / ppm	*Ortho*-substituent	Acylation shift / ppm
COOMe	2.07-2.10	O-alkyl	1.77-1.78
NO_2	1.90-2.20	CN	1.62
CF_3	1.91	Cl	1.70
SO.Me	1.82	Br	1.52
SMe	1.81	Me	0.75-1.02
SO_2Me	1.76	H	0.88-1.05

Rae[236] has studied the effect of solvent on the acylation shifts of the *ortho*-proton of *ortho*-substituted acetanilides. As the polarity of the solvent and, hence, its ability to hydrogen-bond with the amide hydrogen increases, so the deshielding of the *ortho*-proton decreases. Methanol, the only protic solvent examined, does not substantially reduce the *ortho* shift.

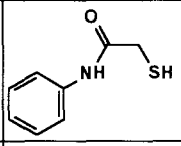
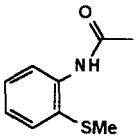
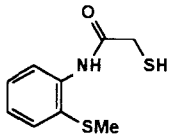
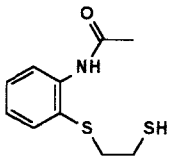
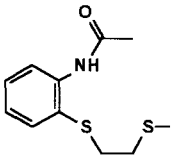
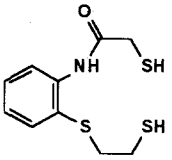
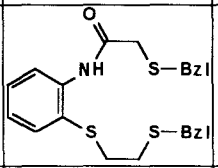
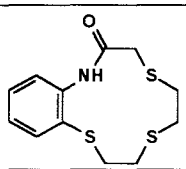
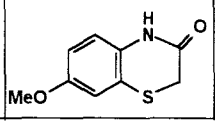
2.3.2 The *ortho* shift in the sulfur-containing monoamide ligands

Because the magnitude of the acylation shift of the *ortho*-proton appears to be a measure of the degree of coplanarity of the aromatic ring and the amide function, a study of these shifts was undertaken to elucidate conformational preferences in the synthetic ligands. The acylation shift for each system was calculated from the difference between the *ortho*-hydrogen chemical shifts of the amide and the aromatic amine precursor, in $CDCl_3$ at 303 K. The *ortho*-hydrogen chemical shifts of the amino compounds in $CDCl_3$ were also used to estimate the acylation shifts in DMSO-d_6. The electrostatic contribution of the acyl group is considered to be more-or-less constant for all the systems examined and, consequently, variations in the observed acyl shift have been attributed to anisotropic and, hence, conformational effects.

When studying the shielding of hydrogen nuclei on aromatic molecules it is important to eliminate intermolecular effects on the shielding[237] and, to minimise these effects, dilute solutions of the compounds [< 5% (m/m)], were used. Substantial variations in concentration were found to cause only slight (< 0.05 ppm) chemical shift changes.

The spectroscopic data relevant to the *ortho* shift in the sulfur-containing monoamide ligands are summarised in Table 9. Comparison of the first three entries show that the introduction of a methyl sulfide group *ortho* to the amide results in a substantial acylation shift. Surprisingly, this shift is not as great for the "ethyl" sulfide analogues (entries 4 to 8). The acylation shifts in DMSO-d_6 were calculated with reference to the chemical shifts of the amino compounds in $CDCl_3$ and, consequently, are less meaningful than the shifts reported in $CDCl_3$. All the acylation shifts decrease in DMSO-d_6, with macrocycle **182a** having the smallest decrease in acylation shift of all the ligands in Table 9, excluding the monosubstituted system **140a** and cyclic sulfide **174b** (entry 9). This is to be expected when one considers the greater rigidity in

Table 9: ^{1}H NMR and infrared spectroscopic data, relevant to the *ortho* shift, for the sulfur-containing monoamide ligands.

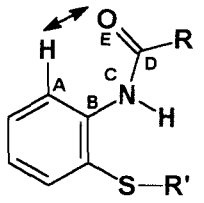
Entry	Compound number	Ligand	^{1}H NMR data /ppm $CDCl_3$		^{1}H NMR data /ppm DMSO-d_6		Infrared data / cm^{-1}	
			Acylation shift	NH	Acylation shift[a]	NH	ν_{NH}	ν_{CO}
1	140a		0.87	8.59	0.89	10.05	3300	1650
2	150a		1.66	8.24	0.75	9.28	3310	1650
3	151a		1.67	9.52			3240	1650
4	166a		1.01	8.52			3290	1660
5	158		1.03	8.56	0.188	9.25	3340	1690
6	172a		1.04	9.76	0.41	9.64	3280	1675
7	159		1.03	9.77	0.41	9.61	3270	1675
8	182a		1.20	10.34	0.70	10.10	3240	1640
9	174b		0.21	8.82	0.295	10.35	3180	1675

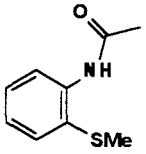
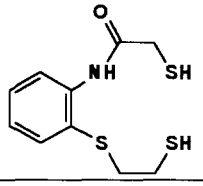
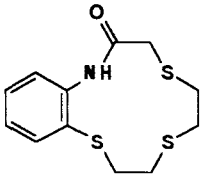
[a] As compared to the amino compound in $CDCl_3$.

the macrocyclic ligand. When one considers that typical acylation shifts of aromatic protons *meta* and *para* to the nitrogen atom are approximately 0.2 and 0.4 ppm respectively,[147] then the acylation shift of the cyclic sulfide **174b** can be completely attributed to electrostatic effects, rather than anisotropic deshielding.

The benzyl protected ligands have very similar acylation shifts to their mercapto analogues, suggesting that increasing the bulk of the *ortho*-substituent at some distance from the ring has very little influence on the *ortho* shift. As expected,[146] the size of the acylating group also has little effect on the acylation shift, in that entries 4 to 7 all show similar shifts.

Table 10: Molecular modelling data pertaining to the *ortho* shift.



Compound number	Ligand	Torsion angle ABCD (°)	Torsion angle BCDE (°)	H-O(C) Distance (Å)
150a		0.0007	0.0002	2.17
172a		1.33	0.35	2.26
182a		10.25 (constrained at 0)	3.3	2.31

Molecular modelling of representative systems, using the software package Hyperchem®, produced models in which the degree of coplanarity of the aromatic and amide functions was in agreement with the acylation shift data. Thus, the methyl sulfide ligand **150a** adopts a low energy conformation in which the carbonyl group is held in the plane of the aromatic ring, the torsion angles are practically zero and the oxygen to *ortho*-hydrogen distance is 2.17Å (Table 10). For the dimercapto ligand **172a**, the torsion angles increase and the hydrogen-oxygen bond distance is significantly greater. When the macrocycle **182a** was modelled, numerous low energy conformations were obtained, in some of which the carbonyl group was approximately perpendicular to the plane of the aromatic ring. Constraining the amide N-(CO) bond-aromatic ring torsion angle to 10^0 and 20^0 resulted in energy minimised conformers in which this angle was approximately 20^0. Constraining this torsion angle to 0^0 gave an energy minimized conformer in which the amide function was at an angle of 10^0 to the aromatic plane.

The amide hydrogens in the ligands which do not have a sulfur donor on the acyl function, entries 2, 4 and 5, resonate significantly further upfield than their analogues which do have a sulfur donor in this position. Maximum deshielding of the amide hydrogen occurs in the tetradentate ligands and particularly in the macrocycle, where there is a large downfield shift of the amide hydrogen upon cyclisation. The stretching frequencies of the NH bond for these deshielded amide hydrogens are generally at a lower wavenumber than the acetamide NH stretching frequencies, suggesting that hydrogen bonding to this sulfur is contributing to the deshielding. This observed hydrogen bonding is in agreement with that proposed in the literature (structure **43**, page 30).[62] In DMSO-d_6 the macrocycle amide hydrogen is less deshielded than in $CDCl_3$, whereas the large downfield solvent shift of the amide hydrogen of the cyclic sulfide **174b** suggests strong interaction with the DMSO-d_6.

In conclusion, the acetanilide ligands with *ortho*-methylthio substituents show the largest *ortho*

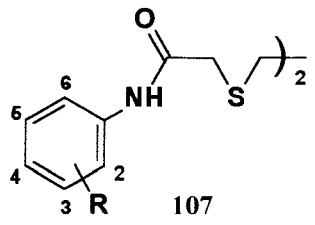
shift, while the fairly large *ortho* shift shown by the macrocyclic ligand **182a** suggests that this ligand adopts a conformation in which the aromatic and amide functions are relatively coplanar.

2.3.3 The *ortho* shift in the sulfur-containing diamide ligands

The acylation shifts and infrared data pertaining to the *ortho* shift in the sulfur-containing diamide ligands **107a-f** are shown in Table 11. The ligands are listed in order of decreasing acylation shift in $CDCl_3$ - an order which is in agreement with the published data shown in Table 8.[147, 230] Many of the acylation shifts quoted in Table 8 are for trisubstituted benzenes, and this could account for the differences between these shift values and the values observed in this study. In all the acylated compounds the *ortho*-hydrogens are the most deshielded aromatic hydrogens. The acylation shifts for the 3-chloro derivative (entry 4) apply to the 2-hydrogen, which is significantly further downfield than the 6-hydrogen.

The ^{1}H NMR spectra show that the amide proton resonates further downfield as the acylation shift increases, an effect which is attributed to hydrogen bonding of the amide proton with the *ortho*-substituent. The relatively low NH stretching frequency of the 2-methoxy compound (entry 1) is also attributed to hydrogen-bonding. In DMSO-d_6 all the amide hydrogen signals shift further downfield and the trend in the relative positions of the amide shifts is approximately reversed, *i.e.* the amide hydrogens in the compounds showing the greatest acylation shift are now the furthest upfield. This is attributed to hydrogen-bonding of the DMSO-d_6 with the amide hydrogen, an interaction which is more readily facilitated in the compounds which do not exhibit the *ortho* effect.

Table 11: Spectral data relevant to the *ortho* shift in the sulfur-containing diamide ligands.



107

Entry	R	Compd. No.	^{1}H NMR data / ppm $CDCl_3$ Acylation shift	$CDCl_3$ NH	DMSO-d_6 Acylation shift [a]	DMSO-d_6 NH	Infrared data / cm^{-1} ν_{NH}	ν_{CO}
1	2-MeO	107f	1.58	9.05	1.26	9.33	3290	1660
2	2-Cl	107d	1.57	9.33	1.01	9.66	3310	1680
3	2-Me	107e	1.18	8.55	0.73	9.42	3275	1650
4	3-Cl	107c	1.00 [b]	8.53	1.13 [b]	10.25	3300 3320	1660
5	H	107a	0.86	8.52	0.88	10.05	3300	1660
6	4-MeO	107b	0.80	8.42	0.83	9.91	3305	1660

[a] As compared to the amino compound in $CDCl_3$.

[b] These shifts apply to the 2-hydrogen.

2.4 COMPLEXATION STUDIES

Our research has been directed towards the development of platinum- and palladium-specific, sulfur-containing ligands. Before discussing the efficacy of these ligands, a brief overview of the complexes formed by platinum and palladium with sulfur-containing ligands is necessary.

2.4.1 Complexes of sulfur-containing ligands with divalent platinum and palladium.

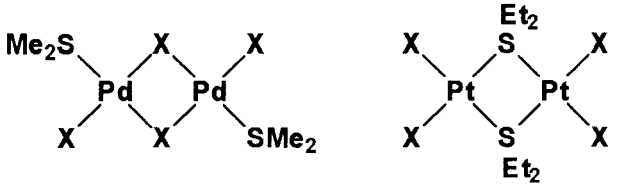
The coordination chemistry of divalent platinum and palladium with sulfur donors is complex and is influenced by many factors, including the type of sulfur donor (thioether or thiol), the substituents attached to these donors and the ligands already coordinated to the metal ion. Under certain conditions, the palladium and platinum complexes may also undergo complicated *S*-dealkylation reactions.

Thiols form strong bonds with divalent nickel, platinum and palladium,[238a] and the characterisation of these complexes is complicated by the strong tendency of the thiolo sulfur to form insoluble, bridged polymers with these metals. Polymer formation is dependent on the *S*-alkyl substituent, the metal and the ligands initially coordinated to the metal. Small *S*-substituents and easily displaceable ligands favour polymerisation, while the ability of the metals to form polymers decreases in the order Ni > Pd > Pt.[239] Palladium-thiolato complexes are highly associated in organic solvents, such as chloroform, and are polymeric in the solid state, with two sulfur atoms bridging two palladium atoms.[240] Nickel-thiolato complexes form insoluble, linear polymers based on square planar nickel(II),[240] while the insoluble nature of the ethyl- and phenylthiolato complexes of palladium suggest that they also have linear polymeric structures. The palladium(II) complexes with 1-propanethiol and higher thiol derivatives are, however, soluble in organic solvents and can be crystallised.[241] Crystallographic evidence[241]

shows that these higher aliphatic palladium-thiolato complexes exist as smaller, cyclic systems. The propyl derivative, for example, exists as a hexamer, in which the palladium atoms form a six-membered, puckered ring, with each adjacent pair of atoms being joined by a double thiolato bridge.[241] Polymers can also be formed in which chloride and thiolato bridges alternate; reaction of diphenyl disulfide with $[PdCl_4]^{2-}$ in methanol yields such a polymer.[242]

The coordination chemistry of thioethers[243] with platinum(II) and palladium(II) is very similar and, with monodentate thioether ligands, complexes of the type *trans*-$M(SR_2)_2X_2$ (where M = Pd, Pt and X = anionic ligand), *cis*-$Pt(SR_2)_2X_2$ and $[Pt(SR_2)_4][PtX_4]$ have been reported.[243] The *trans*-complexes are readily soluble in organic solvents (*e.g.* benzene, chloroform), whereas the *cis*-complexes, including those with chelate rings, are less soluble. A number of studies have been undertaken on chelating, thioether ligands of type $RS(CH_2)_2SR$,[244, 245] and, for platinum, two isomeric complexes were shown to be possible, MS_2X_2 and $[MS_4][MX_4]$. Early work[246] on platinum and palladium thioether complexes showed that the pink $[MS_4][MX_4]$ complexes could be converted to the monomeric, yellow $[MS_2X_2]$ isomers by boiling in water. Dimeric complexes with thioether ligands have also been found; for palladium these complexes are halogen bridged **189**, whereas for platinum the complexes are sulfur bridged **190** (Figure 47).[247]

Figure 47: Dimeric platinum(II) and palladium(II) complexes with bridging ligands.[247]

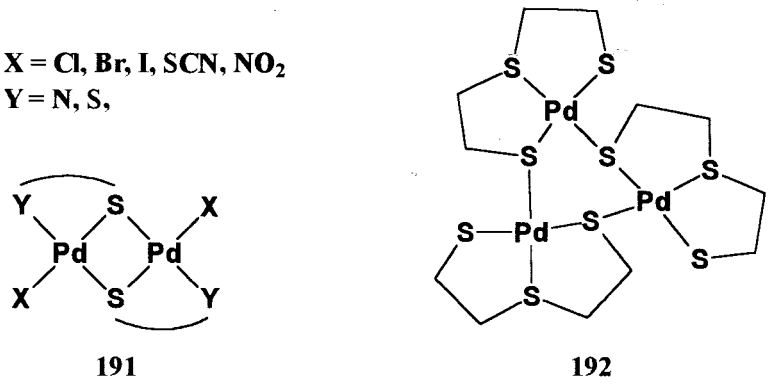


189 **190**

X = Cl, Br

Bidentate and tridentate ligands, which contain the thiol group, often form dimers or trimers by bridging of the thiolo sulfur. For example, *o*-aminobenzenethiol and *o*-methylthiobenzenethiol react with $K_2[PdX_4]$ (where X = Cl, Br, I, SCN, NO_2) in aqueous acetone to give complexes of type **191** (Figure 48).[238b] Bis(2-mercaptoethyl) sulfide forms the insoluble, trimeric, 1:1 complex with palladium(II) **192**, in which each palladium has approximately square-planar coordination geometry, with the squares inclined to each other.[238b]

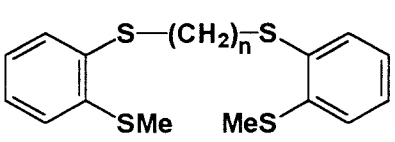
Figure 48: Dimeric and trimeric complexes of palladium and chelating thiol ligands.[238b]



191 **192**

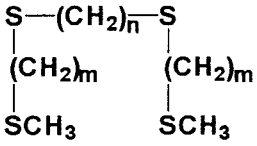
The unpredictability of platinum and palladium chemistry is apparent, however, in the complexation of these metals with the tetrathioether ligands **193** (Figure 49).[248] The reaction of $Na_2[MX_4]$ (where M = Pd^{2+}, Pt^{2+} and X = Cl, Br, I) with these ligands in 1:1, 2:1 or 1:2 molar ratios, in a variety of organic solvents, resulted in the immediate precipitation of $[M_2LX_4]$ complexes as the sole products, ultraviolet and far infrared (400-200 cm^{-1}) spectroscopy ruling out formulation as $[ML][MX_4]$. The dimeric **195** and polymeric **196** complexes were suggested as possible structures.

Figure 49: Complexation of the tetrathioether ligands 193 and 194 with platinum(II) and palladium(II) chlorides. [248, 249]



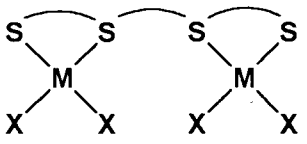
193

n = 2, 3, 4

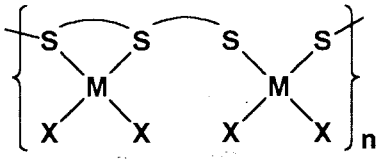


194

n,m = 2, 3



195



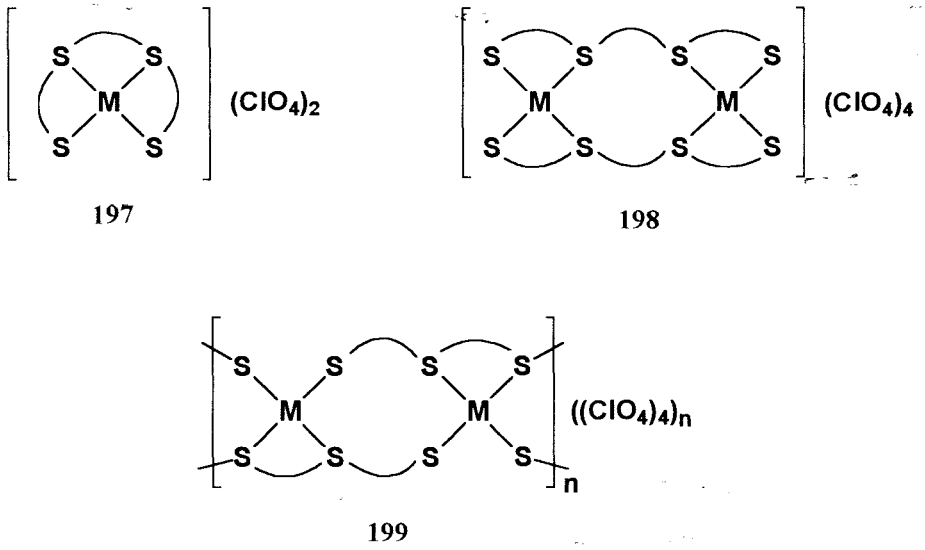
196

X = Cl, Br, I

M = Pd^{2+}, Pt^{2+}

The tetrathioether ligands **194** are also unable to displace all the halide ligands, attached to palladium(II) and platinum(II), to form monomeric complexes of type $[M(S_4)]X_2$; instead complexes of type $[M_2(S_4)X_4]$ are formed, which are probably polymeric.[249] However, when the ligands **193** and **194** are reacted with $[M(CH_3CN)_4](ClO_4)_2$ (where M = Pt^{2+}, Pd^{2+}), the weakly-bound acetonitrile ligands are readily displaced and $[M(S_4)](ClO_4)_2$ complexes are formed,[250] for which three possible structures have been suggested (Figure 50).

Figure 50: Possible structures for Pt^{2+} and Pd^{2+} complexes $[M(S_4)](ClO_4)_2$.[250]



197 198

199

The polymeric structure **199**, however, has been discounted because the complexes are reasonably soluble in polar solvents. Conductivity dilution studies showed the complexes to be the 2:1 electrolytes **197**, as opposed to the 4:1 electrolytes **198**.

2.4.2 Solvent extraction studies

A number of studies have been undertaken on the extraction of platinum group metals (pgm) with simple sulfur-containing extractants.[131] Thiols are selective extractants for palladium, extraction involving formation of the corresponding thiolato complex with polymerisation taking place in the organic phase.[131] Dialkyl thioethers and sulfoxides generally extract palladium very well, partially extract platinum and do not extract any other pgm.[251] A major factor contributing towards the palladium selectivity of these sulfur-containing ligands is the slow rate of reaction of the remaining pgm and, even for palladium, a contact time of one hour is allowed for extraction.[252] After extraction with thioethers the palladium is usually back extracted with aqueous ammonia, forming the stable cationic complex $[Pd(NH_3)_4]^{2+}$.[252] The

nature of the aqueous medium may also play an important role. For example, in nitric and hydrochloric acid solutions, palladium can be separated from platinum, while both metals may be extracted from sulfuric acid solutions.[131]

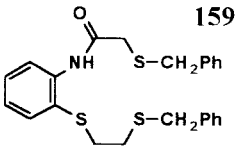
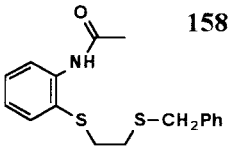
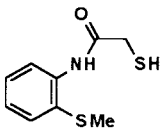
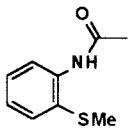
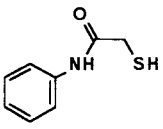
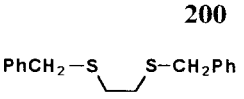
In this study, selected ligands were tested as extractants for achieving separation of platinum(II) and palladium(II) from the base metals, copper(II), nickel(II) and cobalt(II), in 1 **M**-HCl, the metal concentrations all being 0.001 **M**. In view of the importance of extraction kinetics in achieving selectivity, extraction times were kept short (20 or 30 minutes). The extractions were effected at 30 °C and back-extraction of palladium with 16% aqueous ammoniacal solutions was investigated. The aqueous metal concentrations were determined by atomic absorption spectroscopy and the resulting data are presented in the form of distribution coefficients, D (also referred to as the extraction coefficient), defined as the ratio of the metal concentrations in the organic and aqueous phases, {*i.e.* $D = [M]_{org.} / [M]_{aq}$}. Small changes in the experimental conditions can change the distribution coefficients dramatically,[253] and standardisation of the procedures is essential. The protocol adopted in the present study is detailed in the Experimental Section (p. 218).

2.4.2.1 The bis(thioether) and sulfur-containing monoamide ligands as extractants

2.4.2.1.1 Distribution coefficients for the monoamide ligands

The monoamide ligands were dissolved in toluene and the distribution coefficients obtained for the divalent metals palladium, copper, nickel and cobalt after 30 minutes are given in Table 12. These data show that the ligands examined exhibit significant selectivity for palladium over the divalent, base metals, copper, nickel and cobalt. The only ligand with a low distribution coefficient for palladium is the methyl sulfide ligand **150a** (entry 4). For a sulfur-containing ligand this palladium distribution coefficient is uncharacteristically low, and is attributed to the

Table 12: Distribution coefficients[a] for the divalent metals palladium, copper, nickel and cobalt, using bis(thioether) and sulfur-containing monoamide ligands as extractants.

Entry	Ligand	Ligand conc. / x 10^{-3} M	Distribution Coefficients				% Pd back extracted
			Pd	Cu	Ni	Co	
1	159 	1.1	105.4	0.02	0.12	0[b]	1
2	158 	1.1	64.7[c, d]	0[b]	0.11	0[b]	
3	151a 	1.1	152	0.061	0.341	0[b]	25
4	150a 	2.2	0.2	0.009	0.12	0[b]	100
5	140a 	2.2	>212[c,e]	0.16	0.01	0.07	
6	200 	1.1	110.3[d]	0[b]	0.005	0.002	90

[a] After 30 min. [b] No detectable change in aqueous metal conc. [c] Precipitate formed
[d] After 20 min. [e] Residual aqueous metal conc. below detection limits

formation of water soluble complexes, as evidenced by the aqueous phase changing colour from brown to bright yellow. Two of the ligands, **158** and **140a**, (entries 2 and 5 respectively), formed precipitates which resulted in the formation of fairly stable emulsions. The tetradentate ligand **159** (entry 1) and the tridentate ligand **151a** (entry 3) form stable complexes, from which the palladium is not easily back-extracted. Of the ligands examined it is apparent that the bidentate bis(thioether) **200** (entry 6) binds palladium selectively as well as releasing it readily on back-extraction. The amide containing ligands have slightly higher distribution coefficients for the base metals than the sulfur chelating ligand **200** (entry 6).

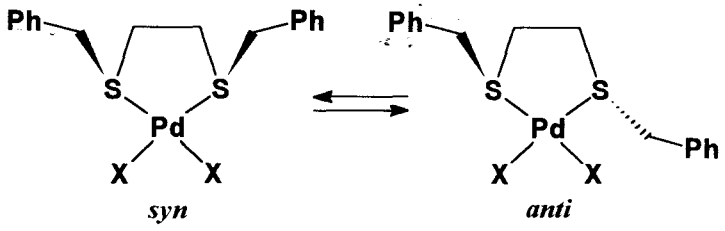
2.4.2.1.2 The mode of complexation of the bis(thioether) and monoamide ligands with palladium under solvent extraction conditions

Selected palladium-containing organic extracts from the solvent extraction studies were examined to determine the mode of complexation. The complexes were characterised mainly by ^{1}H NMR and infrared spectroscopy and, in some cases, the organic palladium extracts were purified by flash chromatography or preparative TLC. In all cases, the extraction solvent was removed *in vacuo* prior to spectroscopic analysis. Unfortunately, numerous attempts to obtain crystals suitable for single crystal X-ray analysis were unsuccessful.

Complexation of Pd^{2+} with the bis(thioether) **200**

The ^{1}H NMR spectrum (Figure 52b) of the palladium complex formed by this ligand, under solvent extraction conditions, indicates a palladium-sulfur chelate **201**. Slow inversion of the coordinated pyramidal sulfur donors results in both *syn*- and *anti*-isomers being observable by NMR spectroscopy. These isomers differ in having the benzyl groups on the same or opposite faces of the chelate ring (Figure 51).

Figure 51: The *syn*- and *anti*- isomers of the palladium-bidentate sulfur ligand complex.



201

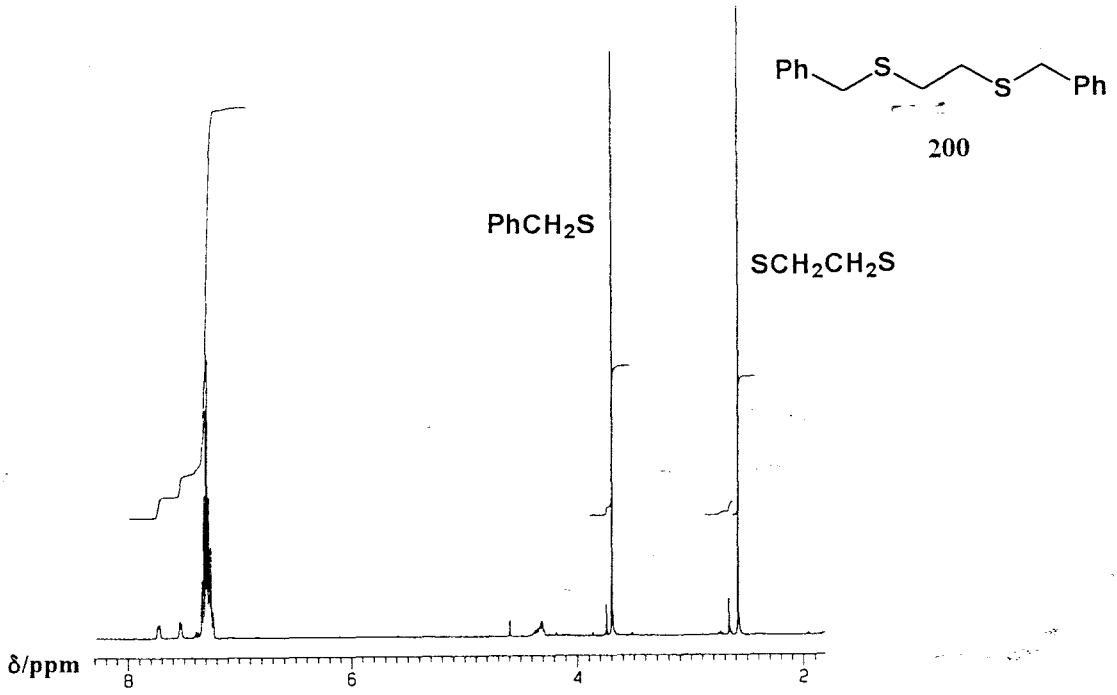
X: variable ligand

The two double doublets centered at 4.17 ppm and 4.48 ppm, arise from the diastereotopic benzyl methylene protons ($PhCH_2S$), each multiplet corresponding to one of the isomers. The upfield double doublet is assigned to the benzyl methylene protons of the *syn* isomer, the upfield shift being attributed to mutual shielding by the secondary magnetic field generated by the ring current of the neighbouring phenyl group. The multiplets corresponding to the chelate ring hydrogens are well separated for each isomer, appearing at *ca.* 2.55 and 2.80 ppm.

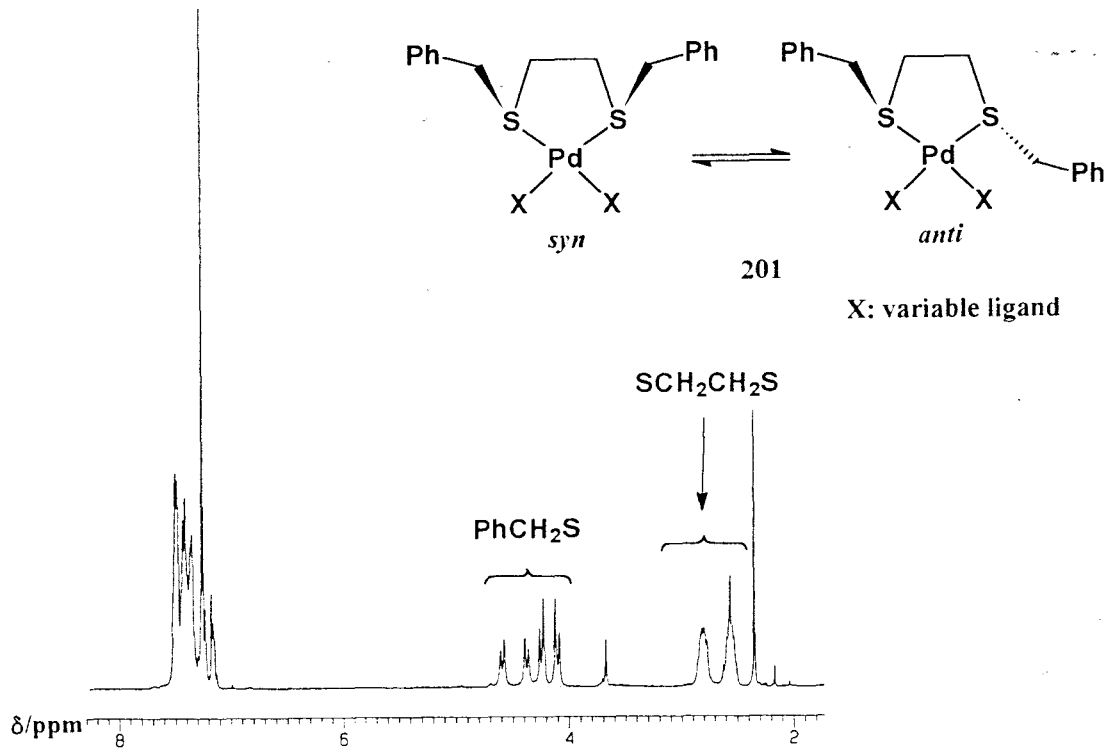
Palladium-chlorine bond-stretching infrared frequencies are usually found between 280 and 350 cm^{-1} and, having very high absorption coefficients, can be treated with a fair degree of confidence.[254] The exact frequency of the metal-chlorine stretch is dependent on the ligand *trans* to it, *cis*-ligands having very little influence over palladium-chlorine stretching frequencies.[254] Coates and Parkin[255] found the infrared active palladium-chlorine stretching frequencies for five-membered sulfur chelates to be in the region 296 to 323 cm^{-1}. However, the far infrared spectrum of the palladium chelate **201** reveals an absence of strong (or even bridging) metal-chlorine absorptions in the region 290 - 400 cm^{-1}, thus excluding a complex of the expected type $[PdLCl_2]$. Consequently, it is assumed that the sulfur donors are also acting as bridging donors. The complex **201** is soluble in chloroform and is readily eluted on silica gel, suggesting a low molecular weight polymer, possibly a cyclic hexamer.

Figure 52: The 400MHz ^{1}H NMR spectra in $CDCl_3$ of: a) the bidentate sulfur ligand 200; and b) the palladium(II) complex 201 of this ligand.

a)



b)



Complexation of Pd^{2+} with the tetradentate dibenzyl ligand **159**

Chromatographic (TLC) analysis of the organic extract showed it to contain three components. Separation by preparative layer chromatography (PLC) afforded a major component (R_F 0.72; 6 mg) and two minor components (R_F 0.34; 1.5mg and R_F 0.29; 1.5mg). Palladium(II) is known to exhibit various complexation modes with tetradentate ligands (*cf.* structures **195-199**, pp. 129 and 130), and IR and NMR spectroscopy was used in an attempt to establish the structure of the major component.

The absence of an NH absorption band in the infrared spectrum, coupled with a substantial decrease (50 cm^{-1}) in the carbonyl stretching frequency, indicates coordination to palladium through the deprotonated amide nitrogen. This conclusion is supported by the apparent absence of an amide proton signal and the downfield shift of the *ortho*-H signal to 8.74 ppm (from 8.41 ppm for the free ligand) in the ^1H NMR spectrum of the complex (Figure 53b). While the ^1H NMR spectrum of the tetradentate ligand is complicated, several features provide useful structural information.

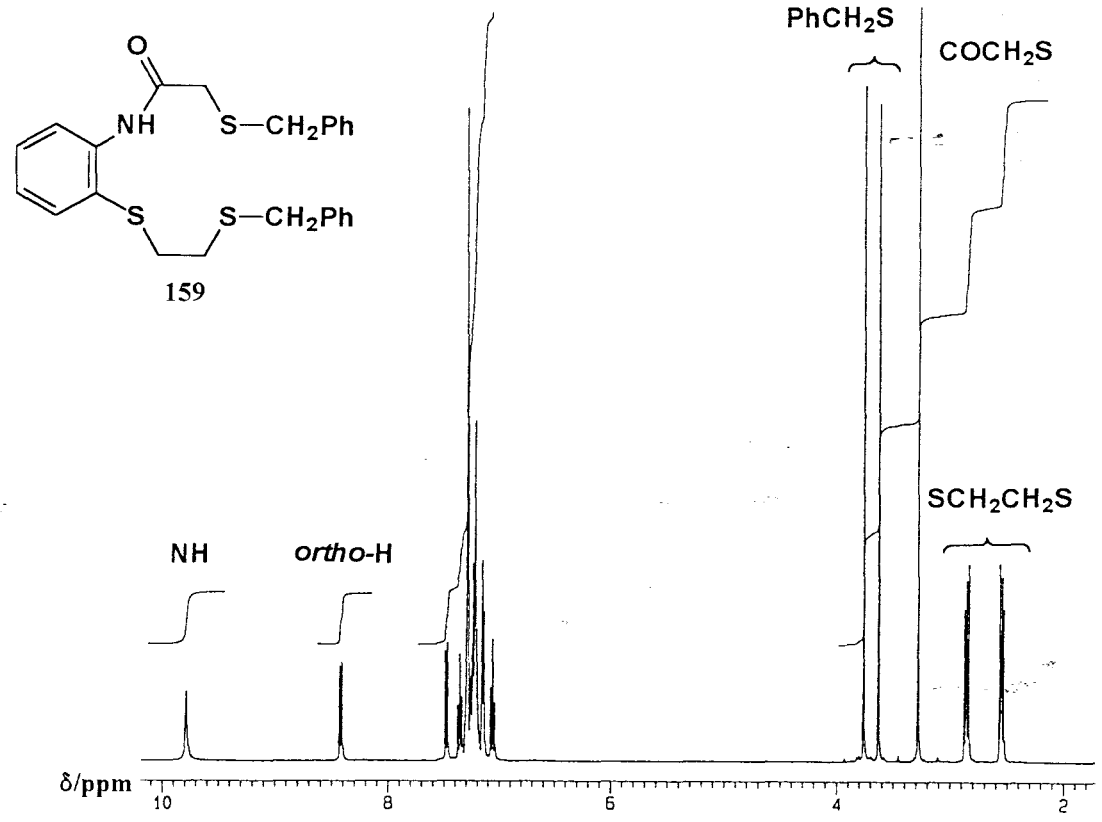
i) Deshielding of the ethylene (SCH_2CH_2S) protons [compared to the free ligand (Figure 53a)] and the multiplicity of their signals, in the region δ 2.5-3.5 ppm, are consistent with chelation of the adjacent sulfur atoms with the metal.[250]

ii) The doubling of signals indicates the presence of *syn*- and *anti*-isomers analogous to those observed on complexation of the bidentate sulfur ligand **200**. This is particularly evident in the signals for the benzyl protons which are rendered diastereotopic on formation of the chelate. Thus, deshielded benzyl protons in the *anti*-isomer account for the double doublet at 4.15 ppm and the broad singlet at 4.32 ppm, while the benzyl protons in the *syn*-isomer contribute to the overlapping multiplets at *ca.* 3.75 ppm.

iii) Theoretically, one would expect to see 8 peaks for the diastereotopic $CO.CH_2S$ methylene protons, a double doublet for each of the two ^1H NMR resolvable isomers (the *syn*- and

. Figure 53: The 400MHz ^{1}H NMR spectra in $CDCl_3$ of a) the tetradentate ligand 159, and b) the palladium(II) complex 202 of this ligand.

a)



b)

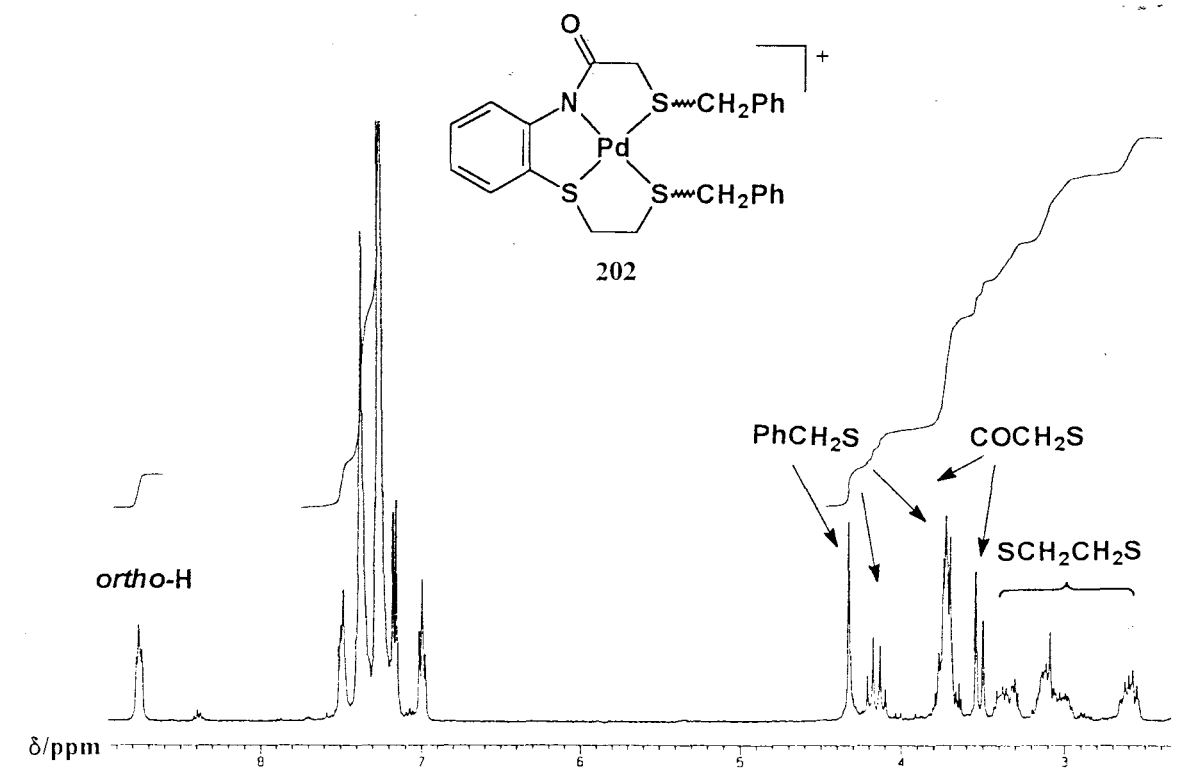
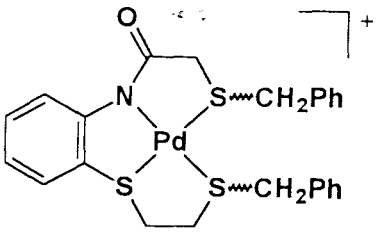
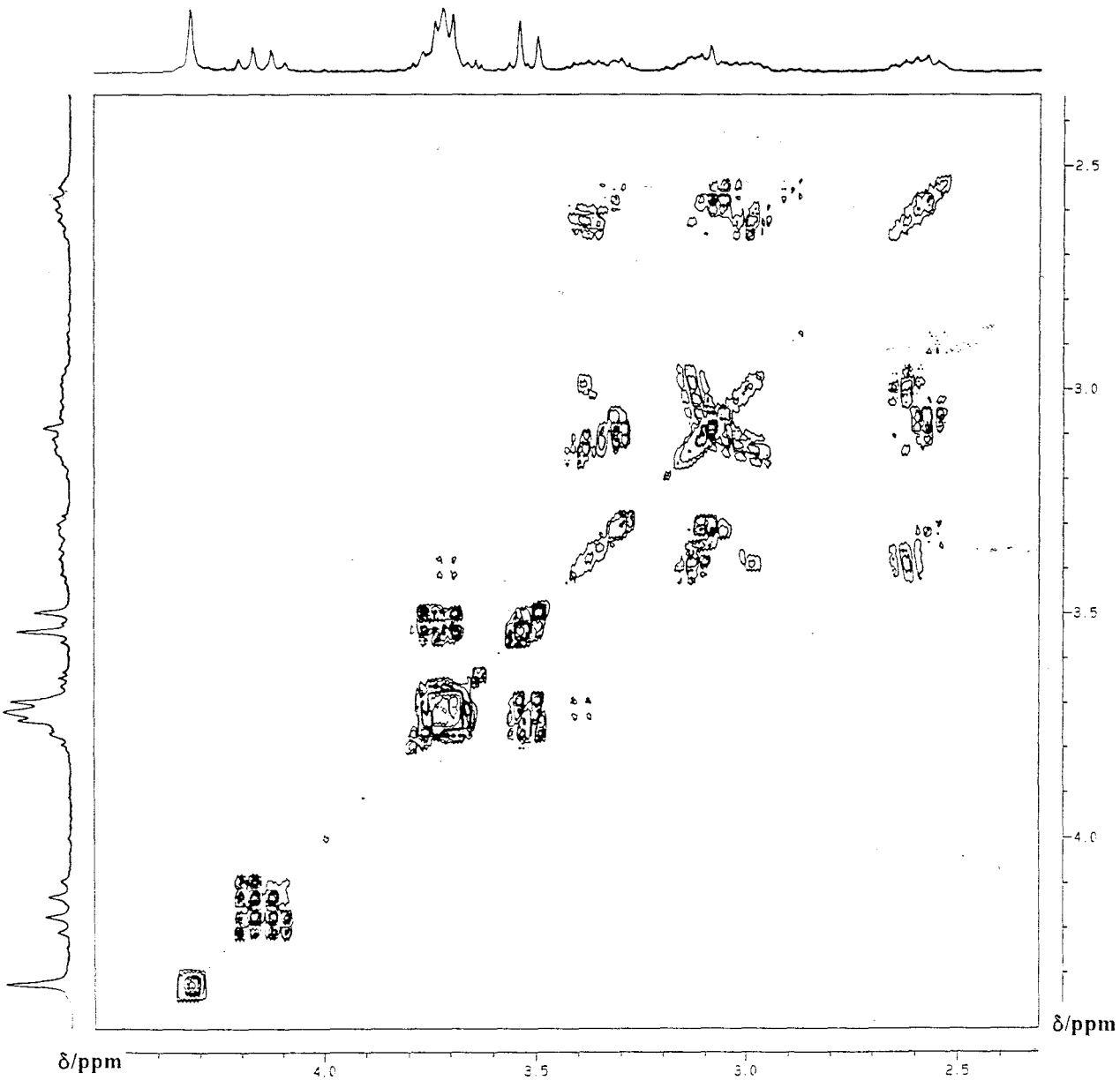


Figure 54: Partial COSY NMR spectrum (2.4 - 4.5 ppm) in $CDCl_3$ of the tetradentate complex 202.



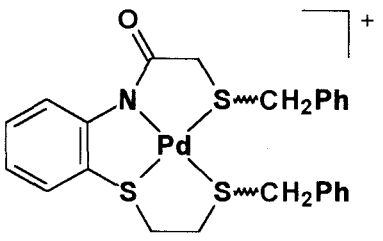
202



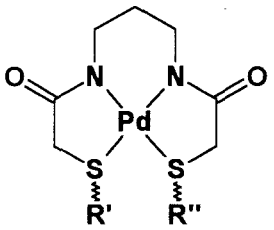
anti-isomers). In the spectrum shown in Figure 53b, however, only one double doublet is resolvable and is partly obscured by the multiplet at 3.75 ppm, the remainder of the signal appearing as the doublet at 3.52 ppm. Further confirmation that the double doublets are overlapping comes from the integrations and from another ^{1}H NMR spectrum of this complex, in which the peaks of the doublet at 3.52 ppm show fine splitting. The downfield shift of these signals (from 3.46 ppm in the free ligand) further indicates involvement of the adjacent sulfur as the fourth donor in the palladium(II) complex. This deduction is strengthened by the apparent absence of metal-chlorine absorptions in the far infrared region.

The foregoing signal assignments are supported by the 2D-NMR (COSY) data (Figure 54) and indicate formation of *syn*- and *anti*-isomers of a tetradentate palladium complex tentatively formulated as structure **202**. Hill and Simpson[256] have prepared a series of tetradentate palladium complexes **203** which, similarly, exhibit *syn-anti* isomerism. The coupling constants for the splitting of the $CO.CH_2S$ methylene protons are very similar for complexes **202** and **203**.

Figure 55: The proposed palladium-tetradentate complex 202 formed in this study and similar complexes 203 synthesised by Hill and Simpson.[256]

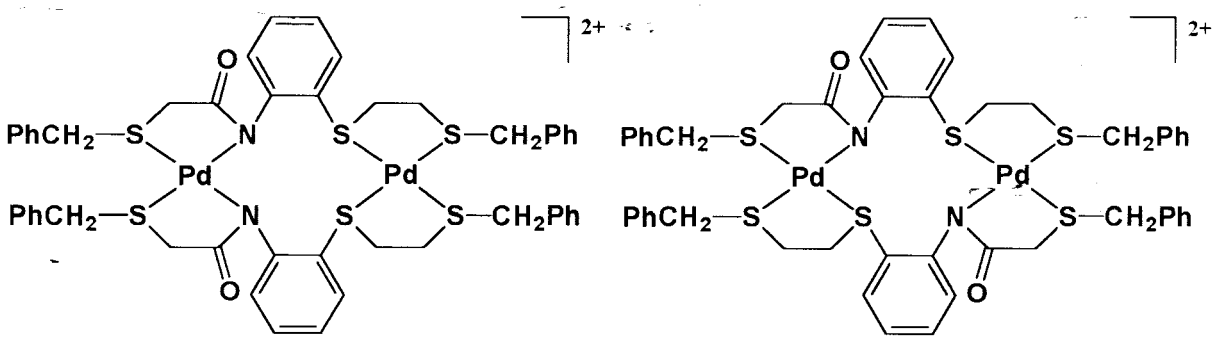


202



203
a R' = R" = Et
b R' = R" = Ph
c R' = Et, R" = Ph

Figure 56: Possible structures of the palladium(II)-tetradentate ligand complex.

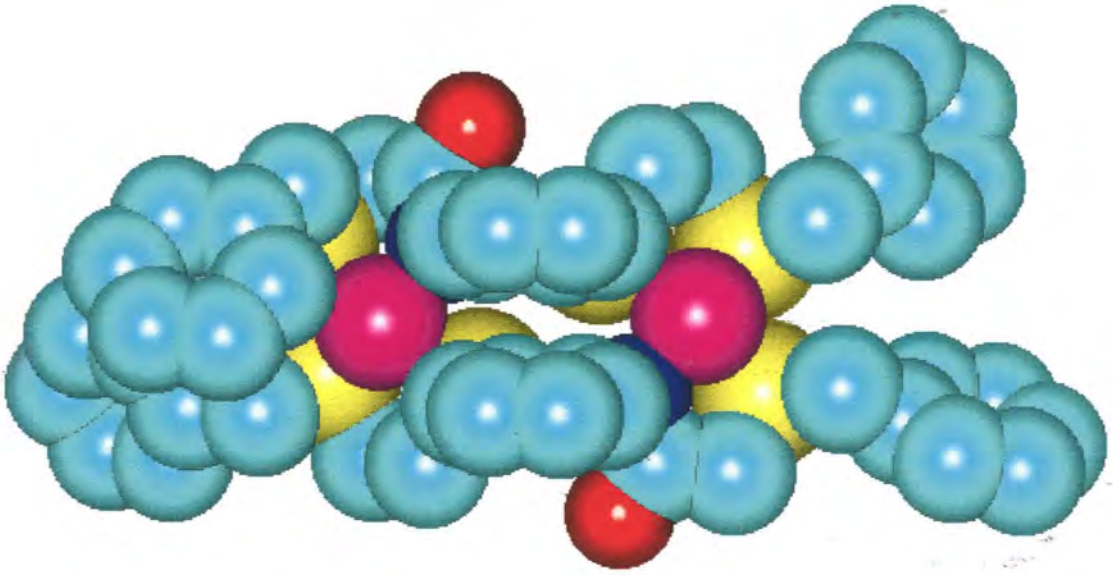


204 **205**

Considering this spectroscopic evidence, there can be little doubt that ligand **159** is coordinating with palladium through all four donors. The complexes are soluble in chloroform and are readily eluted on silica gel and, consequently, are unlikely to be polymeric. In fact, the ease of elution suggests that the complex may be monomeric. Further evidence counting against dimeric structures of type **204** and **205** (Figure 56) comes from molecular modelling. In the energy minimized conformers of the dimers **204** and **205** (illustrated for dimer **205** in Figure 57a), the amide carbonyl is approximately perpendicular to the aromatic plane. Complex **202** has a much lower strain energy than the dimers **203** and **204** and, in the energy minimized conformer, the amide carbonyl is approximately coplanar with the aromatic ring (Figure 57b). This coplanarity is confirmed by the downfield shift of the *ortho*-hydrogen resonance (Figure 53b). We therefore conclude that the major complex formed on extraction of palladium with the ligand **159** is, in fact, the tetradentate monomer **202**.

Considering the unsuccessful attempts by McAuliffe and Murray *et al.*[248, 249, 250] to synthesise monomeric platinum and palladium complexes, in which all four sulfur donors of a tetrathioether ligand are coordinated to the metal, it is surprising that the dibenzyl ligand **159** readily displaces all four chloride ligands on palladium. However, ^{1}H NMR and infrared

Figure 57a: An energy minimised conformer of the putative dimeric complex 205, in space-filling and stick renderings. To simplify the diagrams the hydrogen atoms are not shown.



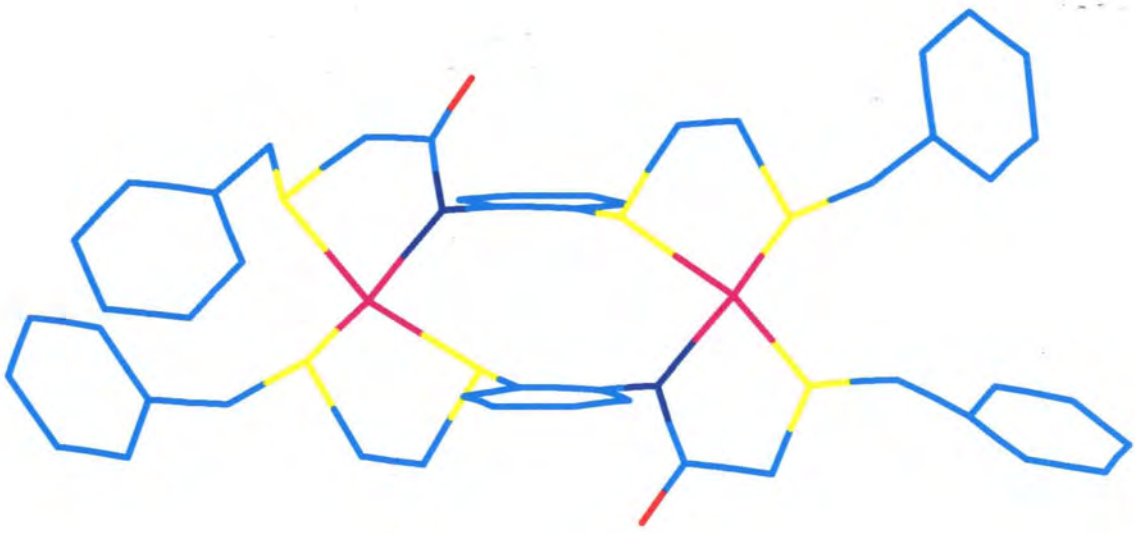
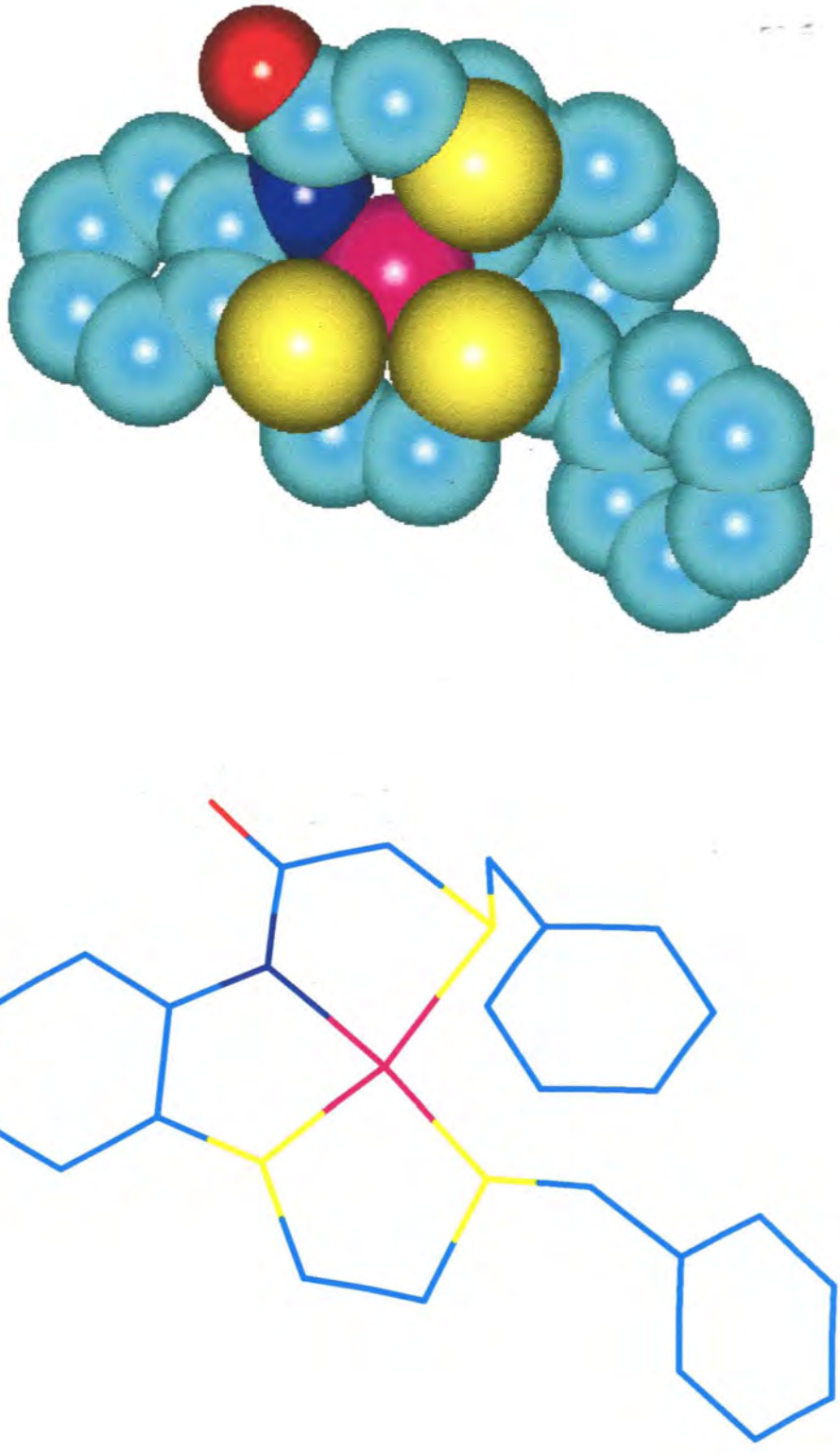


Figure 57b: An energy minimised conformer of the monomeric complex 202, in space-filling and stick renderings. To simplify the diagrams the hydrogen atoms are not shown.



spectroscopy both provide clear evidence that this is the case, and the small percentage of palladium back-extracted from this complex confirms the stability of the complex formed. The ability of ligand **159** to form monomeric tetracoordinate complexes with palladium(II) could stem from the preorganisation afforded by the coplanarity of the aromatic ring and the amide moiety. Coordination of the deprotonated amide nitrogen may also have a greater labilising effect (compared to thioether donors) on the chloride ligands.

Complexation of Pd^{2+} with the tridentate ligand **151a**

The ^1H NMR spectrum of the palladium complex formed by this ligand, under solvent extraction conditions, is difficult to interpret. Three doublets can be distinguished for the *ortho*-hydrogen; these are 0.54 ppm further downfield than the *ortho*-hydrogen doublet of the free ligand and suggest coordination through the amide nitrogen. The MeS hydrogen singlet is also shifted downfield by *ca.* 0.5 ppm, indicating coordination of this sulfur to the metal. The infrared spectrum of the complex shows an absence of both the amide NH and the thiol SH absorptions, confirming that coordination is also taking place through the deprotonated amide nitrogen and the thiolo sulfur. The amide carbonyl stretching frequency is 40 cm^{-1} lower in the complex, confirming coordination through the amide nitrogen. No palladium-chlorine stretching absorptions appear in the far infrared spectrum, but polymer formation is excluded on the basis that the complex is soluble in chloroform and can easily be eluted on silica. Dimeric or trimeric structures with bridging thiolato sulfurs, analogous to complexes **191** and **192** (p. 128), are considered possible in this case.

Complexation of Pd^{2+} with the mercaptoacetanilide **140a**

This ligand formed an orange precipitate with palladium after shaking the combined solutions for five minutes. Using flash chromatography, this precipitate was separated into two components - an insoluble component which could not be eluted on silica and a yellow fraction

which could be eluted. The insoluble product, which was the major component, is sparingly soluble, even in DMSO-d_6, and is undoubtedly polymeric, its ^{1}H NMR spectrum showing broad peaks typical of polymer formation. A broad, low baseline peak at *ca.* 10 ppm is assigned to the amide hydrogen. Infrared spectroscopy confirms that coordination is not taking place through the amide nitrogen, and a thiolato-bridged polymeric structure is proposed for the insoluble major product. The soluble (minor) product was purified by preparative layer chromatography, but broad peaks in the ^{1}H NMR spectrum of this product made characterisation difficult.

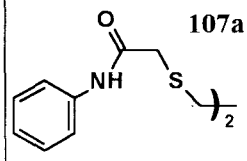
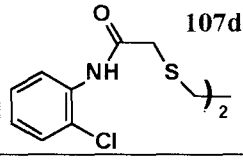
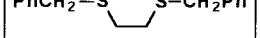
2.4.2.2 The sulfur-containing diamide ligands as extractants

2.4.2.2.1 Distribution coefficients for the diamide ligands

The presence of two, polar amide functions in these ligands reduces their solubility in organic solvents, necessitating dissolution of some of the ligands in twice the normal volume of solvent. For these extractions, 20ml of organic solution was shaken with 10 ml of the aqueous solution of metal salts. Apart from this, the experimental conditions were the same as those used for solvent extraction with the monoamide ligands. The *ortho*-chloro ligand **107d** and the *ortho*-methoxy ligand **107f**, however, readily dissolved in the organic solvents used.

Table 13 compares the distribution coefficients, for two of the diamide ligands and the bis(thioether) ligand **200**, for the divalent metals, palladium, copper, nickel and cobalt. The extraction of palladium was studied in both chloroform and toluene. Similarly to the monoamide ligands, these diamide ligands barely extract the harder base metals, although ligand **107a** does show an above average affinity for nickel. This could be due to the formation of sulfur-oxygen chelates in this particular case.

Table 13 : Distribution coefficients[a] for divalent metals using the diamide ligands 107a,d and the bis(thioether) 200 as extractants.[b]

Entry	Ligand	Toluene	Chloroform			
		Pd	Pd	Cu	Ni	Co
1	 107a	413[c,d,e]	46[c]	0.02	8	0.03
2	 107d	31[c,e]	0.3	0.03	0.02	0[f]
3	 200	110	0.2	0[f]	0.005	0.002

[a] After 20 minutes. [b] Ligand concentration 1.1 x 10^{-3} M. [c] Precipitate formed. [d] Ligand concentration 0.55 x 10^{-3} M. [e] After 10 minutes. [f] No detectable change in the aqueous metal concentration.

The distribution coefficients for palladium, for all three of the ligands listed in Table 13, are substantially reduced when chloroform is used as the organic phase, but this could be a kinetic effect. Normally, reaction between the extractant and the metal takes place at the organic-aqueous interface; [253] however, weak π-bonding between palladium and toluene could enhance the extraction kinetics of palladium.

Equilibrium studies [257] have shown that, for bidentate chelating ligands of type $RS(CH_2)_2SR$, increasing the electron-withdrawing ability of the R group decreases the stability of the thioether complex. Thus, considering inductive effects only, and assuming that only a sulfur-sulfur chelate forms, one would expect the benzyl thioether ligand **200**, not the diamide ligand **107a**, to have the highest distribution coefficient for palladium *(cf.* entries 1 and 3). The lower distribution coefficient for the *ortho*-chloro derivative in toluene (entry 2) could be partly

attributed to the net electron-withdrawing effect of this substituent, but this effect is expected to be small. Intramolecular hydrogen-bonding between the *ortho*-chloro substituent and the amide hydrogen, however, could contribute significantly to the low distribution coefficient. *Ortho*-substituents which hydrogen bond with the amide hydrogen lock the aromatic ring and the amide moiety into a planar conformation, which may be partially disrupted in solvents which also hydrogen-bond with the amide hydrogen. To study the possible effect of conformational change on extraction capability, the diamide ligands **107 a-f** were studied as extractants in the solvents toluene, chloroform and methyl isobutyl ketone (MIBK). The palladium distribution coefficients for these extractions are shown in Table 14.

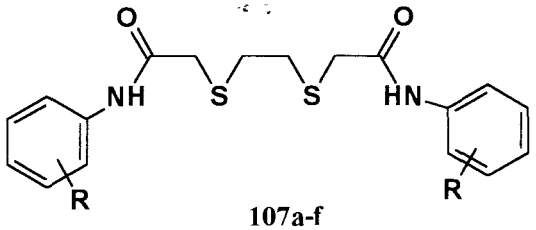
From the tabulated data it is apparent that:-

i) extraction is generally more efficient in toluene and MIBK, the *para*-methoxy ligand **107b** being an exception (entry 2);

ii) *ortho*-Substituents capable of hydrogen-bonding to the amide hydrogen [*i.e.* Cl (entry 4) and MeO (entry 6)] exhibit lower distribution coefficients in MIBK than the parent system **107a** (entry 1) or the *ortho*-methyl analogue **107e** (entry 5).

The enhanced extraction efficiency in toluene and MIBK may simply reflect better solvation of the palladium complexes, and it is difficult to draw any conclusions concerning conformational effects. The diamide ligands **107a-f** and the bis(thioether) ligand **200** were also tested as extractants for platinum, and were unable to extract detectable amounts of platinum(II) from 1 **M**-HCl into $CHCl_3$, over a 20 minute period. This is attributed to the kinetic inertness of platinum(II).

Table 14: Palladium distribution coefficients using the diamides 107a-f and the bis-(thioether) 200 as extractants[a] and chloroform, toluene or MIBK as solvent.



107a-f

Entry	Compd No.	R	$CHCl_3$		Toluene	MIBK	
			10 min	20 min	10 min	10 min	20 min
1	107a	H	11	46[b]	413[b,c]	184	369
2	107b	*para*-MeO	36	132[b]		42[b,c,d]	42[b,c,d]
3	107c	*meta*-Cl	7	40	641[b]	60	227
4	107d	*ortho*-Cl		0.3	31[b]	121[b,c]	167[b,c]
5	107e	*ortho*-Me	1	2.5		341[b,c]	511[b,c]
6	107f	*ortho*-MeO	1	3	24	52	162
7	200	$PhCH_2SCH_2)_2$		0.2	110[e]	20	83

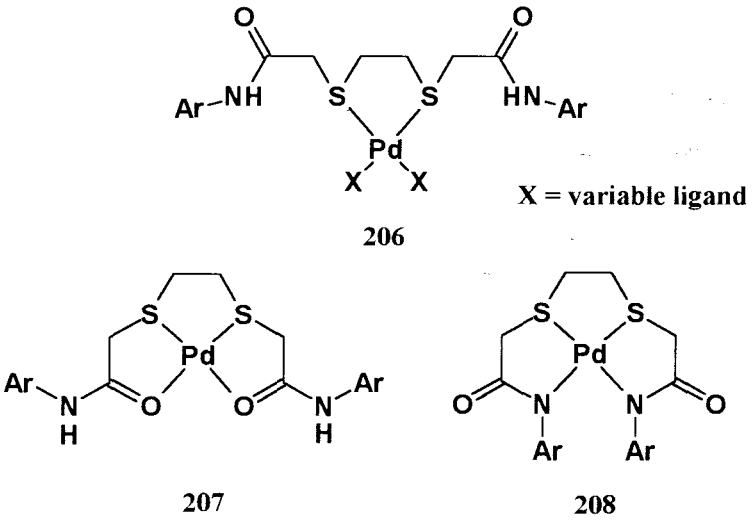
[a] Concentration of ligands 1.1 x 10^{-3} M. [b] Precipitate formed in organic phase. [c] Concentration of ligand 0.55 x 10^{-3} M. [d] Ligand not completely soluble in the organic solvent. [e] After 20 minutes.

2.4.2.2.2 The mode of complexation of the diamide ligands **107a-f** under solvent extraction conditions

The organic palladium-extracts were studied by ^1H NMR and infrared spectroscopy. The high distribution coefficients for the diamide ligands **107**, compared to the bidentate sulfur ligand **200** (entry 7, Table 14), suggest that the sulfur atoms may not be the only donors coordinating with palladium. Possible modes of coordination for the diamide ligands are shown in Figure 58. Although palladium(II) complexes with oxygen donors are not normally very stable, if a chelate ring is formed in which the other donor atom is sulfur, nitrogen or oxygen, as is the case in complex **207**, the complexes tend to be more stable.[238c] Unsaturated systems, such as alkenes,

dialkenes and alkynes, are known to complex with palladium(II), but comprehensive reviews[238] do not report the isolation of complexes with coordination between phenyl rings and palladium(II). Consequently, coordination of the phenyl rings of these ligands with palladium was not considered.

Figure 58: Possible modes of coordination of the diamide ligands 107a-f with palladium(II).



The ^{1}H NMR spectra of the palladium-diamide extracts show peaks corresponding to the formation of a sulfur-sulfur chelate, as well as peaks due to the amide hydrogen resonances. The infrared spectra show the presence of an NH bond and a slight *increase* (10-20 cm^{-1}) in the carbonyl stretching frequencies on coordination. When the carbonyl oxygen of mercaptoacetanilides, or other carbonyl functions, coordinate with metals, the carbonyl stretching frequency is usually *decreased* (by 20 - 90 cm^{-1} in the case of mercaptoacetanilides).[66, 258] The infrared data thus indicate that coordination is not taking place through the amide nitrogen or oxygen donors, *i.e.* complexes of type **207** and **208** are not forming. All the palladium(II) complexes of the diamide ligands **107a-f** have similar spectroscopic features, suggesting that they all extract palladium by formation of the sulfur-

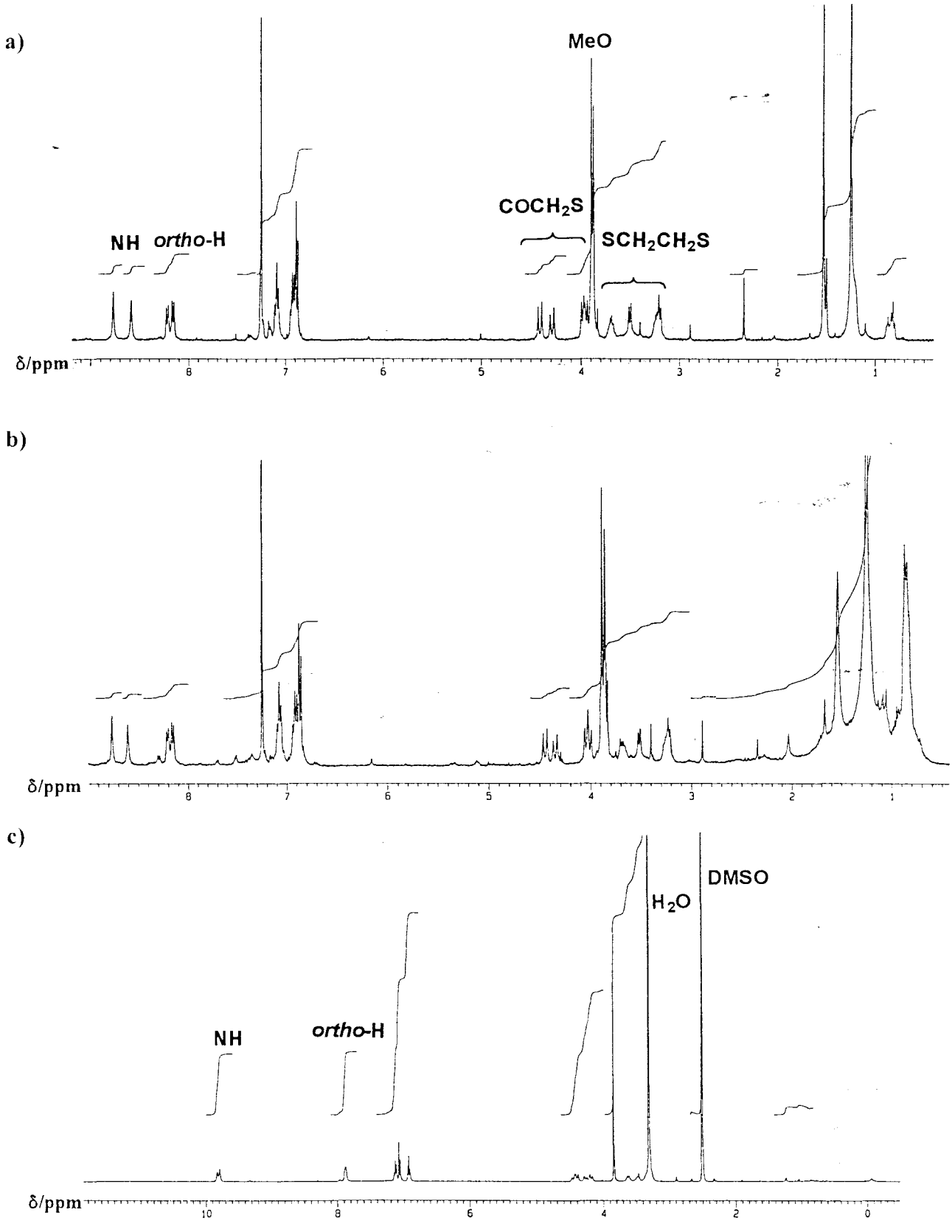
sulfur chelate **206**.

Although oxygen-containing solvents form weak complexes with palladium(II), few such complexes have been isolated. Palladium(II)-acetone complexes have been isolated under the special conditions in which acetone is the solvent and two chloride ligands, which are initially coordinated with a palladium(II) chelate complex, are removed by precipitation with silver.[259] The ^{1}H NMR spectra of all the palladium-diamide complexes from the MIBK extractions contain MIBK peaks; however, the integration indicates these to be due to traces of incompletely removed MIBK rather than the result of MIBK-palladium coordination. This conclusion is supported by the infrared spectra which, in all cases, show only one carbonyl stretching absorption. Palladium-chlorine stretching absorptions are absent in the far infrared spectra of all the complexes formed, irrespective of the solvent used for the extraction. Weak IR absorption bands were observed in the region 290 to 340 cm^{-1}, and these have been assigned to palladium-sulfur stretches, which are usually found in this region.[247] The apparent absence of palladium-chlorine absorptions in the IR spectra of these complexes, coupled with the evidence that coordination is not taking place through either the amide nitrogen or oxygen, suggest that a sulfur-bridged polymer containing sulfur-sulfur chelates of type **206** is being formed in all the solvents studied. Although coordination between palladium and the amide nitrogen or oxygen cannot be proven spectroscopically, weak interactions of this type cannot be discounted and could account for the enhanced extraction of palladium by these ligands. *ortho*-Substituents could inhibit these interactions, and this could explain the low distribution coefficients for the *ortho*-substituted ligands

When the *ortho*-methoxy ligand **107f** was used in toluene for the solvent extraction of palladium, the organic phase remained a clear bright yellow after shaking for ten minutes. After shaking for 20 minutes, a fine yellow-green precipitate had formed in the organic phase. The ^{1}H

NMR spectra (in $CDCl_3$) of the "10-" and "20-minute" organic extracts are shown in Figures 59a and 59b respectively. The deshielded methylene ($CO.CH_2S$) multiplets at *ca.* 4.0 and 4.4 ppm indicate chelation of the metal by both sulfur donors while the presence of amide NH singlets at *ca.* 8.6 and 8.8 ppm (the *syn-* and *anti*-isomers are resolvable by NMR) confirm that the amide nitrogen has not been deprotonated. The spectra of the "10-" and "20-minute" extracts differ mainly in the region δ 0.8-2 ppm. The "10-minute" organic extract was initially soluble in $CDCl_3$, but after standing for two days, in the NMR tube, a yellow precipitate formed and the ^1H NMR spectrum of the sample was similar to that of the "20-minute" extract (Figure 59b). Chromatography (PLC) of the "20-minute" extract afforded a yellow solid, for which ^1H NMR spectra were obtained using different solvents. In $CDCl_3$, the spectrum exhibited broad, high field peaks as in Figure 59b. This suggests that these peaks are not due to an impurity but rather to substantial aggregation in $CDCl_3$, resulting in dramatic shielding effects. The intensity of the high-field peaks (between 0.8 and 2 ppm) are diminished when the spectrum is run in CD_3CN, and are almost completely absent in DMSO-d_6 (Figure 58c). The absence of metal-chlorine absorptions in the far infrared suggests that the aggregation may involve weak sulfur bridges, which are partially cleaved in the weakly coordinating solvent, CD_3CN, and almost completely cleaved in the more strongly coordinating solvent DMSO-d_6. The ^1H NMR spectrum in DMSO-d_6 (Figure 59c) is, in fact, consistent with the monomeric chelate structure **206**, where the additional ligands (**X**) are DMSO molecules.

Figure 59: 400MHz ^{1}H NMR spectra of the *ortho*-methoxy diamide(107f)-palladium complex in $CDCl_3$ a) after shaking for 10 minutes, b) after shaking for 20 minutes, and c) the "20-minute" extract in DMSO-d_6.



2.4.3 Coordination of selected ligands with platinum(II), palladium(II) and cisplatin

2.4.3.1 Coordination reactions of the sulfur-containing amide ligands in acidic and basic media

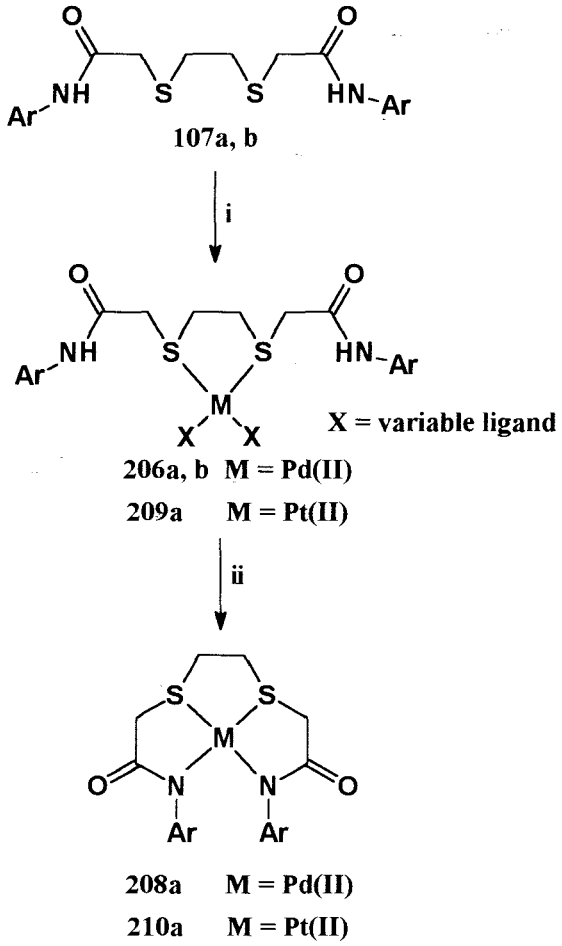
To better understand the coordination properties of the sulfur-containing amide ligands, selected ligands were complexed with platinum(II) and palladium(II) in acidic and basic solutions. A mixture of methanol and water was used as solvent to ensure dissolution of the reactants.

The diamide ligands **107a,b**, in methanol, were mixed with palladium(II) chloride in 1 **M**-hydrochloric acid (Scheme 32). Upon mixing of the ligand and metal solutions, the mixture immediately became yellow and, in the case of the *para*-methoxy derivative **107b**, a yellow precipitate formed within ten minutes. After allowing the mixtures to stand for two days, the methanol was removed and the yellow precipitates were analysed by ^{1}H NMR and infrared spectroscopy. Both spectroscopic methods clearly indicate (for reasons discussed in previous cases) that coordination involves the sulfur donors alone, while the absence of strong metal-chlorine absorptions in the far infrared suggests that the sulfur donors act as bridging ligands with resultant polymer formation. Further evidence for the polymeric nature of the palladium complexes **206a,b** is provided by their relative insolubility in acetone and their complete lack of mobility on silica, even when eluted with methanol-$CHCl_3$ (2:8).

Ligand **107a** was reacted with platinum(II) and palladium(II) in the manner described above but, after two hours of stirring, the homogeneous mixtures were made basic (pH~9) with either sodium carbonate or potassium carbonate in aqueous methanol. After further stirring at room temperature, the methanol was removed to yield a yellow precipitate for the palladium complex and a light-green precipitate for the platinum complex. Both precipitates were shown by ^{1}H NMR and infrared spectroscopy to be the sulfur-nitrogen chelate complexes **208a** and **210a**

(Scheme 32). The ^{1}H NMR spectrum for the palladium complex **208a** contains small amide NH peaks, but comparison of the integrals of these peaks with those of other peaks shows that deprotonation of the amide nitrogen is essentially complete. Moreover, the NH absorption is absent from the infrared spectra of both complexes. The carbonyl stretching frequency of the platinum complex **210a** is 50 cm^{-1} lower than that of the free ligand, whereas the CO absorption frequency is relatively unaffected by palladium coordination. It is thus apparent that in basic

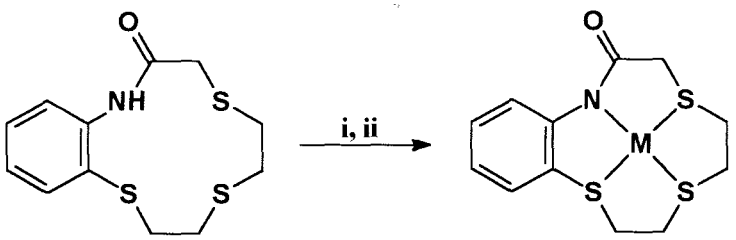
Scheme 32: Coordination of the diamide ligands 107a,b with platinum(II) and palladium(II) in acidic and basic media.



reagents		Ar
i) $PdCl_2$ or K_2PtCl_4 in HCl	a	Ph
ii) Na_2CO_3 or K_2CO_3	b	4-$MeOC_6H_4$

medium (pH~9) the amide moieties are deprotonated permitting formation of the monomeric, tetradentate complexes **208a** and **210a**. Computer modelling of these complexes (illustrated for complex **210a** in Figure 60) show the phenyl rings to be approximately parallel to each other and inclined to the plane of the amide function. This conformation is supported by the ^{1}H NMR spectra of the complexes which show that only a slight downfield shift (< 0.1 ppm) of the *ortho*-hydrogen resonance occurs upon complexation. The Pt-S (2.32 Å) and Pt-N (1.93 Å) bond lengths in the energy minimised model of complex **210a** are comparable to the Pt-S (2.28 and 2.30 Å) and Pt-N (2.02 Å) bond lengths of the Pt(II)-S,S,N,N complex with macrocycle **68** (p. 43).[49]

Scheme 33: Synthesis of macrocyclic platinum(II) and palladium(II) complexes.



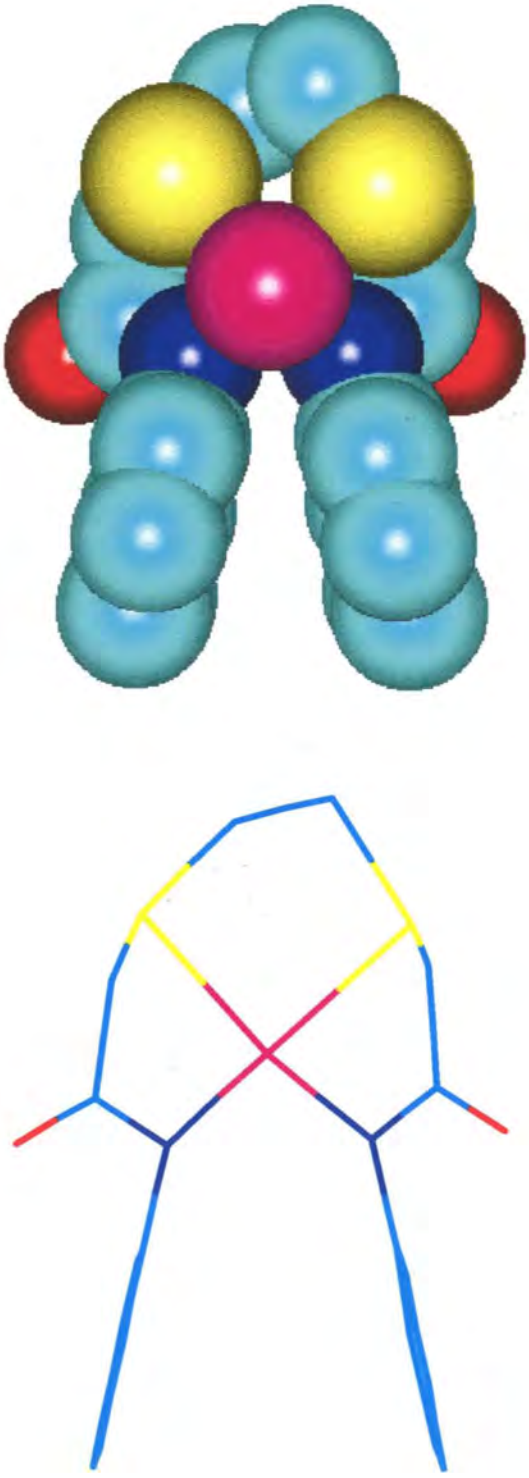
182a **211a,b**

reagents
i) $PdCl_2$ or K_2PtCl_4 in HCl
ii) K_2CO_3

	M
a	Pd(II)
b	Pt(II)

Complexes of the macrocyclic ligand **182a** with platinum(II) and palladium(II) were prepared in an acidic, homogeneous, aqueous methanol-acetone medium which, after two hours of stirring, was basified (pH 8-9) with potassium carbonate. Removal of the organic solvents yielded an orange precipitate for the palladium complex **211a** and a light-green precipitate for the platinum complex **211b** (Scheme 33). Each of these precipitates was shown by TLC to contain only one component, which was readily eluted. The infrared spectra of both complexes confirm the absence of an NH bond, and reveal that the carbonyl stretching frequency has

Figure 60: An energy minimised structure of complex 210a, showing the phenyl rings inclined to the plane of the amide moiety, in space-filling and stick renderings. To simplify the diagrams the hydrogen atoms are not shown.



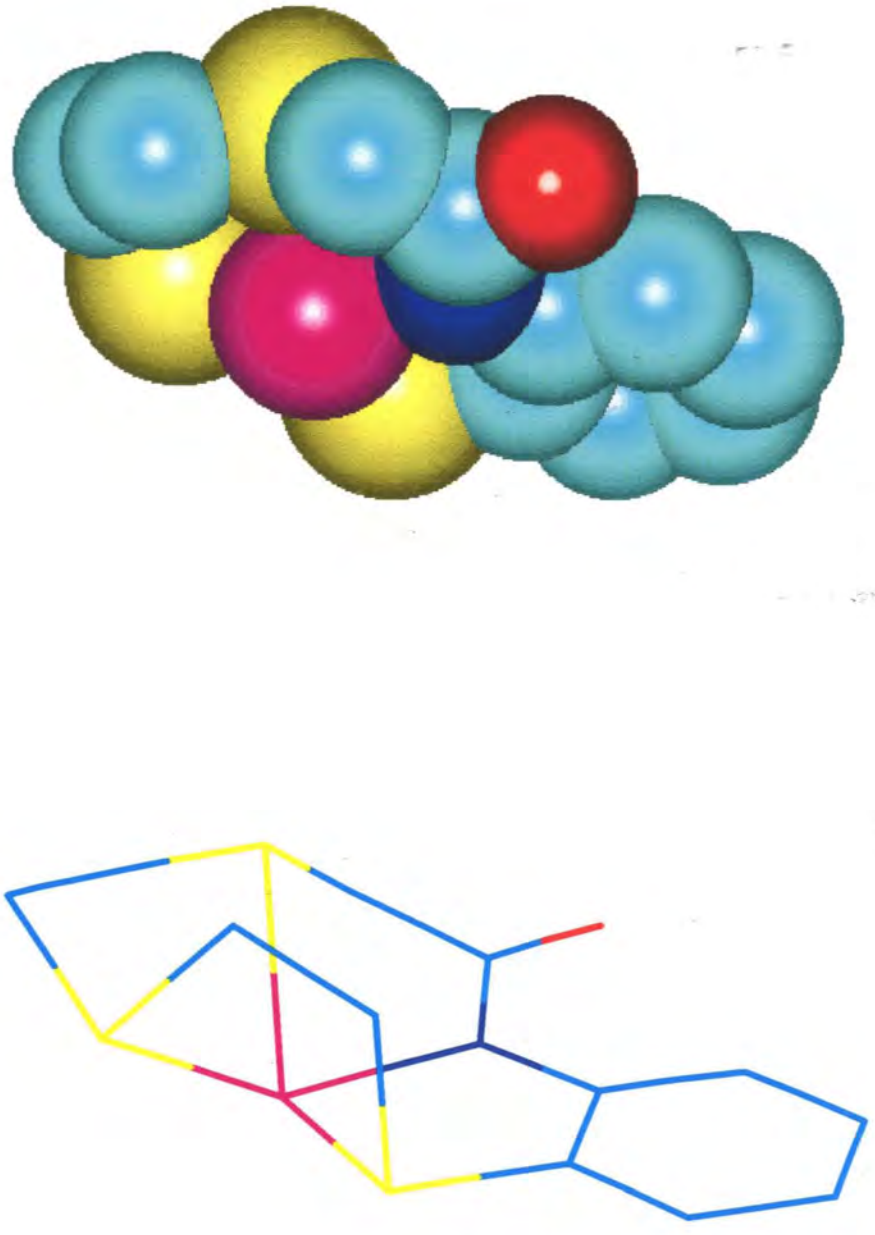
decreased upon complex formation (Table 15). The apparent absence of an amide NH signal in the ^{1}H NMR spectra of both complexes supports deprotonation of the amide group. The doubling of the aromatic hydrogen signals and the presence of numerous overlapping multiplets, too complicated for unambiguous assignment, suggest the presence of at least two conformers of complexes **211a,b**, *i.e.* the conformers arising from slow inversion of coordinated sulfur. The downfield shift of the *ortho*-hydrogen resonance upon coordination is slightly greater for the platinum complex than the palladium complex. While this shift may be attributed to electrostatic deshielding upon coordination of the amide nitrogen, the downfield position of the *ortho*-hydrogen resonance suggests continued anisotropic deshielding by the amide carbonyl group. This indicates that the amide moiety is still, to a certain degree, coplanar with the aromatic ring in the coordinated ligand - a conformation which is supported by molecular modelling, as shown by the energy minimised structure of complex **211b** (Figure 61).

Table 15: ^{1}H NMR and infrared spectroscopic data for macrocycle 182a and its complexes with platinum(II) and palladium(II).

	macrocycle 182a	Pd(II) complex 211a	Pt(II) complex 211b
ν(NH)/cm^{-1}	3240	absent	absent
ν(CO)/cm^{-1}	1640	1605	1615
$\delta(H_{ortho})$/ppm	8.57	8.95	8.99
$\Delta\delta(H_{ortho})$ [a]/ppm		0.38	0.42

[a] **Shift of the *ortho*-hydrogen upon complexation relative to the free ligand.**

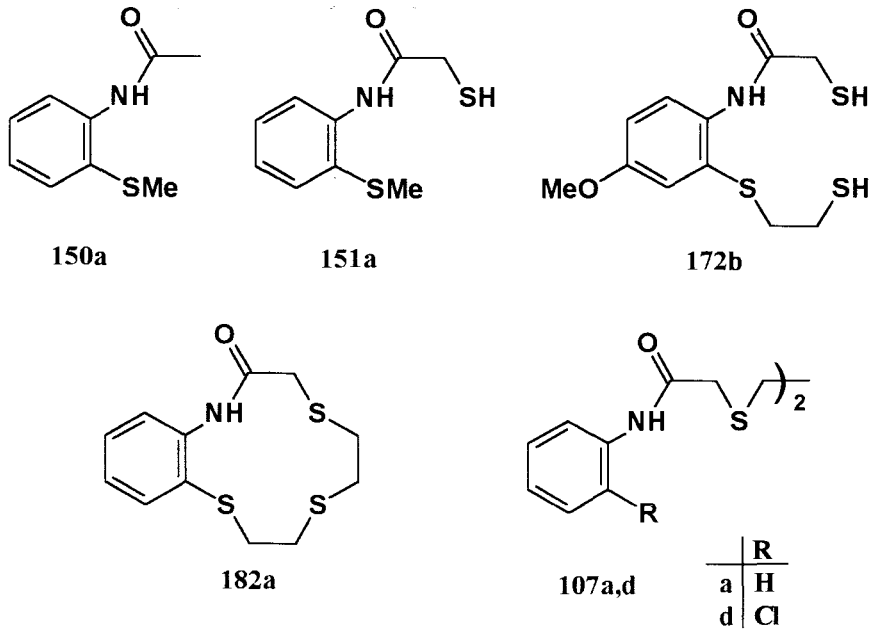
Figure 61: An energy minimised structure of complex 211b, in which the amide group is essentially coplanar with the aromatic ring, in space-filling and stick renderings. To simplify the diagrams the hydrogen atoms are not shown.



2.4.3.2 The reaction of selected ligands with platinum(II) at pH 7

In order to assess the capability of the sulfur-containing amide ligands as rescue agents for platinum, selected systems (**150a**, **151a**, **172b**, **182a**, **107a,d**; Figure 62) were reacted with tetrachloroplatinate at pH 7. Although platinum in the body is likely to be bound to sulfur containing biomolecules, this study aimed to show whether or not platinum(II) is capable of bonding to the amide nitrogen of these synthetic ligands, with the subsequent formation of a strong Pt-N bond, at physiological pH. To ensure homogeneity, the ligands were dissolved in methanol and the tetrachloroplatinate in dilute hydrochloric acid, the composition of the solvent after mixing being 80% aqueous methanol. Buffering this solvent at pH 7 was problematic as the solubility of most inorganic buffers in 80% aqueous methanol is low. Consequently *N,N*-diethylaniline (pK_a 6.56) and dilute (0.1 **M**) HCl were used as the buffer system; this tertiary amine was not expected to interfere with the coordination reactions. Typically, the ligand and *N,N*-diethylaniline were dissolved in methanol, while the tetrachloroplatinate was dissolved in

Figure 62: The ligands which were complexed with K_2PtCl_4 at pH 7.



dilute HCl. The quantities and concentrations of these solutions were calculated such that, upon mixing, an 80% aqueous methanol solution was obtained in which the *N,N*-diethylaniline was 25% protonated, thus giving a pH of approximately 7. The disappearance of free ligand and complex formation were followed by TLC.

Complexation of Pt^{2+} with the methyl sulfide ligand **150a**

The bidentate sulfur ligand **150a** reacted slowly with platinum(II) and, after two hours, the presence of product could barely be detected. After 26 hours, the reaction had gone almost to completion, as evidenced by the faint free ligand spot on TLC. The product, a yellow oil, was purified by flash chromatography and characterised by ^{1}H and ^{13}C NMR and infrared spectroscopy. The downfield shift (0.29 ppm) of the SMe ^{1}H NMR signal confirms coordination of this sulfur to the platinum. Both ^{1}H NMR and infrared spectroscopy indicate the presence of the amide hydrogen thus confirming that coordination is not taking place through the deprotonated amide nitrogen. The substantial increase in the CO ($\Delta\nu$ 40 cm^{-1}) IR stretching frequency, which occurs upon complexation, rules out coordination through the carbonyl oxygen - a conclusion confirmed by the ^{13}C NMR spectrum of the complex, which shows no change in the resonance frequency of the carbonyl carbon upon coordination. Weak absorptions in the far infrared are assigned to platinum-sulfur absorptions, but the presence of metal-chlorine bonds cannot be conclusively proven. The solubility of the complex in chloroform suggests that it could be neutral. Elucidating the possible structure of this complex could be the topic of future work.

Complexation of Pt^{2+} with the tridentate ligand **151a**

The ligand reacted rapidly and quantitatively with platinum(II), forming a light-yellow precipitate within ten minutes. The infrared spectrum of this precipitate shows an absence of NH and SH absorptions, but two carbonyl stretching bands appear between 1700 and

1600 cm^{-1}. The ^1H NMR spectrum of this precipitate contains broad peaks indicative of polymer formation.

Complexation of Pt^{2+} *with the dithiol ligand* **172b**

The ligand reacted rapidly and completely with tetrachloroplatinate forming a light-yellow precipitate within 5 minutes. Very broad peaks in the ^1H NMR spectrum and the low solubility of the precipitate in organic solvents (even DMSO) strongly suggest polymer formation.

Complexation of Pt^{2+} *with the macrocycle* **182a**

The macrocycle reacted completely with platinum(II) within 5 minutes to form a yellow precipitate and an organic-soluble complex in approximately equal amounts. The organic-soluble complex was purified by flash chromatography and was shown by ^1H NMR spectroscopy to be the complex **211b**, formation of which clearly requires deprotonation of the amide function at pH 7. The presence of three *ortho*-hydrogen doublets and an amide peak in the ^1H NMR spectrum of the precipitate (Figure 63b), which do not correspond to the equivalent peaks in the free macrocycle (Figure 63a), suggest the presence of at least two (possibly three) different complexes. Of course the presence of conformers due to slow inversion of sulfur is also possible. Comparison of the integrals for the *ortho*-hydrogen doublet at 8.25 ppm and the amide hydrogen at 10.55 ppm (Figure 63b) suggests that these peaks correspond to a complex in which the amide nitrogen is not deprotonated and hence not coordinated. The deshielding of the two *ortho*-hydrogen doublets at *ca.* 9 ppm, and the apparent absence of corresponding amide hydrogen signals, however, indicate complexes which coordinate the metal through the deprotonated amide nitrogen. Additon of D_2O to the DMSO-d_6 solution of the precipitate caused a decrease in the intensity of the amide hydrogen peak but, more importantly, the disappearance of two of the three *ortho*-hydrogen signals and an overall simplification of the spectrum (Figure 63c). The fact that doubling of the *ortho*-hydrogen

Figure 63: 400MHz ^{1}H NMR spectra, in DMSO-d_6, of the aromatic and amide regions for a) the macrocycle 182a; b) the yellow precipitate formed upon reaction with $PtCl_4^{2-}$; and c) the precipitate after addition of D_2O.

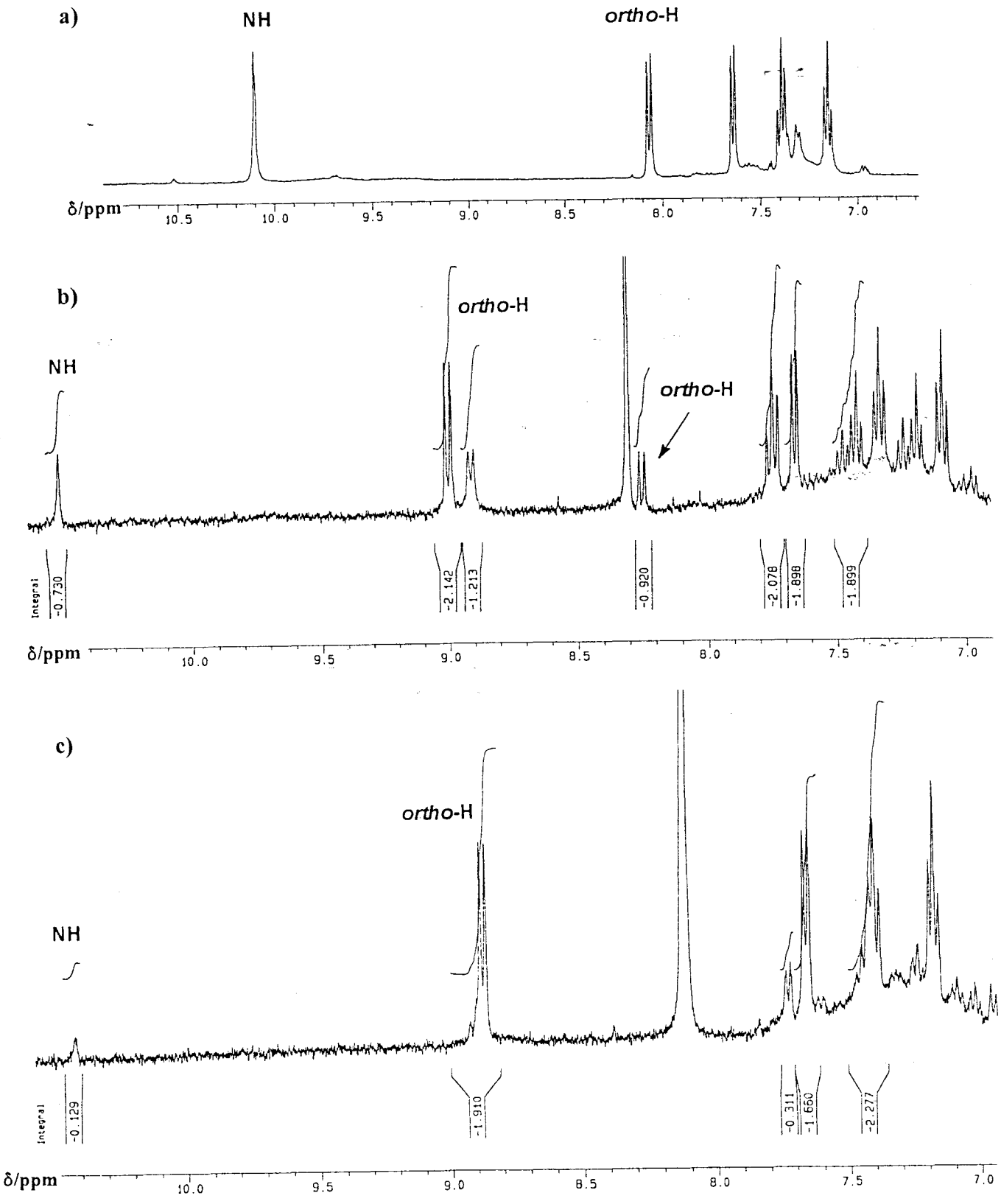
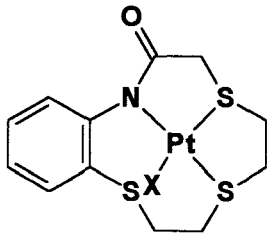


Figure 64: The proposed structure of the major component of the yellow precipitate formed from reaction of macrocycle 182a with $PtCl_4^{2-}$ at pH 7.



212 X unknown

doublet is not observed (as it is in the ^{1}H NMR spectra of complexes **211a,b**), suggests that the aromatic sulfur may not be coordinated to the metal, and that a complex of type **212** is formed (Figure 64). This is supported by the less complex splitting pattern of the aromatic signals (Figure 63 b,c), as compared to the splitting patterns of the aromatic signals in the ^{1}H NMR spectra of complexes **211a,b**. The fourth donor has not been established, but a possible explanation for the spectra shown in Figure 63b and c is that a solvent molecule occupies the fourth coordination site. In Figure 63b, the peaks due to the DMSO-d_6 - coordinated complex dominate, but upon addition of D_2O/H_2O the DMSO-d_6 ligands are displaced and the D_2O/H_2O-coordinated complex (Figure 63c) is the major species. The large singlet at *ca.* 8.3 ppm (Figure 63b) and 8.15 ppm (Figure 63c) is tentatively assigned to platinum-bound H_2O.

Complexation of Pt^{2+} with the diamide ligands **107a,d**

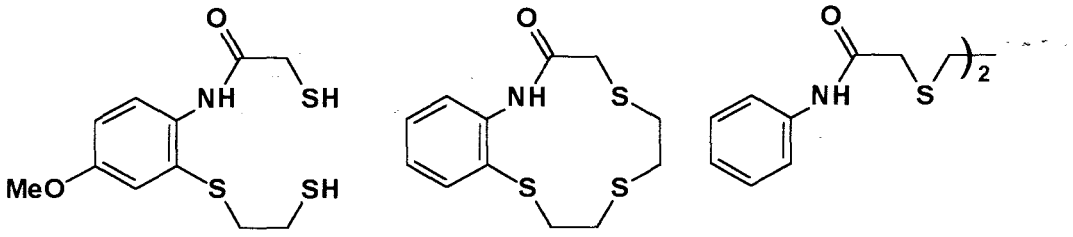
Both of the ligands coordinate with platinum(II) resulting in the formation of light-yellow precipitates and, within two hours, both ligands had been completely consumed. The ^{1}H NMR spectra of the products show amide hydrogen resonances, doubling of signals, and splitting of the $CO.CH_2S$ methylene signals, which all indicate formation of sulfur-sulfur chelates. No platinum-chlorine stretching absorptions appear in the far infrared spectra of the complexes, which suggests that sulfur atoms are acting as bridging ligands.

Thus, while further work will be required to establish the structures of the complexes formed, it is apparent that all of the ligands examined are capable of coordinating platinum(II) at neutral pH. In some cases, at least, there is clear evidence of platinum-amide nitrogen coordination.

2.4.3.3 The reaction of selected ligands with cisplatin

The macrocyclic ligands **67** and **68** (p. 43) are capable of removing platinum from cisplatin in yields of *ca.* 40%.[49] These relatively low yields have been attributed to rupture of the platinum-sulfur bonds before displacement of the ammine ligands by amide nitrogen can take place. In the present studies, selected sulfur-containing amide ligands (**172b**, **182a**, and **107a**; Figure 65) were reacted with cisplatin in aqueous methanol, using *N,N*-diethylaniline-HCl to buffer the solution at pH *ca.* 6.6.

Figure 65: Ligands which were selected for complexation with cisplatin.



172b **182a** **107a**

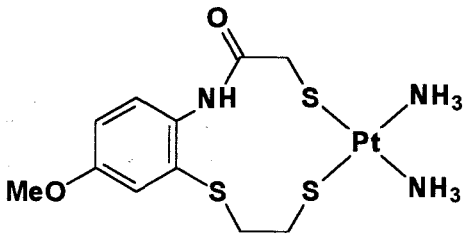
Reaction of the dithiol ligand **172b** *with cisplatin*

Reaction of this ligand with cisplatin was complete in less than 4 hours. A white precipitate formed and was purified by PLC. Two fractions were recovered from the plate in equal amounts - one from the baseline, the other eluted by the ethyl acetate-hexane mixture. Broad peaks in its ^{1}H NMR spectrum indicated the baseline species to be polymeric. Although peaks due to

ammine hydrogen resonances are present in the spectrum, the relative integrals show that most of the ammine ligands have been displaced from platinum in this polymeric complex.

The ^{1}H NMR spectrum of the soluble fraction contains peaks corresponding to the free ligand as well as a cisplatin-ligand adduct. The integral ratios show that 6 ammine hydrogens are present for every coordinated ligand molecule and, since the complex can be eluted on silica and does not show broad peaks in its ^{1}H NMR spectrum, the monomeric structure **213** is proposed (Figure 66). In the ^{1}H NMR spectrum of this adduct the $CO.CH_2S$ methylene hydrogens resonate as a double doublet upfield of the equivalent doublet in the free ligand. Downfield shifts, resulting from withdrawal of electron density from the sulfur donors, are normally associated with sulfur coordination. In the present case, however, deprotonation of the thiol and complexation of the thiolo sulfur has a net shielding effect on the adjacent hydrogens.

Figure 66: The proposed cisplatin-dithiol ligand adduct.



213

Reaction of the macrocycle **182a** *with cisplatin*

This ligand reacted with cisplatin to form small amounts of a complex with similar TLC characteristics to the platinum(II)-macrocyclic complex **211b**. Because this complex eluted fairly easily on silica, its isolation from the relatively large amounts of *N,N*-diethylaniline present proved problematic. Time constraints prevented this reaction from being investigated further.

Reaction of the diamide ligand **107a** *with cisplatin*

This ligand did not complex with the platinum species at all and, after one day of stirring at room temperature, the free ligand was recovered quantitatively. A possible explanation is that cisplatin was partially hydrolysed to give the stable hydroxo complexes $[Pt^{II}(NH_3)_2(\mu\text{-}OH)]_n^{n+}$ (n = 2, 3).[260] Such hydrolyses have, in fact, been reported[49] to occur in methanol-water mixtures at pH 7 when the macrocycles **67** and **68** were reacted with cisplatin.

2.5 CONCLUSIONS

The initial aim of this study, *viz.*, the development of aryl-containing amine and amino acid type ligands, proved synthetically challenging. Many of the problems encountered, however, were successfully overcome. For example, the synthesis and purification of the amino-amide ligands in this study was complicated by the formation of unwanted diamides and polyamides, but direct monoacylation of ethylenediamine was achieved by taking certain experimental precautions, while monoacylation of diethylenetriamine was successfully achieved using the fused piperazine route. The best method for synthesising secondary 1,3-propanediamides was found to be mild aminolysis of the malonate ester or 2-benzyl malonate ester.

In the synthesis of the propanediamide-based tetraacetic acid ligands, targeted as EDTA analogues, the carboxylate groups were initially protected as their methyl esters, but hydrolysis of these esters was not possible without concomitant hydrolysis of the amide functions. Basic hydrolysis of the benzyl esters was found to be the superior route to these ligands, but decomposition of the tetra-acids prevented their full characterisation and raises questions concerning their potential as chelating systems.

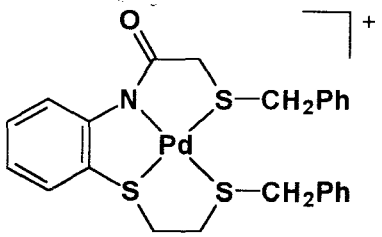
The main aim of this work, *viz.*, the design, synthesis and evaluation of novel, pgm-specific ligands, has been successfully accomplished. A series of carefully designed bidentate, tridentate and tetradentate sulfur-containing monoamide ligands, with substituents on their aromatic rings to fine tune their coordination properties, were synthesised. The first step involved introduction of sulfur at the *ortho*-position of selected *para*-substituted anilines. The "chelate arms" were then attached, with protection of nucleophilic sulfur being afforded by the disulfide linkage and the benzoyl group. Benzyl protected ligands were also synthesised, but deprotection of these ligands was problematic. Finally, the dimercapto ligands were cyclised using a combination of

high dilution techniques and the cesium effect to afford trithia-amide macrocycles. A series of sulfur-containing diamide ligands were also synthesised by attaching ring substituted 2-mercaptoacetanilides to 1,2-dibromoethane. The ligands were characterised by ^{1}H and ^{13}C spectroscopy, infrared spectroscopy, mass spectrometry and elemental analysis.

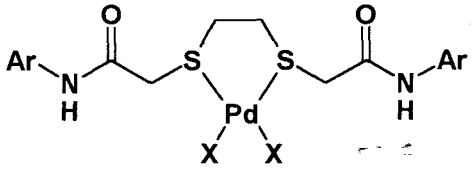
The degree of planarity of the amide and aromatic functions in the acetanilide ligands and their complexes can be gauged from the chemical shift of the *ortho*-proton. This coplanarity was explored using ^{1}H NMR chemical shift and computer modelling data and appears to be greatest in acetanilide ligands with *ortho*-methylthio substituents; the macrocyclic ligands also show above average coplanarity. Coordination of the amide nitrogen in *ortho*-thia substituted acetanilide ligands causes further, substantial deshielding of the *ortho*-proton.

Selected sulfur-containing amide ligands were found to be effective in the selective solvent extraction of palladium(II) from platinum(II) and the base metals copper(II), nickel(II) and cobalt(II). Even though extraction was effected in acidic medium, certain ligands were able to complex palladium(II) with concomitant deprotonation of the amide group, an example being the formation of the tetracoordinate complex **202** (Figure 67). The sulfur-containing diamide ligands appear to extract palladium(II) by the formation of 5-membered sulfur-sulfur chelates, **206**, *ortho*-substituents dramatically reducing their ability to extract palladium(II) into $CHCl_3$ and toluene; when MIBK was used as the solvent, this effect was less pronounced.

Figure 67: Complexes formed during the solvent extraction of palladium(II).



202



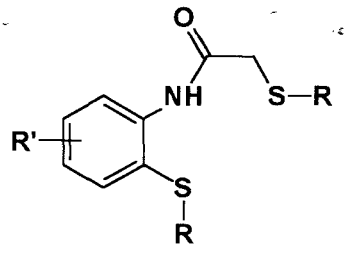
X = variable ligand

206

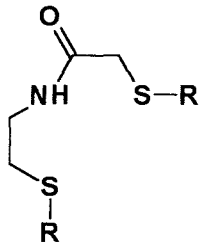
In basic media (pH 8-9), selected sulfur-containing monoamide and diamide ligands were shown to readily complex platinum(II) and palladium(II) through their sulfur and deprotonated amide nitrogen donors. At neutral pH, the macrocyclic trithia amide ligand formed a tetracoordinate platinum(II) complex when reacted with tetrachloroplatinate, and the dimercapto monoamide ligand afforded a polymeric complex with cisplatin, with partial displacement of the ammine ligands from cisplatin.

Although ^{1}H NMR and infrared spectroscopy were sufficient to elucidate the mode of coordination of the ligands, time constraints prevented definitive characterisation of the complexes formed. Consequently, future work should focus on obtaining samples which are suitable for x-ray crystallographic analysis. Future research should also be directed at obtaining more quantitative data relating to the role of the amide nitrogen in complexes of these ligands, and at explaining the ability of substituents to fine tune the properties of the ligand.

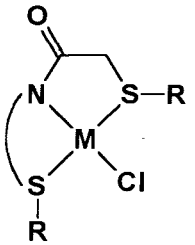
Figure 68: Ligands which need to be investigated further.



214



215



216

$R \neq H$
$M = Pt^{2+}, Pd^{2+}$

From the information gained in this study, ligands of type **214** and **215** (Figure 68) could be targeted for future research into the solvent extraction of platinum and palladium, the present study having shown that, under solvent extraction conditions, the formation of complexes of type **216**, can be expected. The arrangement of sulfur and amide nitrogen donors in these ligands is expected to offer the following advantages.

i) These ligands contain only one amide function and, consequently, should have good organic solubility. Complexes of type **216** are also expected to have good organic solubility owing to their neutrality and the *trans* arrangement of sulfur donors.

ii) The absence of thiol donors should prevent the formation of polymers or strong metal-sulfur bonds, allowing easier stripping (back extraction) of the metal. The tridentate (as opposed to tetradentate) nature of the ligands should also facilitate stripping.

iii) Ligands of this type are expected to show some selectivity for platinum and palladium over other soft metals which cannot deprotonate and, hence, complex with the amide nitrogen.

3 EXPERIMENTAL

3.1 GENERAL

Solvents and commercially available reagents were dried and/or purified by literature methods.[261] Plastic plates, pre-coated with silica gel 60 F_{254}, were used for thin layer chromatography. Preparative layer chromatography (PLC) was achieved using silica gel 60 PF_{254} as the stationary phase, and the plates were prepared and activated as prescribed by the supplier (Merck). Silica gel 60 (particle size 0.040-0.063 mm) was used as the stationary phase for flash chromatography.[262]

60 MHz ^{1}H NMR spectra were recorded on a Perkin Elmer R12 spectrometer, while high field ^{1}H (400MHz) and ^{13}C (100MHz) NMR spectra were recorded on a Bruker AMX400 spectrometer. Chemical shifts are reported relative to the solvent peaks (δ_H: 7.25 ppm for $CHCl_3$, 1.94 ppm for CH_3CN, and 2.50 ppm for DMSO; δ_C: 77.0 ppm for $CDCl_3$ and 39.43 ppm for DMSO-d_6). Infrared spectra were recorded on a Perkin-Elmer 180 spectrophotometer using either KBr discs or NaCl windows. Melting points were determined using either a Gallenkamp melting point apparatus, or a Kofler hot-stage, and are uncorrected.

Low resolution mass spectra were recorded on a Hewlett Packard 5988A mass spectrometer. High resolution mass spectrometry was performed by the Cape Technikon Mass Spectrometry Unit using a Kratos M580RF double-focusing magnetic sector instrument. Combustion analyses were provided by the Chemistry Department of the University of Natal, Pietermaritzburg. The combustion analyses of the samples purified by recrystallisation do not match the required values as closely as the analyses of the chromatographically purified samples do; this is attributed to solvent of crystallisation being present.

3.2 SYNTHETIC PROCEDURES

p-*Toluoyl chloride* **109b**.[149]- Thionyl chloride (7.0 mL, 96 mmol) was added, with stirring, to *p*-toluic acid (5.01 g, 36.7 mmol) in a round-bottomed flask. The flask was then fitted with a reflux condenser with a $CaCl_2$ drying tube, and the mixture was stirred at room temperature for 2 days. Excess thionyl chloride was removed *in vacuo*, and the remaining liquid was distilled *in vacuo* to afford, as a clear liquid, *p*-toluoyl chloride **109b** (4.88 g, 86%), bp 100 °C/0.2 mm Hg (lit.,[263a] 225-227 °C); ν_{max}(thin film)/cm^{-1} 1780 (CO) and 1610 (C=C); δ_H(60 MHz; $CDCl_3$) 2.31 (3H, s, CH_3) and 7.55 (4H, dd, ArH).

N-*(2-Aminoethyl)benzamide* **110a**.-

Method 1

A solution of benzoyl chloride (2.50 g, 17.8 mmol) in dry ether (40 mL) was added dropwise to a cold (5-10 °C), stirred solution of dry ethylenediamine (6.0 mL, 89 mmol) and dry triethylamine (2.5 mL, 18 mmol). After stirring at room temperature for 1 h the white precipitate was filtered off, washed with $CHCl_3$, and shown by TLC to be 1,2-bis(benzamido)ethane **111a**. The filtrate and washings were shown to contain the diamide **111a** as well as the desired monoamide, and were flash chromatographed [elution with MeOH-$CHCl_3$ (2:8)] to yield, as an oil, *N*-(2-aminoethyl)benzamide **110a**[§] (0.65 g, 22%); δ_H(400 MHz; DMSO-d_6) 2.00 (2H, br s, NH_2), 2.71-2.74 (2H, m, CH_2NH_2), 3.29-3.32 (2H, m, CO.NHCH_2), 7.44-7.49 (3H, m, ArH), 7.89 (2H, m, ArH) and 8.46 (1H, br s, CO.NH); δ_C(100 MHz; DMSO-d_6) 41.3 (C-2), 43.0 (C-1), 127.1 (C-3' and C-5'), 128.1 (C-2' and C-6'), 130.9 (C-4'), 134.7 (C-1') and 166.4 (CO).

[§] This amino-amide ligand was prone to rearrangement which prevented full characterisation of the ligand.

Method 2

A solution of benzoyl chloride (5.80 mL, 50.0 mmol) in $CHCl_3$ (250 mL) was added dropwise to a vigorously stirred solution of ethylenediamine (10 mL, 0.15 mol) in $CHCl_3$ (50 mL) at room temperature. After addition of the benzoyl chloride, the reaction mixture was homogeneous but, after stirring for 6 h, a white precipitate formed. The precipitate was removed by filtration and the filtrate was extracted with 1 **M**-HCl (2 x 40 mL). The combined acidic extracts were basified (pH 11) with 10% aqueous NaOH and then extracted with $CHCl_3$ (3 x 30 mL). The $CHCl_3$ was removed *in vacuo* at low temperature to yield the crude product as a clear liquid. Titration of this liquid with HCl showed the product to be 80% pure. Further purification by flash chromatography [elution with MeOH-$CHCl_3$ (2:8)] afforded *N*-(2-aminoethyl)benzamide **110a** (1.26 g, 15%) in *ca.* 95% purity.

1,2-Bis(4-methylbenzamido)ethane **111b**.- A solution of *p*-toluoyl chloride **109b** (2.00 g, 12.9 mmol) in dry Et_2O (20 mL) was added dropwise to a mixture of dry ethylenediamine (4.0 mL, 59 mmol) and dry triethylamine (2.5 mL, 18 mmol) at 0 °C. The mixture was stirred at room temperature overnight, and the white precipitate filtered off and purified by flash chromatography [elution with MeOH-$CHCl_3$ (1:9)] to yield *1,2-bis(4-methylbenzamido)ethane* **111b** (0.51 g, 27%), mp 231-232 °C; ν_{max}(KBr)/cm^{-1} 3010 (NH) and 1640 (CO); δ_H(400 MHz; DMSO-d_6) 2.34 (6H, s, CH_3), 3.43 (4H, m, NCH_2CH_2N), 7.50 (8H, dd, ArH) and 8.50 (2H, br s, NH); δ_C(100 MHz; DMSO-d_6) 20.8 (CH_3), 39.1 (CH_2), 127.1, 128.6, 131.6 and 140.8 (ArC) and 166.3 (CO).

N-*{2-[(2-aminoethyl)amino]ethyl}-4-methylbenzamide* **114b**.- A solution of *p*-toluoyl chloride **109b** (1.67 g, 10.8 mmol) in dry Et_2O (15 mL) was added dropwise to diethylenetriamine (3.34 g; 32.4 mmol) at 0 °C. A white precipitate formed immediately which was filtered off and washed with 10% aqueous NaOH (15 mL) and satd. brine (15 mL). The aqueous washings

were extracted with $CHCl_3$ (3 x 30 mL) and the combined $CHCl_3$ extracts were concentrated *in vacuo* and purified by flash chromatography [elution with MeOH-$CHCl_3$ (2:8)] to afford N-*{2-[(2-aminoethyl)amino]ethyl}-4-methylbenzamide* **114b**[§] (0.37 g, 5%), mp 238-240 °C (from EtOH); ν_{max}(thin film)/cm^{-1} 1620 (CO); δ_H(400 MHz; D_2O) 2.35 (3H, s, CH_3), 3.20-3.40 (6H, m, CH_2), 3.65 (2H, m, CH_2) and 7.65 (4H, dd, ArH).

N-*(8-Amino-3,6-diazaoctyl)-4-methylbenzamide* **115**.- *p*-Toluoyl chloride **109b** (2.00 g, 12.9 mmol) in dry Et_2O (20 mL) was added dropwise to a stirred solution of the dinitric salt of triethylenetetramine[163] (12.0 g, 44.1 mmol) in dry triethylamine (15 mL). The flask was fitted with a $CaCl_2$ drying tube, and the reaction mixture stirred at room temperature for 4 h. The resulting mixture was partitioned between H_2O (20 mL) and $CHCl_3$ (50 mL), and further extracted with $CHCl_3$ (2 x 50 mL). The combined $CHCl_3$ extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$). The $CHCl_3$ and most of the triethylamine were removed *in vacuo* and the residue was purified twice by flash chromatography [elution with MeOH-$CHCl_3$ (1:9)] to afford N-*(8-amino-3,6-diazaoctyl)-4-methylbenzamide* **115**[§] (1.31 g, 38%), mp 260-262 °C; δ_H(60 MHz; DMSO-d_6) 1.08 (1H, br s, NH), 2.33 (3H, s, CH_3), 3.1-3.9 (15H, m, CH_2, NH and NH_2), 6.9-7.4 (4H, m, ArH) and 7.7 (1H, br s, NH).

3-Aza-1,5-bis(4-methylbenzamido)pentane **116**.- *p*-Toluoyl chloride **109b** (1.50 g, 9.71 mmol) was added slowly, dropwise, to a mixture of dry diethylenetriamine (4.12 g, 38.9 mmol) and dry triethylamine (5.5 mL, 39 mmol). After the addition was complete, the flask was fitted with a reflux condenser with a $CaCl_2$ drying tube, and the mixture stirred at room temperature for 1 h. The white precipitate was filtered off and washed with $CHCl_3$. The combined filtrate and $CHCl_3$ washings were extracted with $CHCl_3$ (2 x 20 mL), and the resulting extracts combined, concentrated *in vacuo* and purified by flash chromatography [elution with MeOH-$CHCl_3$ (1:9)] to give *3-aza-1,5-bis(4-methylbenzamido)pentane* **116**[§] (1.31 g, 79%); δ_H(60 MHz; $CDCl_3$)

2.35 (6H, s, CH_3), 2.50 (1H, br s, NH), 3.5 - 4.0 (8H, m, CH_2CH_2), 7.39 (2H, s, CO.NH) and 7.50 (8H, dd, ArH).

Benzoin **117**.[168b]- Benzaldehyde (20 mL, 0.20 mol) was added to a solution of KCN (2.8 g, 43 mmol) in H_2O (28 mL) and EtOH (27 mL). The mixture was gently boiled under reflux for 30 min., and then cooled in ice. The precipitate was filtered off and dried *in vacuo* to give benzoin **117** (11.5 g, 54%), mp 133-135 °C (lit.,[168b] 137 °C).

Benzil **118**.[168a]- A mixture of the crude benzoin **117** (11.5 g, 54.2 mmol) and conc. HNO_3 (58 mL) was heated on a steam bath with occasional shaking for 1.5 h. The mixture was then poured into cold water and the solid filtered off and washed with H_2O. Recrystallisation from EtOH afforded pure benzil **118** (5.0 g, 44%), mp 93-96 °C (lit.,[168a] 94-96 °C).

8,8a-Diphenyl-1,2,3,5,6,8a-hexhydroimidazo[1,2-a]pyrazine **119**.[169]- Acetic acid (40 drops) was added to a solution of benzil **118** (38.1 g, 181 mmol) and freshly distilled diethylenetriamine (18.7 g, 181 mmol) in EtOH (700 mL). The mixture was stirred at room temperature for 3 days and then boiled under reflux for 2 h. The solvent was evaporated *in vacuo* and the residue was recrystallised from EtOH to yield white crystals of 8,8*a*-diphenyl-1,2,3,5,6,8*a*-hexahydroimidazo[1,2-*a*]pyrazine **119** (46 g, 91%), mp 165-166 °C (from EtOH) (lit.,[169] 166-167 °C); δ_H(400 MHz; $CDCl_3$) 2.51 (1H, br s, NH), 2.68-2.78 (1H, m, CH), 2.80-2.98 (3H, m, CH), 3.08-3.18 (1H, m, CH), 3.20-3.40 (1H, m, CH), 3.90-4.15 (2H, m, CH), 7.11-7.29 (6H, m, ArH), 7.55 (2H, d, ArH) and 7.72 (2H, d, ArH); δ_C(100 MHz; $CDCl_3$) 43.4, 43.6, 47.9 and 50.9 (CH_2), 82.0 (C-8), 126.9, 127.2, 127.5, 128.4, 128.7, 128.9, 137.2 and 142.8 (ArC) and 167.1 (CN).

1-Benzoyl-8,8a-diphenyl-1,2,3,5,6,8a-hexahydroimidazo[1,2-a]pyrazine **120a**.[167, 169] - A solution of benzoyl chloride (8.39 mL, 72.2 mmol) in benzene (30 mL) was added to a cold (5 °C), stirred mixture of 8,8*a*-diphenyl-1,2,3,5,6,8*a*-hexahydroimidazo[1,2-*a*]pyrazine **119** (20 g, 72 mmol) in benzene (500 mL) and 1 **M**-NaOH (300 mL). After stirring for 2 days at room temperature the phases were separated and the benzene layer was washed with H_2O (150 mL) and then dried (anhydr. $MgSO_4$). After removal of the benzene *in vacuo* the residue was recrystallised twice from EtOH to yield pure 1-benzoyl-8,8*a*-diphenyl-1,2,3,5,6,8*a*-hexahydroimidazo[1,2-*a*]pyrazine **120a** (16.1 g, 59%), mp 181-183 °C (from EtOH) (lit.,[169] 183 °C); δ_H(400 MHz; $CDCl_3$) 2.79-2.82 (1H, m, CH), 3.12-3.15 (1H, m, CH), 3.46-3.50 (2H, m, CH), 3.71-3.74 (1H, m, CH), 4.23-4.49 (3H, m, CH) and 7.19-7.93 (15H, m, ArH); δ_C(100 MHz, $CDCl_3$) 45.2, 50.3, 53.9 and 54.5 (CH_2); 82.1 (C-8), 127.3, 127.4, 128.2, 128.6, 128.6, 128.8, 129.1, 131.0, 131.4, 134.8, 135.6 and 136.7 (ArC), 169.8 (CN) and 172.1 (CO).

1-p-*Toluoyl-8,8a-diphenyl-1,2,3,5,6,8a-hexahydroimidazo[1,2-a]pyrazine* **120b**.- A solution of *p*-toluoyl chloride (1.82 g, 11.8 mmol) in dry THF (10 mL) was added to a solution of 8,8*a*-diphenyl-1,2,3,5,6,8*a*-hexahydroimidazo[1,2-*a*]pyrazine **119** (3.27 g, 11.8 mmol) in dry THF (40 mL) in a two-necked round-bottomed flask fitted with a reflux condenser and $CaCl_2$ drying tube. After stirring at room temperature for 3 h, the mixture was partitioned between H_2O (30 mL) and EtOAc (30 mL), and further extracted with EtOAc (2 x 30 mL). The combined EtOAc extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$), and the solvent was removed *in vacuo*. The crude residue (5.79 g) was purified by flash chromatography [elution with EtOAc-hexane (1:1)] to give, as white crystals, *1*-p-*toluoyl-8,8a-diphenyl-1,2,3,5,6,8a-hexahydroimidazo[1,2-a]pyrazine* **120b** (1.18 g, 25%), mp 165-168 °C (from EtOAc-hexane); δ_H(400 MHz; $CDCl_3$) 2.42 (3H, s, CH_3), 2.80-2.90 (1H, m, CH), 3.12-3.33 (1H, m, CH), 3.45-3.58 (2H, m, CH), 3.78-3.84 (1H, m, CH), 4.32-4.42 (2H, m, CH), 4.47-4.55 (1H, m, CH), and 7.15-7.80 (14H, m, ArH); δ_C(100 MHz; $CDCl_3$) 21.3 (CH_3), 45.2, 50.4, 54.0 and 54.5

(CH_2), 82.1 (C-8), 127.0, 127.3, 127.4, 127.6, 128.0, 128.6, 128.8, 128.9, 130.9, 131.3, 133.8 and 139.1 (ArC), 169.7 (CN) and 172.2 (CO).

N-*{2-[(2-Aminoethyl)amino]ethyl}benzamide dihydrochloride* **114a**.- A solution of 1-benzoyl-8,8*a*-diphenyl-1,2,3,5,6,8*a*-hexahydroimidazo[1,2-*a*]pyrazine **120a** (2.76 g, 7.25 mmol) in a mixture of EtOH (10 mL) and 1 **M**-HCl (5 mL) was boiled under reflux for 90 minutes. Upon cooling, white crystals formed, which were filtered off and identified by TLC as the starting acylated pyrazine **120a** (1.33 g). These crystals were dissolved in EtOH (4 mL) and 1 **M**-HCl (2 mL) and the resulting solution boiled under reflux for a further 90 minutes. Upon cooling, the acylated pyrazine **120a** (0.79 g, 2.1 mmol) precipitated out and was removed by filtration, dissolved in EtOH (3 mL) and 1 **M**-HCl (1.5 mL) and the resulting solution boiled under reflux for a further 3h. Upon cooling this third solution, the acylated pyrazine **120a** (0.37 g) precipitated out and was removed by filtration. The combined ethanolic filtrates were washed with Et_2O (3 x equal volume) and the aqueous-ethanolic mixture was evaporated to dryness. The residue was recrystallised from EtOH to afford, as white crystals, the dihydrochloride salt of *N*-{2-[(2-aminoethyl)amino]ethyl}benzamide **114a** (0.24 g, 12 %), mp 218-219 °C (from EtOH) (lit.,[169] 221-222 °C); δ_H(400 MHz; D_2O-DMSO-d_6) 2.8-3.3 (4H, m, CH_2), 3.4-3.8 (4H, m, CH_2) and 7.3-7.6 (5H, m, ArH).

N-*{2-[(2-Aminoethyl)amino]ethyl}-4-methylbenzamide dihydrochloride* **114b**.- A solution of 1-*p*-toluoyl-8,8*a*-diphenyl-1,2,3,5,6,8*a*-hexahydroimidazo-[1,2-*a*]pyrazine **120b** (1.02 g, 2.58 mmol) in a mixture of EtOH (5 mL) and 1 **M**-HCl (7.5 mL) was boiled under reflux for 1 h and then left to stand at room temperature for 1 day, during which time crystals of benzil separated out and were removed by filtration. The EtOH was removed from the filtrate *in vacuo* and the remaining aqueous filtrate was washed with EtOAc (10 mL), and the H_2O removed *in vacuo* to give pale yellow crystals, which were recrystallised from EtOH to afford *N*-{2-[(2-

aminoethyl)amino]ethyl}-4-methylbenzamide dihydrochloride **114b** (0.61 g, 81%).

Ethyl 4-methylbenzoate **121**.- Conc. H_2SO_4 (2.5 mL) was added dropwise to a well stirred solution of *p*-toluic acid (5.94 g, 44.0 mmol) in dry EtOH (50 mL). The resulting mixture was boiled under reflux for 8 h, after which the EtOH was distilled off. The remaining solution was neutralised with aqueous $NaHCO_3$ and then extracted with Et_2O (3 x 25 mL). The combined Et_2O extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$), and the Et_2O was evaporated *in vacuo* to afford a clear oil which was distilled to give ethyl 4-methylbenzoate **121** (8.52 g, 84%), bp 100 °C/5 mm Hg (lit.,[264a] 122 °C/22 mm Hg); δ_H(60 MHz; CCl_4) 1.20 (3H, t, CH_3CH_2O), 2.25 (3H, s, $ArCH_3$), 4.15 (2H, q, CH_3CH_2O) and 7.42 (4H, dd, ArH).

p-*Methylbenzyl alcohol* **122**.- A solution of ethyl 4-methylbenzoate **121** (7.35 g, 44.8 mmol) in dry THF (20 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (2.00 g, 52.7 mmol) in dry THF (30 mL) under dry N_2. The resulting mixture was boiled under reflux for 4 h, after which the excess $LiAlH_4$ was quenched by the cautious, sequential addition of H_2O (1 mL), 10% aqueous NaOH (1 mL) and H_2O (3 mL). The white crystalline material was filtered off, the filtrate was added to H_2O (20 mL) and the resulting mixture was extracted with Et_2O (3 x 25 mL). The combined Et_2O extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$). Evaporation of the Et_2O afforded, as a white solid, *p*-methylbenzyl alcohol **122** (2.35 g, 43%), mp 60-61°C (from Et_2O) (lit.,[264b] 61-62 °C), δ_H(60 MHz; CCl_4) 1.42 ppm (1H, s, OH), 2.30 (3H, s, $ArCH_3$), 4.50 (2H, s, CH_2) and 7.13 (4H, s, ArH).

α-*Chloro*-p-*xylene* **123**.- Thionyl chloride (4.5 mL, 60 mmol) was added dropwise to a stirred, pre-cooled (ice) solution of *p*-methylbenzyl alcohol **122** (7.25 g, 59.3 mmol) in a flask fitted with a $CaCl_2$ drying tube. The resulting solution was stirred at room temperature for 2 days. The excess thionyl chloride was removed *in vacuo* and the residue was distilled to give α-

chloro-*p*-xylene **123** (6.63 g, 80%), bp 110 °C/20 mm Hg (lit.,[264c] 200 °C); ν_{max}(thin film)/cm^{-1} 2960 (CH) and 1520 (C=C); δ_H(60 MHz; CCl_4) 2.28 (3H, s, CH_3), 4.42 (2H, s, CH_2) and 7.15 (4H, s, ArH).

Diethyl 2-[(4-methylphenyl)methyl]-1,3-propanedioate **125b**.- A solution of diethyl malonate (7.21 g, 45.0 mmol) in dry EtOH (10 mL) was added dropwise to a well stirred solution of sodium ethoxide in EtOH [generated *in situ* by the addition of sodium metal (1.0 g, 45 mmol) to dry EtOH (50 mL)]. The resulting mixture was boiled under reflux for 2 h. α-Chloro-*p*-xylene **123** (6.35 g, 45.0 mmol) was added dropwise to the hot mixture, which was then boiled under reflux for a further 1 h, during which time a precipitate formed. The cooled reaction mixture was diluted with H_2O (50 mL) and extracted with Et_2O (3 x 50 mL). The Et_2O extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$). Evaporation of the solvent *in vacuo* afforded the crude product (20.6 g) which was vacuum distilled through an 8 cm fractionating column to afford diethyl 2-[(4-methylphenyl)methyl]-1,3-propanedioate **125b** (6.40 g, 57%), bp 155 °C/15 mm Hg; (lit.,[263b] 178-180 °C/20 mm Hg); δ_H(60 MHz; $CDCl_3$) 1.25 (6H, t, CH_3CH_2), 2.40 (3H, s, $ArCH_3$), 3.0-3.4 (3H, m, $ArCH_2CH$), 4.2 (4H, q, CH_3CH_2) and 7.25 (4H, s, ArH).

Diethyl 2-benzyl-1,3-propanedioate **125a**.- The experimental procedure employed for the synthesis of diethyl 2-[(4-methylphenyl)methyl]-1,3-propanedioate **125b** was followed, using benzyl chloride (9.3 mL, 81 mmol) and diethyl malonate (12.3 mL, 81.0 mmol). Distillation *in vacuo* afforded diethyl 2-benzyl-1,3-propanedioate **125a** (11.8 g, 62%), bp 162 °C/0.5 mm Hg (lit.,[264d] 169 °C/12 mm Hg); δ_H(60 MHz; $CDCl_3$) 1.05 (6H, t, CH_3CH_2), 3.05 (2H, d, CH_2CH), 3.34 (1H, t, CH_2CH), 3.95 (4H, q, CH_3CH_2) and 7.10 (5H, s, ArH).

2-Benzyl-1,3-propanedioic acid **129b**.- Diethyl 2-benzyl-1,3-propanedioate **125a** (30.45 g, 121.7 mmol) was dissolved in EtOH (60 mL) and H_2O (18 mL) containing KOH (17.7 g, 315

mmol). The mixture was boiled under reflux for 7 h, after which the EtOH was removed *in vacuo* and the residual aqueous solution was acidified to pH 4 with dil. H_2SO_4. The aqueous phase was then extracted with Et_2O and the combined extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$). Removal of the Et_2O *in vacuo* gave a white crystalline solid which was recrystallised from EtOH to afford 2-benzyl-1,3-propanedioic acid **129b** (13.2 g, 56%), mp 117-118 °C (from EtOH) (lit.,[264d] 117 °C); δ_H(60 MHz; DMSO-d_6) 3.00 (2H, d, CH_2CH), 3.55 (1H, t, CH_2CH), 7.20 (5H, s, ArH) and 11.5-13.0 (2H, br s, OH).

2-Benzylmalonyl dichloride **130b**.[170]- Finely crushed crystals of 2-benzyl-1,3-propanedioic acid **129b** (11.4 g, 58.9 mmol) were added to an Erlenmeyer flask with a quick-fit neck. Thionyl chloride (29.5 mL, 0.404 mol) was added and the flask was fitted with a reflux condenser with a $CaCl_2$ drying tube. The mixture was stirred at 45-50 °C for 3 days and then at 60 °C for 5-6 h. Excess $SOCl_2$ was removed *in vacuo* to give, as a light brown liquid, 2-benzylmalonyl dichloride **130b** [ν_{max}(thin film)/cm^{-1} 1790 (CO) and 1600 and 1500 (C=C); δ_H(400 MHz; $CDCl_3$) 3.40 (2H, d, CH_2CH), 4.50 (1H, t, CH_2CH) and 7.20-7.37 (5H, m, ArH)], which was used without further purification.

N,N'-*Bis(2-aminoethyl)-2-benzyl-1,3-propanediamide* **126b**.[37] -

Method 1

Diethyl 2-benzyl-1,3-propanedioate **125a** (13.5 g, 53.9 mmol), in a pressure equalised dropping funnel, was added to dry ethylenediamine (10.7 mL, 0.162 mmol) at room temperature. The dropping funnel was replaced with a reflux condenser fitted with a $CaCl_2$ drying tube and the mixture was stirred for a further 2 h and then allowed to stand for 2 days, during which time a thick white precipitate formed. Filtration of this precipitate was not possible and, consequently, half the precipitate was triturated with MeOH (300 mL) at room temperature and the solids were removed by filtration. The methanolic filtrate was evaporated to dryness at low

temperature to afford *N,N'*-bis(2-aminoethyl)-2-benzyl-1,3-propanediamide **126b**[§] (4.70 g, 23%); ν_{max}(KBr)/cm^{-1} 3300 (NH) and 1640 (CO); δ_H(400 MHz; DMSO-d_6) 1.25-2.25 (4H, br s, NH_2), 2.50 (4H, m, CH_2NH_2), 2.90-3.20 (6H, m, CO.NHCH_2 and $ArCH_2$), 3.35 (1H, m, COCHCO), 7.10-7.35 (5H, m, ArH) and 7.80 (2H, s, CO.NH); δ_C(100 MHz; DMSO-d_6) 35.2, 41.0, 42.2 and 54.9 (NCH_2CH_2N and CH_2CH), 126.0, 128.0, 128.6 and 139.1 (ArC) and 168.9 (CO).

Method 2

A solution of 2-benzylmalonyl dichloride **130b** (1.9 g, 8.2 mmol) in dry Et_2O (20 mL) was added dropwise to a cooled (ice) mixture of dry ethylenediamine (3.80 g, 63.3 mmol) and dry triethylamine (2.0 g, 20 mmol) in dry Et_2O (5 mL). After stirring for 1 h at room temperature, the pale yellow precipitate was collected by filtration, triturated in hot MeOH and filtered again to remove insoluble material. The methanolic filtrate was concentrated *in vacuo* and the residue purified by flash chromatography [elution with aqueous NH_3-MeOH-$CHCl_3$ (0.25:2:8)] to afford *N,N'*-bis(2-aminoethyl)-2-benzyl-1,3-propanediamide **126b** as a pale yellow solid (0.25g, 8%).

N,N'-*Bis(2-aminoethyl)-1,3-propanediamide* **126a**.[37]- Diethyl malonate (10.0 mL, 65.8 mmol) was added slowly to dry ethylenediamine (40 mL, 0.60 mmol) at 0 °C. After the addition, the flask was fitted with a reflux condenser with a $CaCl_2$ drying tube. The mixture was kept at 0 °C for 1 h and then left for 2 days at room temperature, during which time a white precipitate formed. The precipitate was filtered off, washed with EtOH, and recrystallised from MeOH at room temperature to give white crystals of *N,N'*-bis(2-aminoethyl)-1,3-propanediamide **126a**;[§] ν_{max}(KBr)/cm^{-1} 3030 (NH) and 1630 (CO); δ_H(400 MHz; DMSO-d_6) 1.65 (4H, br s, NH_2), 2.55 (4H, m, CH_2NH_2), 3.05 (6H, m, $COCH_2CO$ and CO.NHCH_2) and 7.99 (2H, s, CO.NH); δ_C(100 MHz; DMSO-d_6) 41.1, 42.3 and 43.5 (NCH_2CH_2N and CH_2) and 167.0 (CO).

Dimethyl iminodiacetate **133**.[173]- Thionyl chloride (5.26 mL, 72.1 mmol) was added cautiously, dropwise, to a suspension of iminodiacetic acid (5.00 g, 37.6 mmol) in MeOH (50 mL). The mixture was boiled under reflux for 3 h in an atmosphere of dry N_2, after which MeOH and excess $SOCl_2$ were removed *in vacuo*. 10% Aqueous NaOH (20 mL) was added to the residue and the aqueous mixture was extracted with EtOAc (3 x 25 mL). The combined EtOAc extracts were dried (anhyd. $MgSO_4$), and the solvent was removed *in vacuo* to give, as a clear oil, dimethyl iminodiacetate **133** (4.62 g, 76%); ν_{max}(thin film)/cm^{-1} 1750 (CO); δ_H(400 MHz; $CDCl_3$) 1.99 (1H, s, NH), 3.41 (4H, s, NCH_2CO) and 3.67 (6H, s, CH_3O).

Dibenzyl iminodiacetate **134**.[172]- A mixture of iminodiacetic acid (3,00 g, 22.5 mmol), *p*-toluenesulfonic acid (5.15 g, 27.1 mmol), benzyl alcohol (95 mL) and benzene (60 mL) was boiled under reflux for 12 h, the water produced being collected in a Dean-Stark trap. Upon cooling, a white precipitate formed. Et_2O (135 mL) was added and the resulting slurry filtered; the solid material was washed with Et_2O (50 mL) and sucked dry. Triethylamine (3.0 g, 30 mmol) was added to a suspension of the solid in $CHCl_3$ (120 mL). The resulting solution was washed with very dilute HCl (3 x 60 mL, each 60 mL portion containing several drops of 32% HCl) and dried (anhyd. $MgSO_4$), and the $CHCl_3$ was removed *in vacuo* to yield, as an oil, *dibenzyl iminodiacetate* **134** (7.23 g, 100%), (Found: $\mathbf{M}^+$, 313.1296. $C_{18}H_{19}NO_4$ requires *M*, 313.1314); ν_{max}(thin film)/cm^{-1} 3340 (NH) and 1730 (CO); δ_H(400 MHz; $CDCl_3$) 2.25 (1H, br s, NH), 3.51 (4H, s, NCH_2CO), 5.15 (4H, s, $ArCH_2$) and 7.34 (10H, s, ArH); δ_C(100 MHz; $CDCl_3$) 50.1 (NCH_2), 66.5 ($ArCH_2$), 128.3, 128.3, 128.5 and 135.5 (ArC) and 171.5 (CO); *m/z* 313 ($\mathbf{M}^+$, 0.1%) and 91 (100%).

Tetramethyl malonamide-N,N,N',N'-*tetraacetate* **135a**.- A solution of malonyl dichloride **130a** (0.52 g, 3.7 mmol) in dry THF (40 mL) was added slowly, with a syringe, to a stirred solution of dimethyl iminodiacetate **133** (1.20 g, 7.45 mmol) and dry triethylamine (0.83 g, 8.2 mmol) in

dry THF (50 mL) under dry N_2. The mixture was stirred at room temperature for 1 day, and then H_2O (25 mL) was added and the THF removed *in vacuo*. Conc. HCl (1 mL) was added to the aqueous solution and the black mixture was extracted with EtOAc (3 x 30 mL). The combined EtOAc extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$). The solvent was evaporated *in vacuo* to yield the crude product as a black oil, which was purified by flash chromatography (elution with EtOAc) to afford, as a yellow oil, *tetramethyl malonamide*-N,N,N',N'-*tetraacetate* **135a** (0.72 g, 50 %), (Found: $\mathbf{M}^+$, 390.1259. $C_{15}H_{22}N_2O_{10}$ requires *M*, 390.1274); ν_{max}(thin film)/cm^{-1} 2970 (CH), 1740 (CO.O) and 1650 (CO.N); δ_H(400 MHz; $CDCl_3$) 3.58 (2H, s, $CO.CH_2CO$), 3.68 and 3.72 (12H, 2 x s, OCH_3), 4.13 and 4.29 (8H, 2 x s, NCH_2CO); δ_C(100 MHz; $CDCl_3$) 41.1 (C-2), 48.3, 50.6, 52.0, 52.4 (OCH_3 and NCH_2), 166.9 (CO.N) and 169.0 and 169.1 (CO.O); *m/z* 390 ($\mathbf{M}^+$, 2.2%) and 102 (100%).

Tetramethyl 2-benzylmalonamide-N,N,N',N'-*tetraacetate* **135b**.- The experimental procedure employed for the synthesis of tetramethyl malonamide-*N,N,N',N'*-tetraacetate **135a** was followed, using 2-benzylmalonyl dichloride **130b** (0.86 g, 3.7 mmol) and dimethyl iminodiacetate **133** (1.20 g, 7.45 mmol). Purification by flash chromatography [elution with EtOAc-hexane (8:2)] afforded, as a pale yellow oil which solidified overnight, *tetramethyl 2-benzylmalonamide*-N,N,N',N'-*tetraacetate* **135b** (0.86 g, 48%), mp 81-83 °C (from EtOAc-hexane) (Found: $\mathbf{M}^+$, 480.1726. $C_{22}H_{28}N_2O_{10}$ requires *M*, 480.1743); ν_{max}(KBr)/cm^{-1} 1750 (CO.O) and 1660 (CO.N); δ_H(400 MHz; $CDCl_3$) 3.27 (2H, d, $ArCH_2CH$), 3.68 and 3.72 (12H, 2 x s, CH_3O), 4.03-4.22 (9H, m, CH_2N and CO.CHCO) and 7.17-7.29 (5H, m, ArH); δ_C(100 MHz; $CDCl_3$) 35.1 ($ArCH_2$), 48.8, 49.8, 52.1 and 52.4 (CH_3O and NCH_2), 50.9 (C-2), 126.7, 128.6, 128.8 and 138.4 (ArC), 169.0 and 169.1 (CO.O) and 169.2 (CO.N); *m/z* 480 ($\mathbf{M}^+$, 25.7%) and 131 (100%).

Tetrabenzyl malonamide-N,N,N',N'-*tetraacetate* **136a**.- The same experimental procedure employed for the synthesis of tetramethyl malonamide-*N,N,N',N'*-tetraacetate **135a** was followed, using malonyl dichloride **130a** (0.24 g, 1.7 mmol), dry triethylamine (0.51 mL, 3.7 mmol) and dibenzyl iminodiacetate **134** (1.05 g, 3.35 mmol). Purification by flash chromatography [elution with EtOAc-hexane (1:1)] afforded colourless crystals of *tetrabenzyl malonamide*- N,N,N',N'-*tetraacetate* **136a** (0.51 g, 43%), mp 103-104 °C (from EtOAc-hexane) (Found: $\mathbf{M}^+$, 694.2515. $C_{39}H_{38}N_2O_{10}$ requires *M*, 694.2536); ν_{max}(KBr)/cm^{-1} 1750 (CO.O) and 1650 (CO.N); δ_H(400 MHz; $CDCl_3$) 3.62 (2H, s, CO.CH_2CO), 4.17 and 4.33 (8H, 2 x s, NCH_2), 5.12 and 5.13 (8H, 2 x s, $ArCH_2$) and 7.28-7.35 (20H, m, ArH); δ_C(100 MHz; $CDCl_3$) 41.1 (C-2), 48.6 and 50.9 (NCH_2), 67.0 and 67.4 (OCH_2Ar), 128.3-128.7,[§§] 135.0 and 135.3 (ArC), 167.0 (CO.N) and 168.4 and 168.6 (CO.O).

Tetrabenzyl 2-benzylmalonamide-N,N,N',N'-*tetraacetate* **136b**.- The experimental procedure employed for the synthesis of tetramethyl malonamide-*N,N,N',N'*-tetraacetate **135a** was followed, using 2-benzylmalonyl dichloride **130b** (1.03 g, 4.47 mmol), dry triethylamine (3.0 mL, 22 mmol) and the tosylate salt of dibenzyl iminodiacetate (4.50 g, 8.93 mmol). Purification by flash chromatography [elution with EtOAc-hexane (4:6)] afforded *tetrabenzyl 2-benzylmalonamide*-N,N,N',N'-*tetraacetate* **136b** (1.80 g, 51%), (Found: $\mathbf{M}^+$, 784.2969. $C_{46}H_{44}N_2O_{10}$ requires *M*, 784.2994); ν_{max}(thin film)/cm^{-1} 1750 (CO.O) and 1680 (CO.N); δ_H(400 MHz; $CDCl_3$) 3.24 (2H, d, $ArCH_2CH$), 3.99-4.17 (9H, m, NCH_2 and CO.CHCO), 5.04-5.12 (8H, m, $ArCH_2O$) and 7.10-7.35 (25H, m, ArH); δ_C(100 MHz; $CDCl_3$) 35.1 (C-2), 49.1 and 50.1 (NCH_2), 50.8 ($ArCH_2$), 66.9 and 67.3 (CH_2O), 126.6-138.4[§§] (ArC), 168.4 and 168.5 (CO.O) and 169.2 (CO.N).

[§§] Multiplicity a result of hindered rotation around the N-(CO) partial double bond.

Malonamide-N,N,N',N'-*tetraacetic acid* **105a**.- A solution of NaOH (0.14 g) in H_2O (7.2 mL) was added to a solution of tetrabenzyl malonamide-*N,N,N',N'*-tetraacetate **136a** (0.10 g, 0.14 mmol) in THF (7.2 mL). The heterogeneous mixture was stirred at room temperature for 1 h and then washed with benzene (2 x 20 mL). The aqueous phase was acidified (pH < 2) with 16% HCl and traces of organic solvent were removed *in vacuo* at room temperature before passing the acidic solution through an Amberlite IR 120 ion exchange resin (4 mL) in acidic form. The acidified aqueous solution was passed through the resin twice, with a flow rate of less than 2 mL.min.$^{-1}$ Removal of the aqueous HCl *in vacuo,* at room temperature, resulted in substantial darkening and decomposition of the product. (Removal of the aqueous acid by freeze drying also resulted in considerable darkening of the product). Purification by flash chromatography [elution with MeOH-$CHCl_3$ (2.5:7.5)] did not improve the appearance of the product. ^{1}H NMR showed hydrolysis to be complete but broad, complex peaks appeared at the expected chemical shifts.

2-Benzylmalonamide-N,N,N',N'-*tetraacetic acid* **105b**.- The experimental procedure employed for the synthesis of malonamide-*N,N,N',N'*-tetraacetic acid **105a** was followed, using tetrabenzyl 2-benzylmalonamide-*N,N,N',N'*-tetraacetate **136b** (0.20 g, 0.25 mmol) in aqueous NaOH [(0.20 g, 5.0 mmol) in H_2O (10 mL)] and THF (10 mL). Evaporation of the acidic aqueous solution gave a dark residue, purification of which by flash chromatography [elution with MeOH-$CHCl_3$ (2:8)] afforded, as a brown solid, *2-benzylmalonamide*-N,N,N',N'-*tetraacetic acid* **105b** (0.091 g, 86%); δ_H(400 MHz; DMSO-d_6) 3.06 (2H, d, $ArCH_2$), 3.85-4.28 (9H, m, NCH_2 and CO.CHCO) and 7.14-7.25 (5H, m, ArH); δ_C(100 MHz; DMSO-d_6) 34.2 ($ArCH_2$), 47.3 (C-2), 48.5 and 49.6 (NCH_2), 126.1, 128.1, 128.5 and 138.9 (ArC), 168.8 (CO.N) and 167.0 and 170.4 (CO.O).

2-Mercaptoacetic acid **138**.[176]- Thiourea (20.1 g, 247 mmol) was added to a solution of 2-chloroacetic acid (25.0 g, 247 mmol) and NaOH (10.6 g, 247 mmol) in H_2O (125 mL) and the resulting mixture was boiled under reflux for 2 h in an atmosphere of dry N_2. After cooling to room temperature, NaOH pellets (23.4 g) were added and the mixture was boiled under reflux for a further 90 minutes in an atmosphere of dry N_2. The mixture was then acidified with 50% H_2SO_4, keeping the temperature below 15 °C, and extracted with $CHCl_3$ (3 x 30 mL). The combined $CHCl_3$ extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$). Evaporation of the $CHCl_3$ *in vacuo* afforded a light yellow oil (8.1 g) which was distilled *in vacuo* to afford 2-mercaptoacetic acid **138** as a clear oil (5.84 g, 24%), bp 55-65 °C/0.2 mm Hg (lit.,[264e] 107-108 °C/16 mm Hg); δ_H(60 MHz; $CDCl_3$) 2.21 (1H, t, SH), 3.47 (2H, d, CH_2) and 12.05 (1H, s,OH).

2-Mercapto-N-*phenylethanamide* **140a**.[54]- A melt of aniline (1.21 g, 13.0 mmol) and 2-mercaptoacetic acid **138** (1.20 g, 13.0 mmol) was stirred for 2 h at 110-120 °C in a stream of dry N_2. The melt solidified on cooling and was crushed into a fine powder in H_2O. The powder was filtered off and washed sequentially with dilute HCl and H_2O, and then dried *in vacuo*. The powder was recrystallised twice from EtOH and washed with cold Et_2O to give, as white crystals, 2-mercapto-*N*-phenylethanamide **140a** (0.67 g, 31%), mp 110-111 °C (from EtOH) (lit.,[60] 110 °C) (Found $\mathbf{M}^+$, 167.0418. Calc. for C_8H_9NOS: *M*, 167.0405); ν_{max}(KBr)/cm^{-1} 3300 (NH), 2570 (SH) and 1650 (CO); δ_H(400 MHz; $CDCl_3$) 2.03 (1H, t, *J* 9.1 Hz, SH), 3.35 (2H, d, *J* 9.1 Hz, CH_2S), 7.12 (1H, t, 4'-H), 7.32 (2H, t, 3'-H), 7.52 (2H, d, 2'-H) and 8.59 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 29.1 (C-2), 119.9, 124.8, 129.0 and 137.3 (ArC) and 167.4 (CO); *m/z* 167 ($\mathbf{M}^+$, 54%) and 93 (100%).

2-Mercapto-N-*(4-methoxyphenyl)ethanamide* **140b**.[54]- The experimental procedure employed for the synthesis of 2-mercapto-*N*-phenylethanamide **140a** was followed, using *p*-methoxyaniline (2.50 g, 20.3 mmol) and 2-mercaptoacetic acid **138** (1.87 g, 20.3 mmol). The

crude product was recrystallised twice from EtOH-H_2O (2:1) to afford, as light grey plates, 2-mercapto-*N*-(4-methoxyphenyl)ethanamide **140b** (2.00 g, 50%), mp 118.5-119.5 °C (from EtOH-H_2O) (lit.,[58] 119 °C) (Found: $\mathbf{M}^+$, 197.0515. Calc. for $C_9H_{11}NO_2S$: *M*, 197.0510); ν_{max}(KBr)/cm^{-1} 3285 (NH), 2580 (SH) and 1650 (CO); δ_H(400 MHz; $CDCl_3$) 2.01 (1H, t, *J* 9.1 Hz, SH), 3.34 (2H, d, *J* 9.1 Hz, CH_2S), 3.77 (3H, s, CH_3O), 7.13 (4H, dd, ArH) and 8.44 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 28.9 (C-2), 55.4 (OCH_3), 114.2 and 121.8 (C-2', C-3',C-5' and C-6'), 130,4 (C-1'), 156.8 (C-4') and 167.1 (CO); *m/z* 197 ($\mathbf{M}^+$, 100 %).

2-(S-*Benzoylthio)ethanoic acid* **141**.[178]- Benzoyl chloride (3.20 g, 22.8 mmol) was added to a stirred mixture of 2-mercaptoacetic acid **138** (2.00 g, 21.7 mmol) in Et_2O (10 mL) and 1 **M**-NaOH (22 mL) keeping the temperature of the reaction mixture below 5 °C. Solid $NaHCO_3$ (1.93 g, 23.0 mmol) was then added and the mixture stirred at room temperature for 20 minutes before acidifying with 32% HCl. The acidic aqueous solution was extracted with Et_2O (3 x 30 mL), the combined Et_2O extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$), and the Et_2O evaporated *in vacuo* to yield the crude product (4.34 g). Purification by flash chromatography [elution with EtOAc-hexane (3:7)] afforded white crystals of 2-(*S*-benzoylthio)ethanoic acid **141** (3.10 g, 73%), mp 104-106 °C (from EtOAc-hexane) (lit.,[265] 107-108 °C); ν_{max} (KBr)/cm^{-1} 1710 (CO.O) and 1665 (CO.S); δ_H(400 MHz; $CDCl_3$) 3.91 (2H, s, CH_2), 7.46 (2H, t, ArH), 7.60 (1H, t, ArH) and 7.97 (2H, d, ArH).

2-(S-Benzoylthio)ethanoyl chloride **142**.- Thionyl chloride (2.30 mL, 31.6 mmol) was added, using a syringe, to stirred 2-(*S*-benzoylthio)ethanoic acid **141** (3.10 g, 15.8 mmol). After the addition, the round-bottomed flask was fitted with a reflux condenser with a $CaCl_2$ drying tube and the mixture was stirred at room temperature for 2 days. The excess thionyl chloride was removed *in vacuo* to yield, as a red precipitate, 2-(*S*-benzoylthio)ethanoyl chloride **142**; ν_{max}(thin film)/cm^{-1} 1800 (CO.Cl) and 1670 (CO.S); δ_H(400 MHz; $CDCl_3$) 4.34 (2H, s, CH_2),

7.45-7.50 (2H, m, ArH), 7.60-7.64 (1H, m, ArH) and 7.94-7.96 (2H, m, ArH).

*Attempted preparation of 2-mercapto-*N*-(4-nitrophenyl)ethanamide* **140c**.- A solution of 2-(*S*-benzoylthio)ethanoyl chloride **142** (1.94 g, 9.03 mmol) in dry THF (40 mL) was added, in portions, to a solution of *p*-nitroaniline (1.24 g, 9.03 mmol) and dry triethylamine (1.4 mL, 9.9 mmol) in dry THF (40 mL), under N_2. The mixture was stirred under N_2 for several hours and the reaction then quenched by addition of H_2O (20 mL). The THF was removed *in vacuo* and the remaining aqueous solution was acidified with conc. HCl (1.5 mL) and then extracted with $CHCl_3$ (30 mL). The solvent was evaporated and TLC showed that a considerable amount of the amide had been hydrolysed by the acid. Basic hydrolysis of the thiol ester, using methanolic KOH, resulted in further hydrolysis of the amide.

2-Amino-6-methoxybenzothiazole **143b**.[188]- A cooled solution of bromine (1.67 mL, 32.5 mmol) in glacial AcOH (20 mL) was added, in portions, to a cold (<10 °C), stirred solution of NaSCN (9.0 g, 0.11 mol) in glacial AcOH (50 mL). During the addition the temperature was kept below 10 °C. This cold thiocyanogen solution was added, in portions, keeping the temperature below 10 °C, to a mechanically stirred, cold (<10 °C) solution of *p*-methoxyaniline (12.0 g, 97.4 mmol) in glacial AcOH (150 mL). Two more solutions of thiocyanogen were made up and added to the methoxyaniline solution in the manner described. When the additions were complete the temperature of the frozen slurry was allowed to rise slowly to room temperature and the mixture was stirred for a further 3 h. The precipitate was filtered off and the filtrate was then concentrated by evaporation of AcOH (~290 mL) *in vacuo* and cooled to produce a second precipitate, which was filtered off. The combined precipitates were dissolved in warm (80-90 °C) water (220 mL), which was filtered to remove insoluble material, and the clear red filtrate was cooled to room temperature and basified with solid Na_2CO_3 and 10% aqueous NaOH. Upon addition of base a red-brown precipitate formed, which was filtered off

and recrystallised from EtOH to afford grey-green crystals of 2-amino-6-methoxybenzothiazole **143b** (6.82 g, 39%), mp 158-161 °C (from EtOH) (lit.,[266] 147 °C); δ_H(400 MHz; $CDCl_3$) 3.81 (3H, s, CH_3O), 5.17 (2H, br s, NH_2), 6.90 (1H, dd, *J* 2.3 and 8.8 Hz, 5-H), 7.12 (1H, d, *J* 2.3 Hz, 7-H) and 7.43 (1H, d, *J* 8.8 Hz, 4-H); δ_C(100 MHz; $CDCl_3$) 55.9 (CH_3O), 105.4, 113.7 and 119.7 (C-4, C-5 and C-7), 132.7, 146.2 and 155.7 (ArC) and 163.9 (CN).

2-Amino-6-chlorobenzothiazole **143c**.[188]- Bromine (10.4 mL, 0.202 mol) in glacial AcOH (100 mL) was added, in portions, keeping the reaction temperature below 10 °C, to a cooled (< 10 °C), mechanically-stirred, solution of *p*-chloroaniline (35.0 g, 0.202 mol) and NH_4SCN (30.7 g, 0.403 mol) in glacial AcOH (400 mL) containing 5% (v/v) H_2O. After addition, the temperature was allowed to rise slowly to room temperature and then the solution was stirred for a further 2 h. The precipitate was filtered off and the filtrate was concentrated by removal of AcOH *in vacuo* and then cooled to produce a second precipitate, which was also collected by filtration. The combined precipitates were dried *in vacuo*, shown (by TLC) to be pure and identified as the dihydrobromide salt of 2-amino-6-chlorobenzothiazole **143c** (23.9 g, 35%); δ_H(400 MHz, DMSO-d_6) 3.45 (4H, br s, NH^+ and NH_3^+), 7.21 (1H, dd, *J* 2.2 and 8.5 Hz, 5-H), 7.29 (1H, d, *J* 8.5 Hz, 4-H) and 7.76 (1H, d, *J* 2.2 Hz, 7-H).

2-Amino-6-methylbenzothiazole **143d**.[188]- The experimental procedure employed for the synthesis of the dihydrobromide salt of 2-amino-6-chlorobenzothiazole **143c** was followed, using *p*-toluidine (12.5 g, 0.116 mol), NH_4SCN (17.8 g, 0.233 mol) and bromine (6.00 mL, 0.117 mol). This produced a precipitate of the dihydrobromide salt which was dissolved in a small amount of warm H_2O and the solution was basified with powdered NaOH. The basic solution was cooled in ice before collecting the precipitate by filtration. Recrystallisation from EtOH afforded light yellow crystals of 2-amino-6-methylbenzothiazole **143d** (5.65 g, 30%), mp 162-167 °C (from EtOH) (lit.,[267] 142 °C); δ_H(60 MHz; $CDCl_3$) 2.45 (3H, s, CH_3), 5.14 (2H, br

s, NH_2) and 7.10-7.65 (3H, m, ArH).

2-Amino-5-methoxybenzenethiol **144b** and *bis(2-amino-5-methoxyphenyl) disulfide* **145b**.[183] - 2-Amino-6-methoxybenzothiazole **143b** (5.30 g, 29.4 mmol) in 50% aqueous KOH (60 mL) was boiled under reflux for 12 h in an atmosphere of N_2. The mixture was then cooled in ice, diluted with H_2O (18 mL) and filtered. The cooled [< 0 °C (ice/NaCl)], basic filtrate was acidified with 5 **M**-AcOH in an atmosphere of N_2, keeping the temperature below 5 °C. The yellow-brown precipitate was collected by filtration, washed with cold H_2O and dried *in vacuo*. Recrystallisation from EtOH (filtering the hot solution to remove the insoluble disulfide) afforded yellow crystals shown, by ^1H NMR, to contain a mixture of 2-amino-5-methoxybenzenethiol **144b** and bis(2-amino-5-methoxyphenyl) disulfide **145b** (2.67 g); δ_H(60 MHz; $CDCl_3$-DMSO-d_6) 3.70 (3H, s, OCH_3), 4.55 (br s, SH, NH_2, H_2O) and 6.75 (3H, m, ArH).

2-Amino-5-chlorobenzenethiol **144c** and *bis(2-amino-5-chlorophenyl) disulfide* **145c**.- The experimental procedure employed for the synthesis of 2-amino-5-methoxybenzenethiol **144b** and bis(2-amino-5-methoxyphenyl) disulfide **145b** was followed using the dihydrobromide salt of 2-amino-6-chlorobenzothiazole **143c** (8.23 g, 44.6 mmol) and 50% aqueous KOH (100 mL). Recrystallisation of the yellow precipitate from EtOH, in the presence of activated carbon, afforded yellow crystals which were shown, by ^1H NMR, to contain 2-amino-5-chlorobenzenethiol **144c** and bis(2-amino-5-chlorophenyl) disulfide **145c** (4.42 g); δ_H(400 MHz; $CDCl_3$) 4.35 (br s, NH_2, SH), 6.61 (1H, d, ArH) and 7.20-7.30 (2H, m, ArH).

2-Amino-5-methylbenzenethiol **144d** and *bis(2-amino-5-methylphenyl) disulfide* **145d**.- The experimental procedure employed for the synthesis of 2-amino-5-methoxybenzenethiol **144b** and bis(2-amino-5-methoxyphenyl) disulfide **145b** was followed using 2-amino-6-

methylbenzothiazole **143d** (5.50 g, 33.5 mmol) and 50% aqueous KOH (75 mL). Recrystallisation from EtOH under N_2 produced crystals which were shown, by ^1H NMR, to contain 2-amino-5-methylbenzenethiol **144d** and bis(2-amino-5-methylphenyl) disulfide **145d** (1.8 g); δ_H(400 MHz, $CDCl_3$) 2.15 (s, $ArCH_3$), 2.22 (s, $ArCH_3$), 2.95 (br s, SH and NH_2), 3.98 (br s, SH or NH_2), 4.18 (br s, SH or NH_2) and 6.61-7.19 (m, ArH).

2-(Methylthio)aniline **146a**.[193]- A solution of methyl iodide (5.27 g, 37.3 mmol) in MeOH (30 mL) was added dropwise, under N_2, to a vigorously stirred, cool (< 20 °C) solution of 2-aminobenzenethiol (4.65 g, 37.1 mmol) and KOH (2.08 g, 37.1 mmol) in MeOH (90 mL). After stirring for 2 h at room temperature, H_2O (20 mL) was added and the MeOH was evaporated *in vacuo*. The aqueous residue was extracted with EtOAc (3 x 20 mL) and the combined EtOAc extracts were dried (anhyd. $MgSO_4$) and evaporated to leave an oil which was distilled *in vacuo* to afford, as a clear oil, 2-(methylthio)aniline **146a** (3.91 g, 76%), bp 118-120 °C/ *ca.* 15 mm Hg (lit.,[193] 121-123 °C/18 mm Hg); δ_H(60 MHz; $CDCl_3$) 2.32 (3H, s, CH_3S), 4.20 (2H, s, NH_2) and 6.57-7.45 (4H, m, ArH).

4-Methoxy-2-(methylthio)aniline **146b**.- A solution of 2-amino-6-methoxybenzothiazole **143b** (6.0 g, 33 mmol) in 50% aqueous KOH (60 mL) was boiled under reflux for 6 h in an atmosphere of N_2. The mixture was cooled in ice and a solution of methyl iodide (4.80 g, 34.0 mmol) in MeOH (15 mL) was added dropwise with vigorous stirring. The mixture was stirred for 2 h at room temperature and then extracted with $CHCl_3$ (3 x 30 mL). The combined $CHCl_3$ extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$), and the $CHCl_3$ was evaporated *in vacuo* to afford a black oil (6.2 g) which was distilled *in vacuo* to yield 4-methoxy-2-(methylthio)aniline **146b** (4.0 g, 71%), bp 105-108 °C/0.25 mm Hg [lit.,[263c] mp 210-211 °C (HCl salt)]; δ_H(60 MHz; $CDCl_3$) 2.29 (3H, s, SCH_3), 3.66 (3H, s, OCH_3), 3.90 (2H, br s, NH_2) and 6.40-7.08 (3H, m, ArH).

4-Chloro-2-(methylthio)aniline **146c**.- The experimental procedure employed for the synthesis of 4-methoxy-2-(methylthio)aniline **146b** was followed using the dihydrobromide salt of 2-amino-6-chlorobenzothiazole **143c** (15.0 g, 43.3 mmol), 50% aqueous KOH (120 mL) and methyl iodide (4.52 g, 31.8 mmol). Distillation *in vacuo* afforded, as a light yellow oil, 4-chloro-2-(methylthio)aniline **146c** (6.92 g, 92%), bp 95-104 °C/0.02-0.05 mm Hg; δ_H(400 MHz; $CDCl_3$) 2.34 (3H, s, CH_3S), 4.16 (2H, br s, NH_2), 6.60 (1H, d, *J* 9.0 Hz, 6-H), 7.07 (1H, dd, *J* 2.7 and 9.0 Hz, 5-H) and 7.28 (1H, d, *J* 2.7 Hz, 3-H); δ_C(100 MHz; $CDCl_3$) 17.2 (CH_3S) and 115.6, 121.8, 122.5, 128.2, 131.6 and 145.2 (ArC).

4-Methyl-2-(methylthio)aniline **146d**.- Bis(2-amino-5-methylphenyl) disulfide **145d** (3.67 g, 13.3 mmol) was dissolved in 10% aqueous MeOH (100 mL) 0.1 **M** in $HClO_4$. Ph_3P (3.83 g, 14.6 mmol) was added and the mixture was stirred for 3 h at room temperature, under an atmosphere of N_2, in a round-bottomed flask covered with aluminium foil. KOH pellets (5.0 g, 89 mmol) were added to the mixture which was then cooled in ice. A solution of methyl iodide (3.77 g, 25.6 mmol) in MeOH (15 mL) was added dropwise with rapid stirring. After stirring at room temperature for 2 h, the mixture was filtered to remove the white precipitate. H_2O (30 mL) was added to the filtrate and the MeOH was evaporated *in vacuo*. The black, viscous oil which separated out was washed with water and distilled *in vacuo* to yield, as an oil, 4-methyl-2-(methylthio)aniline **146d** (1.68 g, 43%), bp 71 °C/0.03 mm Hg; δ_H(60 MHz; $CDCl_3$) 2.25 (3H, s, SCH_3), 2.35 (3H, s, $ArCH_3$), 4.15 (2H, br s, NH_2) and 6.58-7.25 (3H, m, ArH).

2-Methylbenzothiazole **147**.[194]- 2-Aminobenzenethiol (10.6 g, 84.8 mmol) was added in portions, to Ac_2O (21.1 g), allowing the temperature to rise to 90 °C. *N,N*-Dimethylaniline (41 mL) was added and the mixture was heated on a water bath for 10 minutes with occasional stirring. The solution was cooled and poured into cold 4 **M**-HCl (250 mL), and the white precipitate that formed was filtered off. The acidic filtrate was partially neutralised (pH 5) with

NaOH pellets, Na_2CO_3 and aqueous 10% NaOH, and then extracted with $CHCl_3$ (3 x 40 mL). The combined $CHCl_3$ extracts were dried (anhyd. $MgSO_4$) and the $CHCl_3$ evaporated *in vacuo* to afford a transparent light blue oil (37.3 g) comprising the product and *N,N*-dimethylaniline. Distillation *in vacuo* (*ca.* 15 mmHg) afforded, as a clear oil, 2-methylbenzothiazole **147** (7.91 g, 62.5%), bp 160-170 °C/*ca.* 15 mm Hg (lit.,[264f] 150-1 °C/15 mm Hg); δ_H(400 MHz; $CDCl_3$) 2.82 (3H, s, CH_3), 7.32 and 7.42 (2H, m, 5-H and 6-H) and 7.80 and 7.94 (2H, 2 x d, *J* 8.0 Hz, 4-H and 7-H).

2-Methyl-6-nitrobenzothiazole **148**.[195]- 2-Methylbenzothiazole **147** (7.90 g, 52.9 mmol) was added in portions, to a stirred solution of conc. H_2SO_4 (12.5 mL), keeping the temperature below 20 °C. Conc. HNO_3 (6.3 mL) was then added dropwise to the stirred mixture, again keeping the temperature below 20 °C. The solution was stirred at 10 °C for 1 h and then poured on to crushed ice (63 g). The aqueous mixture was partially neutralised (pH 2-3) with aqueous 35% NH_3, and the precipitate was filtered off and washed with cold, dilute ammonia. Recrystallisation from boiling EtOH (170 mL) afforded orange-yellow needles of 2-methyl-6-nitrobenzothiazole **148** (3.91 g, 38%), mp 150-158 °C (from EtOH) (lit.,[264g] 131-132 °C); δ_H(400 MHz; $CDCl_3$) 2.90 (3H, s, CH_3), 8.02 (1H, d, *J* 8.9 Hz, 4-H), 8.31 (1H, dd, *J* 8.9 and 2.2 Hz, 5-H) and 8.75 (1H, d, *J* 2.2 Hz, 7-H); δ_C(100 MHz; $CDCl_3$) 20.6 (CH_3), 118.0, 121.5 and 122.6 (C-4, C-5 and C-7), 136.1, 144.8 and 157.2 (ArC) and 173.2 (CN).

Attempted preparation of 2-methylthio-4-nitroaniline **149**.- A solution of 2-methyl-6-nitrobenzothiazole **148** (3.80 g, 19.6 mmol) in 50% aqueous KOH (50 mL) was boiled under reflux for 12 h under an atmosphere of N_2. After cooling to 20 °C, a solution of methyl iodide (2.78 g, 19.6 mmol) in MeOH (20 mL) was added, in portions, with vigorous stirring. After the addition, the mixture was stirred for a further 3 h at room temperature and then extracted with $CHCl_3$ (3 x 30 mL). The combined $CHCl_3$ extracts were dried (anhyd. $MgSO_4$) and the $CHCl_3$

was removed *in vacuo* to afford a black residue (0.3 g) which was difficult to characterise.

2-(Methylthio)acetanilide **150a**.- A solution of sodium acetate trihydrate [(15 g) in H_2O (75 mL)] and Ac_2O (17 mL) were added sequentially to a solution of 2-(methylthio)aniline **146a** (1.70 g, 12.2 mmol) in 2 **M**-HCl (55 mL). The resulting mixture was stirred for 2.5 h, during which time a white precipitate formed. The precipitate was filtered off and recrystallised twice from EtOH-H_2O (8:2) to afford, as white crystals, 2-(methylthio)acetanilide **150a** (0.94 g, 47%), mp 101.5-102.5 °C (from EtOH-H_2O) (lit.,[193] 96-97 °C) (Found: $\mathbf{M}^+$ 165.0237. Calc. for C_8H_7NOS: *M*, 165.0249); ν_{max}(KBr)/cm^{-1} 3310 (NH) and 1650 (CO); δ_H(400 MHz; $CDCl_3$) 2.15 (3H, s, $CO.CH_3$), 2.37 (3H, s, SCH_3), 7.05 and 7.23 (2H, 2 x t, 4-H and 5-H), 7.45 (1H, d, 3-H), 8.24 (1H, br s, NH) and 8.28 (1H, d, 6-H); δ_C(100 MHz; $CDCl_3$) 18.7 (SCH_3), 24.8 ($CO.CH_3$), 120.7, 124.3, 128.8 and 132.7 (C-3, C-4, C-5 and C-6), 125.1 and 138.3 (C-1 and C-2) and 168.3 (CO); *m/z* 165 ($\mathbf{M}^+$, 0.7%) and 124 (100%).

4-Methoxy-2-(methylthio)acetanilide **150b**.- The experimental procedure employed for the synthesis of 2-(methylthio)acetanilide **150a** was followed, using 4-methoxy-2-(methylthio)aniline **146b** (1.50 g, 8.86 mmol). Purification by flash chromatography [elution with EtOAc-hexane (6:4)] followed by recrystallisation from EtOH-H_2O afforded *4-methoxy-2-(methylthio)acetanilide* **150b** (1.06 g, 61%), mp 93.5-94.5 °C (from EtOH-H_2O) (Found: C, 56.6; H, 6.4; N, 6.7; $\mathbf{M}^+$, 211.0664. $C_{10}H_{13}NO_2S$ requires C, 56.85; H, 6.2; N, 6.6%; *M*, 211.0665); ν_{max}(KBr)/cm^{-1} 3250 (NH) and 1650 (CO); δ_H(400 MHz; $CDCl_3$) 2.19 (3H, s, $CO.CH_3$), 2.39 (3H, s, SCH_3), 3.78 (3H, s, OCH_3), 6.80 (1H, dd, *J* 9.0 and 2.6 Hz, 5-H), 6.95 (1H, d, *J* 2.6 Hz, 3-H), 7.80 (1H, br s, NH) and 8.04 (1H, d, *J* 9.0 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 18.2 (SCH_3), 24.5 ($CO.CH_3$), 55.6 (OCH_3), 113.1, 116.9 and 122.9 (C-3, C-5 and C-6), 128.0, 130.9 and 156.3 (C-1, C-2 and C-4) and 168.2 (CO); *m/z* 211 ($\mathbf{M}^+$, 73 %) and 154 (100%).

4-Chloro-2-(methylthio)acetanilide **150c**.- The experimental procedure employed for the synthesis of 2-(methylthio)acetanilide **150a** was followed, using 4-chloro-2-(methylthio)aniline **146c** (1.50 g, 8.64 mmol). The crude white precipitate was recrystallised twice from aqueous EtOH to afford 4-chloro-2-(methylthio)acetanilide **150c** (1.21 g, 65%), mp 104-106 °C (from aqueous EtOH) (lit.,[268] 110 °C) (Found: C, 49.9; H, 4.6; N, 6.3; $\mathbf{M}^+$, 215.0170. $C_9H_{10}ClNOS$ requires C, 50.1; H, 4.7; N, 6.5%; *M*, 215.0170); ν_{max}(KBr)/cm^{-1} 3270 (NH) and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 2.19 (3H, s, $CO.CH_3$), 2.37 (3H, s, SCH_3), 7.18 (1H, dd, *J* 2.5 and 9.2 Hz, 5-H), 7.35 (1H, br s, 3-H), 8.04 (1H, br s, NH) and 8.16 (1H, d, *J* 9.2 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 18.3 (SCH_3), 24,6 ($CO.CH_3$), 122.0, 128.2 and 131.1 (C-3, C-5 and C-6), 127.6, 129.1 and 136.2 (C-1, C-2 and C-4) and 168.3 (CO).

2-Mercapto-N-*[2-(methylthio)phenyl]ethanamide* **151a**.- A melt of 2-(methylthio)aniline **146a** (2.00 g, 14.4 mmol) and 2-mercaptoacetic acid **138** (1.30 g, 14.4 mmol) was heated for 2 h at 110-120 °C, with stirring, in a stream of dry N_2. The melt was poured into cold water (50 mL), but did not solidify and was thus extracted with EtOAc (3 x 30 mL). The EtOAc extracts were washed (1 **M**-HCl) and dried (anhyd. $MgSO_4$), and the EtOAc evaporated *in vacuo*. The residue was purified by flash chromatography [elution with EtOAc-hexane (1:9)] followed by recrystallisation from EtOH-H_2O (7:3) to afford *2-mercapto*-N-*[2-(methylthio)phenyl]ethanamide* **151a** (0.44 g, 15%), mp 51.5-53 °C (from EtOH-H_2O) (Found: C, 50.55; H, 5.2; N, 6.5; $\mathbf{M}^+$ 213.0285. $C_9H_{11}NOS_2$ requires C, 50.7; H, 5.2, N, 6.6%; *M*, 213.0285); ν_{max}(KBr)/cm^{-1} 3240 (NH), 2550 (SH) and 1650 (CO); δ_H(400 MHz; $CDCl_3$) 2.05 (1H, t, *J* 9.2 Hz, SH), 2.40 (3H, s, SCH_3), 3.44 (2H, d, *J* 9.2 Hz, CH_2S), 7.08 and 7.29 (2H, t, 4-H and 5-H), 7.47 (1H, d, 3-H), 8.29 (1H, d, 6-H) and 9.52 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 18.7 (SCH_3), 29.6 (CH_2S), 120.4, 124.8, 128.7 and 132.7 (C-3, C-4, C-5 and C-6), 126.1 and 137.7 (C-1 and C-2) and 167.3 (CO); *m/z* 213 (M^+, 23%) and 139 (100%).

*2-Mercapto-*N*-[4-methoxy-2-(methylthio)phenyl]ethanamide* **151b**.- The experimental procedure employed for the synthesis of 2-mercapto-*N*-[(methylthio)phenyl]ethanamide **151a** was followed, using 4-methoxy-2-(methylthio)aniline **146b** (2.14 g, 12.7 mmol) and 2-mercaptoacetic acid (1.17 g, 12.7 mmol). The melt solidified on cooling and was transferred to aqueous 1 **M**-HCl (100 mL), in which medium it was crushed into a powder. The powder was collected by filtration, washed with water and recrystallised twice from 50% aqueous EtOH to afford *2-mercapto-*N*-[4-methoxy-2-(methylthio)phenyl]ethanamide* **151b** (1.23 g, 43%), mp 91.5-92.5 °C (from aqueous EtOH) (Found: C, 49.2; H, 5.5; N, 5.6; $\mathbf{M}^+$, 243.0388. $C_{10}H_{13}NO_2S_2$ requires C, 49.4; H, 5.4; N, 5.8%; *M*, 243.0377); ν_{max}(KBr)/cm^{-1} 3240 (NH), 2550 (SH) and 1640 (CO); δ_H(400 MHz; $CDCl_3$) 2.03 (1H, t, *J* 9.2 Hz, SH), 2.41 (3H, s, SCH_3), 3.43 (2H, d, *J* 9.2 Hz, $CO.CH_2S$), 3.79 (3H, s, OCH_3), 6.81 (1H, dd, *J* 2.8 and 8.9 Hz, 5-H), 6.98 (1H, d, *J* 2.8 Hz, 3-H), 8.08 (1H, d, *J* 8.9 Hz, 6-H) and 9.16 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 18.1 (SCH_3), 29.4 ($CO.CH_2S$), 55.6 (OCH_3), 113.1, 117.0 and 122.4 (C-3, C-5 and C-6), 128.7, 130.1 and 156.6 (C-1, C-2 and C-4) and 167.04 (CO); *m/z* 243 ($\mathbf{M}^+$, 30%) and 55 (100%).

*2-Mercapto-*N*-[4-chloro-2-(methylthio)phenyl]ethanamide* **151c**.- The experimental procedure employed for the synthesis of 2-mercapto-*N*-[(methylthio)phenyl]ethanamide **151a** was followed, using 4-chloro-2-methylthioaniline **146c** (3.30 g, 19.0 mmol) and 2-mercaptoacetic acid (1.75 g, 19.0 mmol). The melt solidified upon pouring into cold water. The precipitate was crushed, collected by filtration and washed sequentially with dilute HCl and H_2O. Three recrystallisations from aqueous EtOH afforded, as white crystals, *2-mercapto-*N*-[4-chloro-2-(methylthio)phenyl]ethanamide* **151c** (1.48 g, 31%), mp 86-87 °C (from aqueous EtOH) (Found: C, 43.45; H, 4.3; N, 5.7; $\mathbf{M}^+$, 246.9883. $C_9H_{10}ClNOS_2$ requires C, 43.6; H, 4.1; N, 5.65%; *M*, 246.9891); ν_{max}(KBr)/cm^{-1} 3230 (NH), 2540 (SH) and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 2.04 (1H, t, *J* 9.3 Hz, SH), 2.42 (3H, s, SCH_3), 3.44 (2H, d, *J* 9.2 Hz, CH_2S), 7.23 (1H,

dd, *J* 2.3 and 8.8 Hz, 5-H), 7.41 (1H, d, *J* 2.3 Hz, 3-H), 8.22 (1H, d, *J* 8.8 Hz, 6-H) and 9.40 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 18.2 (SCH_3), 29.5 (CH_2S), 121.6, 128.2 and 131.1 (C-3, C-5 and C-6), 128.3, 129.6 and 135.8 (C-1, C-2 and C-4) and 167.3 (CO).

2-(Benzylthio)ethanol **152**.- A solution of benzyl chloride (62.0 g, 0.489 mol) in MeOH (20 mL) was added slowly, dropwise, to a solution of 2-mercaptoethanol (33.4 g, 0.428 mol) in 50% aqueous MeOH (150 mL). The mixture was boiled under reflux for 1 h and the MeOH was removed *in vacuo*. The remaining aqueous mixture was extracted with benzene and worked up in the normal manner. Distillation *in vacuo* afforded 2-(benzylthio)ethanol **152** (62,5 g, 87%), bp 128 °C/0.1 mm Hg (lit.,[269] 169 °C/18 mm Hg; δ_H(60 MHz; $CDCl_3$) 2.61 (3H, m, SCH_2 and OH), 3.70 (2H, m, OCH_2), 3.75 (2H, s, $ArCH_2S$) and 7.35 (5H, s, ArH).

Benzyl 2-chloroethyl sulfide **153**.[200]- Thionyl chloride (23.8 g, 0.200 mol) was added dropwise to a stirred solution of 2-(benzylthio)ethanol **152** (30.0 g, 0.178 mol) in pyridine (15.8 g, 0.200 mmol) at 0 °C. After the addition, the flask was fitted with a reflux condenser with a $CaCl_2$ drying tube and the mixture was stirred for 3 h at room temperature. The $SOCl_2$ was quenched by addition of ice (~30 mL) to the cold mixture and the aqueous phase was extracted with benzene (3 x 40 mL). The combined benzene extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$), and the benzene was evaporated *in vacuo*. The remaining oil was distilled *in vacuo* to afford, as a clear oil, benzyl 2-chloroethyl sulfide **153** (28.5 g, 85.5%), bp 122-125 °C/0.5 mm Hg (lit.,[270] 113-115/1 mm Hg); δ_H(60 MHz, $CDCl_3$) 2.65 (2H, m, CH_2S), 3.49 (2H, m, CH_2Cl), 3.70 (2H, s, $ArCH_2S$) and 7.30 (5H, s, ArH).

2-(Benzylthio)ethanoic acid **154**.- Benzyl chloride (4.12 g, 32.6 mmol) in MeOH (20 mL) was added, in portions under an atmosphere of N_2, to a stirred solution of 2-mercaptoacetic acid (3.00 g, 32.6 mmol) and KOH (3.65 g, 65.1 mmol) in MeOH (50 mL). The mixture was boiled

under reflux for 2 h in an atmosphere of N_2. After cooling, the mixture was acidified with 16% HCl and extracted with EtOAc (3 x 30 mL). The combined EtOAc extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$), and the EtOAc was evaporated *in vacuo* leaving an oil, which was distilled *in vacuo* to afford, as a clear oil, 2-(benzylthio)ethanoic acid **154** (4.02 g, 68%), bp 120-140 °C/0.2 mm Hg (lit.,[264e] mp 61-62 °C); δ_H(60 MHz, $CDCl_3$) 3.14 (2H, s, SCH_2CO), 3.89 (2H, s, $ArCH_2S$), 7.34 (5H, s, ArH) and 11.82 (1H, s, OH).

2-(Benzylthio)ethanoyl chloride **155**.- Thionyl chloride (4.20 mL, 57.3 mmol) was added dropwise, with stirring, to 2-(benzylthio)ethanoic acid **154** (4.02 g, 22.1 mmol). After the addition, the flask was fitted with a reflux condenser with a $CaCl_2$ guard tube and the mixture was stirred at room temperature for 2 days. The excess thionyl chloride was removed *in vacuo* and the remaining oil was distilled *in vacuo* to afford 2-(benzylthio)ethanoyl chloride **155** (3.28 g, 74%), bp 100 °C/0.07 mm Hg (lit.,[271] 144-5 °C/11 mm Hg); δ_H(60 MHz, $CDCl_3$) 3.45 (2H, s, SCH_2CO), 3.78 (2H, s, $ArCH_2S$) and 7.31 (5H, s, ArH).

2-(5-Phenyl-1,4-dithiapentyl)aniline **156**.- A solution of KOH (3.73 g, 66.5 mmol) in H_2O (50 mL) and a solution of benzyl 2-chloroethyl sulfide **153** (12.43 g, 66.59 mmol) in MeOH (30 mL) were added, sequentially, to a stirred solution of 2-aminobenzenethiol (8.34 g, 66.6 mmol) in MeOH (50 mL), under N_2. The resulting mixture was boiled gently under reflux for 1 h, during which time a black oil (18 g) separated out. A portion of this black oil (5.0 g) was purified by flash chromatography [elution with EtOAc-hexane (1:9)] to afford, as a dark yellow oil, *2-(5-phenyl-1,4-dithiapentyl)aniline* **156** (4.0 g, 80%); δ_H(400 MHz; $CDCl_3$) 3.13 (2H, m, CH_2S), 3.42 (2H, m, $ArSCH_2$), 4.21 (2H, s, $ArCH_2S$), 4.76 (2H, br s, NH_2), 7.21-7.29 (2H, m, ArH) and 7.67-7.91 (7H, m, ArH); δ_C(100 MHz; $CDCl_3$) 30.9, 34.3 and 36.0 ($ArCH_2S$ and SCH_2CH_2S) and 114.9, 116.6, 118.4, 126.9, 128.4, 128.7, 132.0, 136.3, 138.1 and 148.5 (ArC).

N-*(2-Mercaptoethanoyl)-2-(5-phenyl-1,4-dithiapentyl)aniline* **157**.- A melt of 2-(5-phenyl-1,4-dithiapentyl)aniline **156** (5.23 g, 19.0 mmol) and 2-mercaptoacetic acid **138** (1.75 g, 19.0 mmol) was heated at 110-120 °C in a stream of dry N_2. After heating for 5 h, only a small amount of product had formed (as detected by TLC). The components of the melt were separated by flash chromatography [elution with EtOAc-hexane (1:9)] to afford *N-(2-mercaptoethanoyl)-2-(5-phenyl-1,4-dithiapentyl)aniline* **157** (0.29 g, 4%); δ_H(400MHz; $CDCl_3$) 1.98 (1H, t, *J* 8.9 Hz, SH), 2.52 (2H, m, CH_2S), 2.83 (2H, m, $ArSCH_2$), 3.38 (2H, d, *J* 8.9 Hz, $CO.CH_2S$), 3.61 (2H, s, $ArCH_2S$), 6.98-7.51 (8H, m, ArH), 8.41 (1H, d, ArH) and 9.70 (1H, br s, NH); δ_C(100MHz; $CDCl_3$) 29.7, 30.7, 35.8 and 36.2 ($SCH_2CH_2SCH_2$ and $COCH_2S$), 119.9, 124.4, 127.0, 128.4, 128.6, 128.7, 130.0, 135.7, 137.9 and 139.5 (ArC) and 167.3 (CO).

2-(5-Phenyl-1,4-dithiapentyl)acetanilide **158**.- Conc. H_2SO_4 (5 drops) was added to a solution of 2-(5-phenyl-1,4-dithiapentyl)aniline **156** (2.29 g, 8.31 mmol) in Ac_2O (46 mL). The mixture was stirred for 5 h at room temperature, after which the mixture was poured into warm water (200 mL). The aqueous mixture was extracted with EtOAc (3 x 40 mL) and the combined EtOAc extracts were dried (anhyd. $MgSO_4$). Removal of the EtOAc *in vacuo* afforded a brown oil (3.7 g) which was purified by flash chromatography [elution with EtOAc-hexane (2:8)] to afford, as a white solid, *2-(5-phenyl-1,4-dithiapentyl)acetanilide* **158** (1.94 g, 73%), mp 48-49 °C (from EtOAc-hexane) (Found: C, 64.1; H, 6.1; N, 4.2; $\mathbf{M}^+$, 317.0910. $C_{17}H_{19}NOS_2$ requires C, 64.3; H, 6.0; N, 4.4%; *M*, 317.0904); ν_{max}(KBr)/cm^{-1} 3340 (NH) and 1690 (CO); δ_H(400 MHz; $CDCl_3$) 2.11 (3H, s, $CO.CH_3$), 2.44 (2H, m, CH_2S), 2.75 (2H, m, $ArSCH_2$), 3.56 (2H, s, $ArCH_2S$), 6.90-7.38 (8H, m, ArH), 8.32 (1H, d, ArH) and 8.49 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 24.8, 30.7, 36.0 and 36.1 (C-2, C-3, C-5 and CH_3), 120.2, 121.2, 123.9, 127.1, 128.5, 128.6, 130.0, 135.5, 137.7 and 140.0 (ArC) and 168.3 (CO).

N-*[2-(Benzylthio)ethanoyl]-2-(5-phenyl-1,4-dithiapentyl)aniline* **159**.-

Method 1

A solution of 2-(benzylthio)ethanoyl chloride **155** (3.28 g, 16.3 mmol) in dry THF (30 mL) was added dropwise, using a syringe, to a stirred solution of 2-(5-phenyl-1,4-dithiapentyl)aniline **156** (4.49 g, 16.3 mmol) and dry triethylamine (2.51 mL, 18.0 mmol) in dry THF (30 mL). The mixture was stirred at room temperature for 2 h before addition of H_2O (30 mL). The THF was evaporated *in vacuo* and the aqueous residue was extracted with EtOAc (3 x 30 mL) and the combined EtOAc extract was dried (anhyd. $MgSO_4$). Evaporation of the EtOAc yielded a brown solid which was recrystallised twice from EtOH-EtOAc (9:1) to afford, as white crystals, N-*[2-(benzylthio)ethanoyl]-2-(5-phenyl-1,4-dithiapentyl)aniline* **159** (4.34 g, 60%), mp 81-81.5 °C (from EtOH-EtOAc) (Found: C, 65.3; H, 5.85; N, 3.1; $\mathbf{M}^+$, 439.1086. $C_{24}H_{25}NOS_3$ requires C, 65.6; H, 5.7; N, 3.2%; *M*, 439.1098); ν_{max}(KBr)/cm^{-1} 3270 (NH) and 1675 (CO); δ_H(400 MHz; $CDCl_3$) 2.53-2.57 (2H, m, SCH_2), 2.84-2.88 (2H, m, $ArSCH_2$), 3.28 (2H, s, $CO.CH_2S$), 3.63 (2H, s, $ArCH_2S$), 3.76 (2H, s, $ArCH_2S$), 7.03-7.49 (13H, m, ArH), 8.41 (1H, d, ArH) and 9.78 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 30.8, 38.8, 36.2, 36.6 and 37.1 (C-2, C-3, C-5 and $CO.CH_2SCH_2$), 120.0, 122.2, 124.3, 127.1, 127.4, 128.6, 128.7, 128.7, 129.1, 129.9, 135.6, 136.6, 137.9 and 139.5 (ArC) and 166.8 (CO).

Method 2

A solution of 2-(benzylthio)ethanoic acid **154** (3.85 g, 16.9 mmol) in dry THF (40 mL) was added dropwise, using a cannula, to a solution of 1,1'-carbonyldiimidazole (CDI) (2.92 g, 18.0 mmol) in dry THF (30 mL) under dry N_2. The mixture was stirred for 20 minutes before the dropwise addition of a solution of 2-(5-phenyl-1,4-dithiapentyl)aniline **156** (4.50 g, 16.9 mmol) in THF (40 mL). The mixture was stirred for a further 1.5 h before the addition of H_2O (30 mL). The THF was removed *in vacuo* and the aqueous residue was extracted with EtOAc (3 x 30 mL) and the combined EtOAc extracts were dried (anhyd. $MgSO_4$). Removal of the EtOAc *in vacuo* followed by flash chromatography [elution with EtOAc-hexane (1:9)] afforded *N*-[2-

(benzylthio)ethanoyl]-2-(5-phenyl-1,4-dithiapentyl)aniline **159** (4.48 g, 60%).

Attempted reductive fission of the dibenzyl ligand **159**.[91] - Liquid ammonia was added to a 2-necked round-bottomed flask until it was approximately half full (this addition was done outside the building), and the flask was placed in an acetone-liquid nitrogen bath to minimise loss of ammonia. *N*-[2-(benzylthio)ethanoyl]-2-(5-phenyl-1,4-dithiapentyl)aniline **159** (4.00 g, 9.10 mmol) was added in portions. Small pieces of freshly cut sodium were also added until the blue colour persisted for at least 30 minutes. A few spatula tips of NH_4Cl were then added to destroy excess sodium and the ammonia was allowed to evaporate overnight. H_2O (30 mL) was added to the residue and the aqueous mixture was washed with Et_2O and then acidified with 10% HCl. Sequential extraction of the acidified, aqueous solution with Et_2O, EtOAc and $CHCl_3$, followed by drying (anhyd. $MgSO_4$) and evaporation of the solvents *in vacuo* afforded a black residue, the components of which were separated by flash chromatography. ^{1}H NMR showed the main component to contain the partial function **160**, δ_H(60MHz, $CDCl_3$) 2.94 (2H, s, $CO.CH_2S$) and 7.37-8.18 (4H, m, ArH).

Bis(2-hydroxyethyl) disulfide **161**.[208]- Aqueous 30% H_2O_2 (40 mL) was added, in portions, to a stirred, cooled (ice) solution of 2-mercaptoethanol (22.3 g, 0.285 mmol). When necessary, crushed ice was added to the solution to keep the temperature below 50 °C. After stirring overnight, the excess H_2O_2 was quenched by the sequential addition of conc. H_2SO_4 (3 mL), conc. aqueous $KMnO_4$ and $KMnO_4$ crystals. Removal of most of the H_2O, using a rotary evaporator (CAUTION: an explosive mixture can form upon removal of the H_2O), afforded bis(2-hydroxyethyl) disulfide **161** as a clear oil which was used without further purification.

Bis(2-chloroethyl) disulfide **162**.[209]- 32% HCl (90 mL) was added to the crude bis(2-hydroxyethyl) disulfide **161** (*ca.* 22 g, 0.14 mol), and the mixture was heated at 100 °C for 1 h.

After cooling to room temperature, the aqueous solution was extracted with Et_2O (3 x 40 mL) and the combined Et_2O extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$). Distillation of the residue *in vacuo* afforded, as a straw-coloured liquid, bis(2-chloroethyl) disulfide **162** (8.80 g, 32%), bp 150 °C/15 mm Hg (lit.,[209] 155 °C/30 mm Hg); δ_H(60MHz; $CHCl_3$) 3.18 (4H, m, CH_2S) and 3.92 (4H, m, CH_2Cl).

1,6-Bis(2-aminophenylthio)-3,4-dithiahexane **164a**.- A solution of bis(2-chloroethyl) disulfide **162** (4.88 g, 25.5 mmol) in MeOH (50 mL) was added dropwise to a stirred solution of 2-aminobenzenethiol (6.39 g, 51.1 mmol) and KOH (2.86 g, 51.1 mmol) in MeOH (100 mL) under N_2. The resulting mixture was boiled under reflux for 2 h and then H_2O (30 mL) was added and the MeOH removed *in vacuo*. The aqueous residue was extracted with $CHCl_3$ and the combined $CHCl_3$ extract was washed (satd. brine), dried (anhyd. $MgSO_4$) and the $CHCl_3$ evaporated *in vacuo* to afford, as a dark yellow oil which was not purified further, *1,6-bis(2-aminophenylthio)-3,4-dithiahexane* **164a** (9.59 g, 100%), (Found: $\mathbf{M}^+$, 368.0504. $C_{16}H_{20}N_2S_4$ requires *M*, 368.0514); ν_{max}(thin film)/cm^{-1} 3360 (NH); δ_H(60 MHz; $CDCl_3$) 2.70-3.40 (8H, m, SCH_2CH_2S), 4.51 (4H, s, NH_2) and 6.72-7.70 (8H, m, ArH).

1,6-*Bis(2-amino-5-methoxyphenylthio)-3,4-dithiahexane* **164b**.- A mixture of 2-amino-6-methoxybenzothiazole **143b** (3.80 g, 21.1 mmol) in 50% aqueous KOH (50 mL) was boiled under reflux for 12 h in an atmosphere of dry N_2. The solution was then cooled to room temperature and bis(2-chloroethyl) disulfide **162** (2.01 g, 10.5 mmol) in MeOH (40 mL) was added with vigorous stirring. The resulting mixture was stirred under N_2 for 3 h and then extracted with $CHCl_3$ (3 x 30 mL). The combined $CHCl_3$ extracts were washed (satd. brine), dried (anhyd. $MgSO_4$) and the $CHCl_3$ removed *in vacuo* to afford, as a black oil which was not purified further, *1,6-bis(2-amino-5-methoxyphenylthio)-3,4-dithiahexane* **164b** (4.87 g, 100%), (Found: $\mathbf{M}^+$, 396.0648. $C_{14}H_{26}N_2O_3S_4$ requires *M*, 396.0670); ν_{max}(thin film)/cm^{-1} 3360 (NH)

and 1490 (C=C); δ_H(400 MHz; $CDCl_3$) 2.73-2.76 (4H, m, CH_2SSCH_2), 2.97-3.01 (4H, m, $ArSCH_2$), 3.71 (6H, s, OCH_3), 4.05 (4H, br s, NH_2), 6.62-6.74 (4H, m, ArH) and 6.94 (2H, d, ArH); δ_C(100 MHz; $CDCl_3$) 33.8 and 38.1 (C-1, C-2, C-5 and C-6), 55.8 (OCH_3) and 116.1, 116.5, 117.4, 120.3, 142.3 and 152.1 (ArC).

1,6-Bis(2-acetamidophenylthio)-3,4-dithiahexane **165a**.[168e]- Conc. H_2SO_4 (19 drops) was added to a solution of 1,6-bis(2-aminophenylthio)-3,4-dithiahexane **164a** (9.59 g, 29.9 mmol) in Ac_2O (190 mL) and the mixture was stirred at room temperature for 30 minutes. The excess Ac_2O was hydrolysed by pouring the solution into warm H_2O (400 mL) and stirring the solution for 30 minutes. (The temperature of this solution was kept below 90 °C by the addition of cold water when necessary). The aqueous solution was cooled (ice), and the pale pink precipitate was filtered off and recrystallised from aqueous EtOH to afford white crystals of *1,6-bis(2-acetamidophenylthio)-3,4-dithiahexane* **165a** (4.90 g, 40%), mp 125-127 °C (from aqueous EtOH) (Found: C, 52.6; H, 5.4; N, 5.8; $\mathbf{M}^+$, 404.0938. $C_{20}H_{24}N_2O_2S_4$ requires C, 53.1; H, 5.3; N, 6.2%; *M*, 404.0928); ν_{max}(KBr)/cm^{-1} 3300 (NH) and 1650 (CO); δ_H(400 MHz; $CDCl_3$) 2.22 (6H, s, $CO.CH_3$), 2.69 (4H, m, CH_2SSCH_2), 3.01 (4H, m, $ArSCH_2$), 7.03 (2H, m, ArH), 7.32 (2H, m, ArH), 7.49 (2H, dd, ArH), 8.37 (2H, d, ArH) and 8.45 (2H, br s, NH); δ_C(100 MHz; $CDCl_3$) 24.9 and 35.2 (C-1, C-2, C-5 and C-6), 37.4 (CH_3), 120.5, 121.5, 124.1, 130.2, 135.4 and 140.0 (ArC) and 169.0 (CO).

1,6-*Bis(2-acetamido-5-methoxyphenylthio)-3,4-dithiahexane* **165b**.- The experimental procedure employed for the synthesis of 1,6-bis(2-acetamidophenylthio)-3,4-dithiahexane **165a** was followed, using 1,6-bis(2-amino-5-methoxyphenylthio)-3,4-dithiahexane **164b** (2.66 g, 6.71 mmol), Ac_2O (100 mL) and conc. H_2SO_4 (10 drops). The crude precipitate was purified by recrystallising twice from EtOH-H_2O (2:1) to afford *1,6-bis(2-acetamido-5-methoxyphenylthio)-3,4-dithiahexane* **165b** (1.36 g, 40%), mp 131-133 °C (from EtOH-H_2O)

(Found: C, 51.2; H, 5.6; N, 5.4; $\mathbf{M}^+$, 512.0918. $C_{22}H_{28}N_2O_4S_4$ requires C, 51.5; H, 5.5; N, 5.5%; *M*, 512.0932); ν_{max}(KBr)/cm^{-1} 3290 (NH) and 1655 (CO); δ_H(400 MHz; $CDCl_3$) 2.20 (6H, s, CH_3CO), 2.71 (4H, m, CH_2SSCH_2), 3.04 (4H, m, $ArSCH_2$), 3.77 (6H, s, OCH_3), 6.86 (2H, dd, *J* 2.6 and 9.0 Hz, ArH), 7.02 (2H, d, *J* 2.7 Hz, ArH), 8.12 (2H, br s, NH) and 8.18 (2H, d, *J* 9.0 Hz, ArH); δ_C(100 MHz; $CDCl_3$) 24.7 (CH_3CO), 34.9 and 37.4 (C-1, C-2, C-5 and C-6), 55.6 (OCH_3), 114.9, 119.8, 122.4, 123.3, 133.0 and 156.0 (ArC) and 168.1 (CO); *m/z* 512 ($\mathbf{M}^+$, 18%) and 196 (100%).

2-[(2-Mercaptoethyl)thio]acetanilide **166a**.- A mixture of 1,6-bis(2-acetamidophenylthio)-3,4-dithiahexane **165a** (0.50 g, 1.2 mmol) and Ph_3P (0.36 g, 1.4 mmol) in 10% aqueous MeOH (100 mL) was stirred in an atmosphere of N_2 for 3 h, at 60 °C. H_2O (10 mL) was added and the MeOH was removed *in vacuo*. Benzene (30 mL) and NaOH pellets (2.0 g) were added, sequentially, to the aqueous residue, and the mixture was stirred vigorously until the NaOH pellets had dissolved. The phases were separated and the aqueous phase was extracted again with benzene (40 mL). The aqueous solution was acidified with 16% HCl, extracted with benzene (3 x 30 mL), and the combined benzene extracts were washed (satd. brine) and dried(anhyd. $MgSO_4$), and the benzene was evaporated *in vacuo*. The solid residue was purified by flash chromatography [elution with EtOAc-hexane (3:7)] to afford, as a white precipitate, *2-[(2-mercaptoethyl)thio]acetanilide* **166a** (0.33 g, 65%), mp 58.5-59.5 °C (from EtOAc-hexane) (Found: C, 52.7; H, 5.75; N, 6.0; $\mathbf{M}^+$, 227.0421. $C_{10}H_{13}NOS_2$ requires C, 52.8; H, 5.8; N, 6.2%; *M*, 227.0438); ν_{max}(KBr)/cm^{-1} 3295 (NH) and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 1.62 (1H, t, *J* 7.9 Hz, SH), 2.22 (3H, s, $CO.CH_3$), 2.59-2.65 (2H, m, CH_2SH), 2.91-2.95 (2H, m, $ArSCH_2$), 7.02 (1H, t, ArH), 7.32 (1H, t, ArH), 7.49 (1H, d, ArH), 8.38 (1H, d, ArH) and 8.52 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 24.1 (CH_3), 24.9 and 39.9 (SCH_2CH_2S), 120.3, 124.0, 130.1, 130.8, 135.5 and 139.9 (ArC) and 168.3 (CO); *m/z* 227 ($\mathbf{M}^+$, 9.4%) and 125 (100%).

2-[(2-Mercaptoethyl)thio]-4-methoxyacetanilide **166b**.- The experimental procedure employed for the synthesis of 2-[(2-mercaptoethyl)thio]acetanilide **166a** was followed, using 1,6-bis(2-acetamido-5-methoxyphenylthio)-3,4-dithiahexane **165b** (0.35 g, 1.4 mmol) and Ph_3P (0.43 g, 1.6 mmol) in 10% aqueous MeOH (140 mL). Purification by flash chromatography [elution with EtOAc-hexane (4:6)] afforded, as pale yellow crystals, *2-[(2-mercaptoethyl)thio]-4-methoxyacetanilide* **166b** (0.28 g, 40%), mp 78-79.5 °C (from EtOAc-hexane) (Found: C, 51.0; H, 6.1; N, 5.5; $\mathbf{M}^+$, 257.0528. $C_{11}H_{15}NO_2S_2$ requires C, 51.3; H, 5.9; N, 5.4%; *M*, 257.0544); ν_{max}(KBr)/cm^{-1} 3290 (NH) and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 1.62 (1H, t, *J* 8.0 Hz, SH), 2.19 (3H, s, CH_3CO), 2.61-2.66 (2H, m, CH_2SH), 2.93-2.97 (2H, m, $ArSCH_2$), 3.76 (3H, s, OCH_3), 6.86 (1H, dd, *J* 2.8 and 9.0 Hz, ArH), 7.02 (1H, d, *J* 2.7 Hz, ArH) and 8.19-8.21 (2H, m, ArH and NH); δ_C(100 MHz; $CDCl_3$) 24.1 (CH_3CO), 24.7 and 39.7 (SCH_2CH_2S), 55.5 (OCH_3), 115.0, 120.0, 122.2, 123.1, 133.0 and 155.7 (ArC) and 168.1 (CO); *m/z* 257 ($\mathbf{M}^+$, 12.6%) and 155 (100%).

N-*Ethyl-2-[(2-mercaptoethyl)thio]aniline* **167**.- 1,6-Bis(2-acetamidophenylthio)-3,4-dithiahexane **165a** (0.50 g, 1.2 mmol) was added to a slurry of $NaBH_4$ (0.38 g, 9.9 mmol) and $AlCl_3$ (0.63 g, 4.7 mmol) in dry THF (50 mL), and the mixture was stirred overnight, at room temperature, in an atmosphere of dry N_2. The mixture was cooled (< 8 °C) and quenched by the cautious, sequential addition of 1 **M**-NaOH (5 mL) and 3 **M**-HCl (20 mL). The THF was removed *in vacuo* and the aqueous residue was extracted with benzene and the combined benzene extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$), and the benzene was evaporated *in vacuo*. Purification by flash chromatography [elution with EtOAc-hexane (1:9)] afforded two fractions, *viz.*,

(i) 2-[(2-mercaptoethyl)thio]acetanilide **166a** (0.12 g, 25%) as white crystals, and

(ii) as an oil, N-*ethyl-2-[(2-mercaptoethyl)thio]aniline* **167** (0.14 g, 30%); δ_H(400 MHz; $CDCl_3$) 1.24 (3H, t, CH_3CH_2), 1.59 (1H, t, SH), 2.54-2.59 (2H, m, CH_2SH), 2.80-2.84 (2H, m,

$ArSCH_2$), 3.13 (2H, q, NCH_2), 4.94 (1H, br s, NH), 6.53-6.57 (2H, m, ArH), 7.16 (1H, dt, *J* 1.7 and 8.0 Hz, ArH) and 7.34 (1H, dd, *J* 1.7 and 8.0 Hz, ArH); δ_C(100 MHz; $CDCl_3$) 14.6 (CH_3), 24.4, 38.1 and 38.4 (SCH_2CH_2S, and NCH_2) and 110.0, 115.6, 116.3, 130.4, 136.5 and 149.3 (ArC).

2-[(2-Mercaptoethyl)thio]aniline **168**.- A mixture of 1,6-bis(2-acetamidophenylthio)-3,4-dithiahexane **165a** (0.50 g, 1.2 mmol) and Ph_3P (0.36 g, 1.4 mmol) in 10% aqueous MeOH 0.1 **M** in $HClO_4$ (100 mL) was boiled under reflux for 3 h in an atmosphere of N_2. The mixture was then cooled; H_2O (10 mL) was added and the MeOH removed *in vacuo*. Benzene (20 mL) and NaOH pellets (2.0 g) were added, sequentially, to the aqueous residue and the heterogenous mixture was stirred vigorously for 10 minutes. The phases were separated and the basic aqueous phase was washed again with benzene (20 mL) before acidification with 16% HCl. The acidic, aqueous solution was extracted with benzene and the combined benzene extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$), and the benzene was evaporated *in vacuo*. Purification by flash chromatography [elution with EtOAc-hexane (1:9)] afforded two fractions, *viz.*,

(i) 2-[(2-mercaptoethyl)thio]acetanilide **166a** (0.14 g, 28%), and

(ii) as an oil, *2-[(2-mercaptoethyl)thio]aniline* **168** (0.16 g, 33%); δ_H(400 MHz; $CDCl_3$) 1.68 (1H, t, *J* 7.7 Hz, SH), 2.60-2.68 (2H, m, CH_2SH), 2.89-2.93 (2H, m, $ArSCH_2$), 4.30 (2H, br s, NH_2), 6.66-6.71 (2H, m, ArH), 7.10-7.15 (1H, m, ArH) and 7.37 (1H, dd, *J* 1.5 and 7.6 Hz, ArH); δ_C(100 MHz; $CDCl_3$) 24.3 and 38.2 (SCH_2CH_2S), 114.8, 116.0, 118.2, 129.9, 136.1 and 148.3 (ArC).

Bis(carboxymethyl) disulfide **169**.[217]-

Method 1

A solution of chloroacetic acid (19.0 g, 0.200 mol) in H_2O (90 mL) was neutralised with anhyd. Na_2CO_3. A solution of $Na_2S_2O_3$ (50.0 g, 0.200 mol) in H_2O (60 mL) was added and the mixture was boiled under reflux for 1 h. While the solution was still hot iodine (25.4 g, 0.200 mmol) was added cautiously, in small portions, with stirring. The mixture was acidified with conc. H_2SO_4 (6 mL), extracted with Et_2O (7 x 50 mL) and the combined Et_2O extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$). The Et_2O was evaporated *in vacuo* to afford a brown oil which was eluted through a plug of silica (elution with EtOAc) and recrystallised from $CHCl_3$-CCl_4 (1:9) to afford white crystals of bis(carboxymethyl) disulfide **169** (8.07 g, 44%), mp 103-105 °C (from $CHCl_3$-CCl_4) (lit.,[217] 106 °C); δ_H(60 MHz; $CDCl_3$) 3.72 (4H, s, CH_2) and 10.78 (2H, br s, CO.OH).

Method 2[220]

A solution of iodine (13.8 g, 54.3 mmol) and potassium iodide (12.8 g, 77.1 mmol) in H_2O (30 mL) was added in portions to mercaptoacetic acid (5.0 g, 54 mmol), keeping the temperature below 40 °C, until the brown colour of iodine remained. Unreacted iodine was reduced by the addition of satd. aqueous $Na_2S_2O_3$, and the aqueous mixture was extracted with Et_2O (3 x 30 mL). During the Et_2O extractions three layers formed, the upper 2 organic layers were kept. Evaporation of the Et_2O *in vacuo* left a brown liquid which was basified with 10% aqueous NaOH. The basic solution was washed with Et_2O and then acidified with 32% HCl . The acidic solution was extracted with several portions of Et_2O (extraction with Et_2O was continued until the aqueous phase lost its yellow tinge). The combined Et_2O extracts were dried (anhyd. $MgSO_4$), and the Et_2O was evaporated *in vacuo* to afford crystals of bis(carboxymethyl) disulfide **169** (4.39 g, 88%).

Bis[(chloroformyl)methyl] disulfide **170**.- Thionyl chloride (13.3 mL, 0.182 mol) was added dropwise to bis(carboxymethyl) disulfide **169** (6.68 g, 36.7 mmol) with stirring. After the

addition, the flask was fitted with a reflux condenser with a $CaCl_2$ drying tube, and the mixture stirred at room temperature for 2 days. Unreacted thionyl chloride was removed *in vacuo* and the remaining oil was distilled *in vacuo* (with difficulty and with some decomposition) to afford bis[(chloroformyl)methyl] disulfide **170** (6.75 g, 84%), bp 110 °C/0.02 mm Hg; δ_H(400MHz, $CDCl_3$) 4.07 (4H, s, CH_2); δ_C(100MHz, $CDCl_3$) 52.0 (SCH_2) and 169.7 (CO).

The polymeric disulfide **171a**.- A solution of bis[(chloroformyl)methyl] disulfide **170** (2.38 g, 10.9 mmol) in dry THF (50 mL) was added, under N_2, to a stirred solution of 1,6-bis(2-aminophenylthio)-3,4-dithiahexane **164a** (4.00 g, 10.9 mmol) and dry triethylamine (2.42 g, 23.8 mmol) in dry THF (100 mL). After stirring under N_2 for 3 h the THF was evaporated *in vacuo* and the residue was triturated with H_2O, filtered, and washed with H_2O to afford, as a light brown precipitate, the polymeric disulfide **171a** (5.71 g, 100%), which was used without further purification.

The polymeric disulfide **171b**.- The experimental procedure employed for the synthesis of the polymeric disulfide **171a** was followed, using bis[(chloroformyl)methyl] disulfide **170** (1.24 g, 5.66 mmol), 1,6-bis(2-amino-5-methoxyphenylthio)-3,4-dithiahexane **164b** (2.24 g, 5.65 mmol) and dry triethylamine (1.26 g, 12.5 mmol). The brown precipitate was washed with H_2O and dried *in vacuo* to afford the polymeric disulfide **171b** (3.71 g, 100%), which was used without further purification.

N-*(2-Mercaptoethanoyl)-2-[(2-mercaptoethyl)thio]aniline* **172a**.- A mixture of the polymeric disulfide **171a** (1.00 g, 3.88 mmol) and Ph_3P (1.12 g, 4.27 mmol) in 10% aqueous MeOH (150 mL) was stirred for 2 h under N_2. The MeOH was evaporated *in vacuo* and H_2O (15 mL), benzene (30 mL) and NaOH pellets (3.0 g) were added sequentially, and the mixture was stirred for 5 minutes. The phases were separated, and the aqueous phase was washed again with

benzene before acidifying with 16% HCl. The acidic aqueous phase was extracted with benzene (3 x 30 mL) and the combined benzene extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$). The benzene was evaporated *in vacuo* and the residue was purified by flash chromatography [elution with EtOAc-hexane (3:7)] to afford N-*(2-mercaptoethanoyl)-2-[(2-mercaptoethyl)thio]aniline* **172a** (0.50 g, 50%), mp 45-46 °C (from EtOAc-hexane) (Found: C, 46.4; H, 5.0; N, 5.4; $\mathbf{M}^+$, 259.0127. $C_{10}H_{13}NOS_3$ requires C, 46.3; H, 5.05; N, 5.4%; *M*, 259.0159); ν_{max}(KBr)/cm^{-1} 3280 (NH) and 1675 (CO); δ_H(400 MHz; $CDCl_3$) 1.65 (1H, t, *J* 8.1 Hz, SH), 2.07 (1H, t, *J* 9.2 Hz, SH), 2.62-2.68 (2H, m, CH_2SH), 2.95-2.99 (2H, m, $ArSCH_2$), 3.46 (2H, d, *J* 9.2 Hz, $CO.CH_2S$), 7.07 and 7.35 (2H, dt, *J* 1.4 and 7.8 Hz, 4-H and 5-H), 7.53 (1H, dd, *J* 1.4 and 7.8 Hz, 3-H), 8.41 (1H, d, *J* 8.2 Hz, 6-H) and 9.75 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 24.2 ($CO.CH_2S$), 29.7 and 39.9 (SCH_2CH_2S), 120.1, 124.5, 130.2, and135.7 (C-3, C-4,C-5 and C-6), 122.0 and 139.4 (C-1 and C-2) and 167.3 (CO); *m/z* 259 ($\mathbf{M}^+$, 4.4%) and 152 (100%).

The polymeric disulfide **173**.- A solution of bis[(chloroformyl)methyl] disulfide **170** (1.75 g, 8.02 mmol) in dry THF (40 mL) was added dropwise, through a cannula, to a mixture of bis(2-amino-5-methoxyaniline) disulfide **145b** (3.18 g, 14.0 mmol) and dry triethylamine (1.78 g, 17.6 mmol) in dry THF (50 mL). The mixture was stirred overnight and the THF was evaporated *in vacuo*. The remaining brown precipitate was triturated with H_2O, filtered, washed with H_2O and dried *in vacuo* to afford the polymeric disulfide **173** (4.08 g).

The cyclic sulfide **174b**.- A mixture of the polymeric disulfide **173** (1.00 g, 4.40 mmol) and Ph_3P (1.00 g, 3.83 mmol) was heated (60 °C) under reflux in an atmosphere of N_2. After cooling, the mixture was filtered and the filtrate concentrated *in vacuo* and purified by flash chromatography [elution with EtOAc-hexane (4:6)] to afford, as an orange solid, the cyclic sulfide **174b** (0.28 g, 28%), mp 172-175 °C (from EtOAc-hexane) (Found: $\mathbf{M}^+$ 195.0402. Calc.

for $C_9H_9NO_2S$ *M*, 195.0354); ν_{max}(KBr)/cm^{-1} 3180 (NH) and 1675 (CO); δ_H(400 MHz; $CDCl_3$) 3.41 (2H, s, $CO.CH_2S$); 3.77 (3H, s, OCH_3), 6.72 (1H, dd, *J* 2.6 Hz and 8.7 Hz, ArH), 6.81 (1H, d, ArH), 6.84 (1H, d, *J* 2.6 Hz, ArH) and 8.82 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 30.1 ($CO.CH_2S$), 55.7 (OCH_3), 112.6, 113.5, 118.3, 121.2, 130.0 and 155.9 (ArC) and 165.8 (CO); *m/z* 195 ($\mathbf{M}^+$, 100%).

Bis(2-{2-[2-(benzoylthio)ethanamido]-5-methoxyphenyl}thioethyl) disulfide **178**.-

Method 1

A solution of 2-(*S*-benzoylthio)ethanoic acid **141** (1.28 g, 6.52 mmol) in dry THF (40 mL) was added to CDI (1.37 g, 8.48 mmol) under dry N_2. The solution was stirred for 20 minutes before the addition of a solution of 1,6-bis(2-amino-5-methoxyphenylthio)-3,4-dithiahexane **164b** (1.19 g, 3.00 mmol) in dry THF (40 mL). The resulting mixture was stirred for 4 h and then quenched by the addition of H_2O (20 mL). The THF was evaporated *in vacuo* and the aqueous residue was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$) and the $CHCl_3$ was evaporated *in vacuo*. Purification of the residue by flash chromatography [elution with EtOAc-hexane (4:6)] afforded *bis(2-{2-[2-(benzoylthio)ethanamido]-5-methoxyphenyl}thioethyl) disulfide* **178** (0.464 g, 20%), mp 86-87 °C (from EtOAc-hexane) (Found: $\mathbf{M}^+$, 784.0888. $C_{36}H_{36}N_2O_6S_6$ requires *M*, 784.0903); ν_{max}(thin film)/cm^{-1} 3290 (NH) and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 2.56-2.59 (4H, m, CH_2SSCH_2), 2.85-2.88 (4H, m, $ArSCH_2$), 3.75 (6H, s, OCH_3), 3.93 (4H, s, $CO.CH_2S$), 6.85 (2H, dd, *J* 2.9 and 9.1 Hz, 4-H), 7.00 (2H, d, *J* 2.9 Hz, 6-H), 7.46 (4H, t, ArH), 7.59 (2H, t, ArH), 7.98-8.00 (4H, m, ArH), 8.21 (2H, d, *J* 9.1 Hz, 3-H) and 8.95 (2H, br s, NH); δ_C(100 MHz; $CDCl_3$) 33.7, 34.7 and 37.3 (SCH_2CH_2S and $CO.CH_2S$), 55.6 (CH_3O), 114.9, 120.1, 122.3, 123.9, 127.5, 128.9, 132.6, 134.17, 135.9 and 156.0 (ArC), 166.0 (CO.N) and 190.9 (CO.S).

Method 2

2-(*S*-benzoylthio)ethanoyl chloride **142** (1.45 g, 6.75 mmol) in dry THF (20 mL) was added dropwise, through a cannula, to a solution of 1,6-bis(2-amino-5-methoxyphenylthio)-3,4-dithiahexane **164b** (1.38 g, 3.22 mmol) and dry triethylamine (0.74 g, 7.3 mmol) in dry THF (40 mL). The mixture was stirred overnight under dry N_2, and H_2O (20 mL) was then added and the THF evaporated *in vacuo*. The aqueous residue was extracted with $CHCl_3$ and the combined $CHCl_3$ extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$). Evaporation of the $CHCl_3$ *in vacuo* afforded crude bis(2-{2-[2-(benzoylthio)ethanamido]-5-methoxyphenyl}thioethyl) disulfide **178**, which was shown (by TLC) to contain one component and, consequently, used without further purification.

N-*(2-Mercaptoethanoyl)-2-(2-mercaptoethyl)thio-4-methoxyaniline* **172b**.-

Method 1

A solution of bis(2-{2-[2-(benzoylthio)ethanamido]-5-methoxyphenyl}thioethyl) disulfide **178** (0.53 g, 0.68 mmol) and Ph_3P (0.23 g, 0.88 mmol) in acetone (50 mL) and 10% aqueous MeOH (100 mL) was boiled under reflux for 3 h in an atmosphere of N_2. The mixture was cooled to room temperature and KOH pellets (2.0 g) and H_2O (10 mL) were added. The mixture was stirred until the KOH pellets had dissolved and the MeOH and acetone were then removed *in vacuo*. The aqueous residue was washed with benzene (2 x 20 mL) and adjusted to pH 6 with 16% HCl before extracting with benzene (3 x 20 mL). The combined benzene extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$) and the benzene evaporated *in vacuo* to afford crude product (0.36 g, 93%), which was purified by flash chromatography [elution with EtOAc-hexane (4:6)] to afford N-*(2-mercaptoethanoyl)-2-(2-mercaptoethyl)thio-4-methoxyaniline* **172b**, mp 69-71°C (from EtOAc-hexane) (Found: C, 45.8; H, 5.2; N, 4.8; $\mathbf{M}^+$, 289.0261. $C_{11}H_{15}NO_2S_3$ requires C, 45.65; H, 5.2; N, 4.8%; *M*, 289.0270); ν_{max}(KBr)/cm^{-1} 3290 (NH), 2560 (SH) and 1655 (CO); δ_H(400 MHz; $CDCl_3$) 1.65 (1H, t, *J* 8.0 Hz, SH), 2.05 (1H, t, *J* 9.2 Hz, SH), 2.63-2.69 (2H, m, CH_2SH), 2.97-3.01 (2H, m, $ArSCH_2$), 3.44 (2H, d, *J*

9.2 Hz, $CO.CH_2S$), 3.78 (3H, s, OCH_3), 6.79 (1H, dd, *J* 2.8 and 9.0 Hz, 5-H), 7.05 (1H, d, *J* 2.8 Hz, 3-H), 8.24 (1H, d, *J* 9.0 Hz, 6-H) and 9.45 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 24.2, 29.5 and 39.6 (SCH_2CH_2S and $COCH_2S$), 55.5 (OCH_3), 115.0, 120.2 and 121.7 (C-3, C-5 and C-6), 123.8, 132.5 and 156.0 (C-1, C-2 and C-4) and 166.9 (CO); *m/z* 289 (M^+, 30%) and 182 (100%).

Method 2

A solution of the polymeric disulfide **171b** (1.00 g, 3.48 mmol) and Ph_3P (1.00 g, 3.83 mmol) in 10% aqueous MeOH (150 mL) and acetone (20 mL) was heated (60 °C) for 2 h under N_2. The mixture was filtered while still hot, and the MeOH and acetone were evaporated from the filtrate *in vacuo*. H_2O (15 mL), benzene (30 mL) and NaOH pellets (3 g) were added sequentially to the aqueous residue, which was vigorously stirred for 5 minutes. The phases were separated and the basic aqueous phase was washed again with benzene before acidification with 16% HCl. The acidic, aqueous phase was extracted with benzene and the combined benzene extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$), and the benzene evaporated *in vacuo* to yield crude *N*-(2-mercaptoethanoyl)-2-(2-mercaptoethyl)thio-4-methoxyaniline **172b** (0.14 g).

The macrocyclic ligand **182a**.[225]- To a stirred suspension of Cs_2CO_3 (1.11 g, 3.39 mmol) in dry DMF[272] (400 mL) in a 2 L round-bottomed flask fitted with a reflux condenser, an N_2 line and two burettes (entering the flask through septa) were added, slowly and simultaneously from the burettes, a solution of *N*-(2-mercaptoethanoyl)-2-[(2-mercaptoethyl)thio]aniline **172a** (0.80 g, 3.08 mmol) in dry DMF (100 mL) and a solution of 1,2-dibromoethane (0.58 g, 3.1 mmol) in dry DMF (100 mL). The reactants were added dropwise, in portions (15 mL), with a pause of 45-60 minutes between each portion. The temperature of the solution was maintained between 30 and 60 °C. After the addition was complete, stirring was continued for a further 3 h and the DMF then removed *in vacuo*. The residue was taken up in CH_2Cl_2 (80 mL) and H_2O (40 mL).

The phases were separated and the CH_2Cl_2 extract was dried (anhyd. $MgSO_4$). Removal of the CH_2Cl_2 *in vacuo* produced an orange-brown precipitate (0.83 g), which was purified by flash chromatography [elution with EtOAc-hexane (3:7)] to afford, as pale yellow crystals, *the macrocyclic ligand* **182a** (0.27 g, 31%), mp 158-160 °C (from EtOAc-hexane) (Found: C, 50.9; H, 5.15; N, 5.0; $\mathbf{M}^+$, 285.0331. $C_{12}H_{15}NOS_3$ requires C, 50.5; H, 5.3; N, 4.9%; *M*, 285.0315); ν_{max}(KBr)/cm^{-1} 3240 (NH) and 1640 (CO); δ_H(400 MHz; $CDCl_3$) 2.72-2.75 (2H, m, SCH_2), 2.85-2.88 (2H, m, SCH_2), 2.92-2.95 (2H, m, SCH_2), 2.98-3.01 (2H, m, SCH_2), 3.58 (2H, s, $CO.CH_2S$), 7.08 (1H, dt, *J* 1.2 and 7.6 Hz, ArH), 7.36-7.40 (1H, m, ArH), 7.62 (1H, dd, *J* 7.7 and 1.4 Hz, ArH), 8.56 (1H, d, *J* 8.3 Hz, ArH) and 10.34 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 32.2, 32.7, 33.9, 38.3 and 39.1 (SCH_2CH_2S and $COCH_2S$), 119.6, 124.7, 129.8, 130.7, 137.1 and 140.9 (ArC) and 167.4 (CO); *m/z* 285 ($\mathbf{M}^+$, 34%) and 152 (100%).

The macrocyclic ligand **182b**.- The experimental procedure employed for the synthesis of the macrocyclic ligand **182a** was followed, using Cs_2CO_3 (0.743 g, 2.28 mmol) in dry DMF (400 mL), *N*-(2-mercaptoethanoyl)-2-(2-mercaptoethyl)thio-4-methoxyaniline **172b** (0.60 g, 2.1 mmol) in dry DMF (100 mL) and 1,2-dibromoethane (0.39 g, 2.1 mmol) in dry DMF (100 mL). Flash chromatography [elution with EtOAc-hexane (3:7)] afforded white crystals of *the macrocyclic ligand* **182b** (0.11 g, 17%), mp 157-160 °C (from EtOAc-hexane) (Found: C, 49.6; H, 5.4; N, 4.5; $\mathbf{M}^+$, 315.0417. $C_{13}H_{17}NO_2S_3$ requires C, 49.5; H, 5.4; N, 4.4%; *M*, 315.0414); ν_{max}(KBr)/cm^{-1} 3270 (NH) and 1640 (CO); δ_H(400 MHz; $CDCl_3$) 2.72-2.75 (2H, m, CH_2S), 2.84-2.87 (2H, m, CH_2S), 2.92-2.94 (2H, m, CH_2S), 3.00-3.03 (2H, m, CH_2S), 3.55 (2H, s, $COCH_2S$), 3.79 (3H, s, OCH_3), 6.94 (1H, dd, *J* 2.9 and 9.2 Hz, ArH), 7.17 (1H, d, *J* 3.0 Hz, ArH), 8.47 (1H, d, *J* 9.2 Hz, ArH) and 10.12 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 32.2, 32.9, 33.8, 38.2 and 39.0 (SCH_2CH_2S and $COCH_2S$), 116.1, 120.9, 121.7, 123.6, 134.3 and 155.9 (ArC) and 166.9 (CO); *m/z* 315 ($\mathbf{M}^+$, 35%) and 57 (100%).

Attempted synthesis of 2-[(2-chloroethyl)thio]ethanoic acid **179**.- A solution of 2-mercaptoacetic acid (1.83 g, 19.9 mmol) and NaOH (1.75 g, 43.8 mmol) in 50% aqueous MeOH (40 mL) was added, in portions, to 1,2-dichloroethane (3.93 g, 39.7 mmol). The solution was boiled under reflux for 1.5 h and then acidified with 16% HCl. The MeOH was removed *in vacuo*, and the aqueous residue was extracted with EtOAc and the combined EtOAc extracts were dried (anhyd. $MgSO_4$) and the EtOAc evaporated *in vacuo* to afford white crystals. TLC showed that the mercaptoacetic acid had been consumed in the reaction, but the white crystals were not conclusively identified.

N-*(3-Chlorophenyl)-2-mercaptoethanamide* **183c**.- The experimental procedure employed for the synthesis of 2-mercapto-*N*-phenylethanamide **140a** was followed, using 3-chloroaniline (2.08 g, 16.3 mmol) and 2-mercaptoacetic acid (1.50 g, 16.3 mmol), to afford, as a white solid, *N*-(3-chlorophenyl)-2-mercaptoethanamide **183c** (1.91 g, 58%), mp 70-73 °C (lit.,[83] 75 °C), which was shown by TLC to be pure and, consequently, used without further purification.

N-*(2-Chlorophenyl)-2-mercaptoethanamide* **183d**.- The experimental procedure employed for the synthesis of 2-mercapto-*N*-phenylethanamide **140a** was followed, using 2-chloroaniline (2.76 g, 21.6 mmol) and 2-mercaptoacetic acid (2.00 g, 21.7 mmol). No precipitate formed upon pouring the melt into cold water. Several drops of conc. HCl were added and the mixture was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with 10% aqueous NaOH and the NaOH washings were acidified with 32% HCl before being extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried (anhyd. $MgSO_4$), and the $CHCl_3$ was evaporated *in vacuo* to afford, as a white residue, *N*-(2-chlorophenyl)-2-mercaptoethanamide **183d** (0.67 g, 15%), mp 56-59 °C (lit.,[54] 61 °C), which was shown by TLC to be pure and, consequently, used without further purification.

2-Mercapto-N-*(2-methylphenyl)ethanamide* **183e**.- The experimental procedure employed for the synthesis of 2-mercapto-*N*-phenylethanamide **140a** was followed, using 2-methylaniline (1.75 g, 16.3 mmol) and 2-mercaptoacetic acid (1.50 g, 16.3 mmol). A precipitate of 2-mercapto-*N*-(2-methylphenyl)ethanamide **183e** was obtained (1.25 g, 42%), mp 88-90 °C (lit.,[58] 91 °C) which was shown by TLC to be pure and, consequently, used without further purification.

2-Mercapto-N-*(2-methoxyphenyl)ethanamide* **183f**.- The experimental procedure employed for the synthesis of 2-mercapto-*N*-phenylethanamide **140a** was followed, using 2-methoxyaniline (2.00 g, 16.3 mmol) and 2-mercaptoacetic acid (1.50 g, 16.3 mmol). A light grey precipitate of 2-mercapto-*N*-(2-methoxyphenyl)ethanamide **183f** was obtained (1.36 g, 42%), mp 64-66 °C (lit.,[58] 68 °C) which was shown by TLC to be pure and, consequently, used without further purification.

N,N'-*Diphenyl-3,6-dithiaoctanediamide* **107a**.- A solution of 1,2-dibromoethane (0.954 g, 5.07 mmol) in MeOH (20 mL) was added, in portions, to a stirred solution of 2-mercapto-*N*-phenylethanamide **140a** (1.70 g, 10.2 mmol) and KOH (0.57 g, 10.2 mmol) in MeOH (60 mL). The mixture was stirred at room temperature for 24 h and then H_2O (30 mL) was added and the MeOH evaporated *in vacuo*. The remaining aqueous solution was extracted with EtOAc (3 x 30 mL) and the combined EtOAc extract dried (anhyd. $MgSO_4$) and the EtOAc evaporated *in vacuo*. The residue was recrystallised from EtOH to afford, as white crystals, N,N'-*diphenyl-3,6-dithiaoctanediamide* **107a** (0.68 g, 37%), mp 150-152 °C (from EtOH) (Found: C, 58.7; H, 5.6; N, 7.5; $\mathbf{M}^+$, 360.0957. $C_{18}H_{20}N_2O_2S_2$ requires C, 60.0; H, 5.6; N, 7.8%; *M*, 360.0964); ν_{max}(KBr)/cm^{-1} 3295 (NH) and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 2.88 (4H, s, SCH_2CH_2S), 3.55 (4H, s, $CO.CH_2S$), 7.13 (2H, t, 4-H), 7.33 (4H, t, 3-H and 5-H), 7.55 (4H, d, 2-H and 6-H) and 8.51 (2H, br s, NH); δ_C(100 MHz; $CDCl_3$) 32.1 (C-4 and C-5), 36.5 (C-2 and C-7),

119.8, 124.8, 129.1 and 137.5 (ArC) and 167.0 (CO).

N,N'-*Bis(4-methoxyphenyl)-3,6-dithiaoctanediamide* **107b**.- The experimental procedure employed for the synthesis of *N,N'*-diphenyl-3,6-dithiaoctanediamide **107a** was followed, using 2-mercapto-*N*-(4-methoxyphenyl)ethanamide **140b** (1.76 g, 8.92 mmol), 1,2-dibromoethane (0.84 g, 4.5 mmol) and KOH (0.55g, 9.8 mmol). The grey precipitate was recrystallised from EtOH-H_2O to afford, as light grey crystals, N,N'-*bis(4-methoxyphenyl)-3,6-dithiaoctanediamide* **107b** (0.52 g, 28%), mp 163-165 °C (from EtOH-H_2O) (Found: $\mathbf{M}^+$, 420.1174. $C_{20}H_{24}N_2O_4S_2$ requires *M*, 420.1175); ν_{max}(KBr)/cm^{-1} 3305 (NH) and 1660 (CO); δ_H(400 MHz; DMSO-d_6) 3.31 (4H, s, SCH_2CH_2S), 3.36 (4H, s, $CO.CH_2S$), 3.71 (6H, s, OCH_3), 7.17 (8H, dd, *J* 8.9 and 242.1 Hz, ArH) and 9.91 (2H, br s, NH); δ_C(100 MHz; $CDCl_3$) 32.0 (C-4 and C-5), 37.1 (C-2 and C-7), 56,0 (OCH_3), 114.2, 121.7, 130.8 and 156.8 (ArC) and 167.1 (CO).

N,N'-*Bis(3-chlorophenyl)-3,6-dithiaoctanediamide* **107c**.- The experimental procedure employed for the synthesis of *N,N'*-diphenyl-3,6-dithiaoctanediamide **107a** was followed, using *N*-(3-chlorophenyl)-2-mercaptoethanamide **183c** (1.90 g, 9.42 mmol), 1,2-dibromoethane (0.88 g, 4.7 mmol) and KOH (0.58 g, 10 mmol). The aqueous phase was extracted with $CHCl_3$, and the combined $CHCl_3$ extracts were washed with 10% aqueous NaOH before drying (anhyd. $MgSO_4$) and evaporating the $CHCl_3$ *in vacuo*. The yellow residue was recrystallised from aqueous EtOH to afford N,N'-*bis(3-chlorophenyl)-3,6-dithiaoctanediamide* **107c** (1.14 g, 57%), mp 114-117 °C (from aqueous EtOH) (Found: C, 49.6; H, 4.25; N, 6.3; $\mathbf{M}^+$, 428.0178. $C_{18}H_{18}N_2O_2S_2Cl_2$ requires C, 50.35; H, 4.2; N, 6.5%; *M*, 428.0185.); ν_{max}(KBr)/cm^{-1} 3300 (NH) and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 2.87 (4H, s, SCH_2CH_2S), 3.35 (4H, s, $CO.CH_2S$), 7.09-7.11 (2H, m, ArH), 7.22-7.29 (2H, m, ArH), 7.38-7.40 (2H, m, ArH), 7.66 (2H, br s, ArH) and 8.55 (2H, br s, NH); δ_C(100 MHz; DMSO-d_6) 31.4 (C-4 and C-5), 35.2 (C-2 and C-

7), 117.4, 118.5, 123.0, 130.2, 133.0 and 140.2 (ArC) and 168.3 (CO).

N,N'-*Bis(2-chlorophenyl)-3,6-dithiaoctanediamide* **107d**.- The experimental procedure employed for the synthesis of *N,N'*-bis(3-chlorophenyl)-3,6-dithiaoctanediamide **107c** was followed, using *N*-(2-chlorophenyl)-2-mercaptoethanamide **183d** (0.95 g, 4.7 mmol), 1,2-dibromoethane (0.44 g, 2.3 mmol) and KOH (0.29 g, 5.2 mmol). The crude precipitate was recrystallised from EtOH (an insoluble component was removed by filtration before cooling the EtOH) to afford white crystals (0.197 g) which were purified further by flash chromatography [elution with EtOAc-hexane (1:1)] to afford N,N'-*bis(2-chlorophenyl)-3,6-dithiaoctanediamide* **107d** (0.12 g, 12%), mp 165-167 °C (from EtOAc-hexane) (Found: C, 49.6; H, 4.2; N, 6.1; $\mathbf{M}^+$, 428.0190. $C_{18}H_{18}Cl_2N_2O_2S_2$ requires C, 50.35; H, 4.2; N, 6.5%; *M*, 428.0180); ν_{max}(KBr)/cm^{-1} 3310 (NH) and 1680 (CO); δ_H(400 MHz; $CDCl_3$) 2.92 (4H, s, SCH_2CH_2S), 3.44 (4H, s, $CO.CH_2S$), 7.03-7.07 and 7.24-7.28 (4H, dt, 4-H, and 5-H), 7.35 (2H, dd, 3-H), 8.32 (2H, d, 6-H) and 9.15 (2H, br s, NH); δ_C(100 MHz; $CDCl_3$) 32.5 (C-4 and C-5), 37.3 (C-2 and C-7), 121.4, 125.1, 127.7, 129.1, 123.3 and 134.1 (ArC) and 166.5 (CO).

N,N'-*Bis(2-methylphenyl)-3,6-dithiaoctanediamide* **107e**.- The experimental procedure employed for the synthesis of *N,N'*-bis(3-chlorophenyl)-4,7-dithiaoctanediamide **107c** was followed, using 2-mercapto-*N*-(2-methylphenyl)ethanamide **183e** (1.25 g, 6.91 mmol), 1,2-dibromoethane (0.65 g, 3.5 mmol) and KOH (0.43 g, 7.6 mmol). The crude precipitate was recrystallised from EtOH to afford N,N'-*bis(2-methylphenyl)-3,6-dithiaoctanediamide* **107e** (0.67 g, 50%), mp 176-178 °C (from EtOH) (Found: C, 60.9; H, 6.4; N, 7.1; $\mathbf{M}^+$, 388.1268. $C_{20}H_{24}N_2O_2S_2$ requires C, 61.8; H, 6.2; N, 7.2%; *M*, 388.1277); ν_{max}(KBr)/cm^{-1} 3275 (NH) and 1650 (CO); δ_H(400 MHz; $CDCl_3$) 2.21 (6H, s, CH_3), 2.95 (4H, SCH_2CH_2S), 3.40 (4H, $CO.CH_2S$), 7.07-7.10 and 7.14-7.17 (4H, m, 4-H and 5-H), 7.20-7.22 (2H, d, 3-H), 7.40 (2H, d, 6-H) and 9.42 (2H, br s, NH); δ_C(100 MHz; DMSO-d_6) 17.6 (CH_3), 31.5 (C-4 and C-5),

34.6 (C-2 and C-7), 124.7, 125.1, 125.8, 130.2, 131.4 and 135.9 (ArC) and 167.9 (CO).

N,N'-*Bis(2-methoxyphenyl)-4,7-dithiaoctanediamide* **107f**.- The experimental procedure employed for the synthesis of *N,N'*-bis(3-chlorophenyl)-3,6-dithiaoctanediamide **107c** was followed, using 2-mercapto-*N*-(2-methoxyphenyl)ethanamide **183f** (1.36 g, 6.89 mmol), 1,2-dibromoethane (0.65 g, 3.5 mmol) and KOH (0.43 g, 7.6 mmol). The brown precipitate was recrystallised twice from aqueous EtOH to afford N,N'-*bis(2-methoxyphenyl)-3,6-dithiaoctanediamide* **107f** (0.41 g, 28%), mp 137-140 °C (from aqueous EtOH) (Found: M^+, 420.1166. $C_{20}H_{24}N_2O_4S_2$ requires *M*, 420.1175); ν_{max}(KBr)/cm^{-1} 3300 (NH) and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 2.89 (4H, s, SCH_2CH_2S), 3.40 (4H, s, $CO.CH_2S$), 3.83 (6H, s, OCH_3), 6.84 (2H, d, 3-H), 6.94 and 7.05 (4H, t, 4-H and 5-H), 8.29 (2H, d, 6-H) and 9.05 (2H, br s, NH); δ_C(100 MHz; DMSO-d_6) 32.4 (C-4 and C-5), 37.3 (C-2 and C-7), 55.7 (OCH_3), 110.1, 119.8, 121.0, 124.2, 127.1 and 148.4 (ArC) and 166.3 (CO).

1,2-Bis(benzylthio)ethane **200**.- Benzyl chloride (8.06 g, 63.7 mmol) in MeOH (20 mL) was added, in portions, to a solution of 1,2-dimercaptoethane (3.0 g, 32 mmol) and KOH (3.57 g, 63.7 mmol) in MeOH (70 mL). The mixture was stirred at room temperature for several hours before the addition of H_2O (30 mL). The MeOH was evaporated *in vacuo* and the aqueous residue was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with 10% aqueous NaOH and dried (anhyd. $MgSO_4$), and the $CHCl_3$ was removed *in vacuo* to afford 1,2-bis(benzylthio)ethane **200**; δ_H(400MHz, $CDCl_3$) 2.58 (4H, s, SCH_2CH_2S), 3.70 (4H, s, $ArCH_2S$) and 7.25-7.34 (10H, m, ArH).

3.3 SOLVENT EXTRACTION PROCEDURES AND THE ISOLATION AND ALTERNATIVE SYNTHESES OF PALLADIUM(II) COMPLEXES FORMED DURING SOLVENT EXTRACTION

3.3.1 General Method

The metal solutions were made up by dissolving an appropriate quantity of K_2PtCl_4, $PdCl_2$, $CuCl_2.6H_2O$, $NiCl_2.6H_2O$ or $CoCl_2.6H_2O$ in 1 **M**-HCl such that the concentration of the metal was 1.0×10^{-3} **M**. The concentrations of the metal solutions were verified by atomic absorption spectroscopy and, when necessary, adjustments were made to obtain the required concentration. The ligands were dissolved in either toluene, $CHCl_3$ or MIBK, and the concentration of the ligand solutions was typically 1.1×10^{-3} **M**. However, the solutions of the bidentate ligands **140a** and **150a** were 2.2×10^{-3} **M**, and some ligands with low solubility had to be dissolved in twice the normal amount of solvent; consequently the concentration of these latter, ligand solutions was 0.55×10^{-3} **M**. Equal volumes (10 mL) of each phase were shaken together, except for the 0.55×10^{-3} **M** ligand solutions, in which case 20 mL of organic phase was shaken with 10 mL of the aqueous metal solution. The phases were shaken in stoppered 100 mL conical flasks which were partially submerged in a waterbath, the temperature of which was maintained at 30 °C using a Braun thermostat. The flasks were shaken with a Griffin flask shaker, the speed of shaking was the same for all the extractions (within the limits of the shaker) and was sufficient to ensure thorough mixing of the phases. All extractions were duplicated. Sampling was accomplished by removing a portion (2mL) of each phase; in the case of the 0.55×10^{-3} **M** ligand solutions, 4 mL of the organic phase was removed for every 2 mL of aqueous phase. Samples were taken every 10 minutes for either 20 minutes or 30 minutes. The Cu(II), Ni(II), Co(II) and Pt(II) samples (2mL) were diluted to 25 mL with 0.5 **M**-HCl before measurement of the aqueous metal concentration. Back extraction (stripping) of the metal from

the organic phase was studied for selected ligands. In these cases, the loaded organic phase was shaken for 10 minutes (at 30 °C) with 17% aqueous ammonia.

The aqueous metal concentrations were determined using a Varian Atomic Absorption Spectrophotometer. A series of standard metal solutions were made up by diluting commercially obtained (Vacutec, Perkin Elmer Division) 1000 ppm stock solutions with 1 **M**-HCl. All measurements were a running mean of several absorbance readings.

To determine the mode of coordination of the ligands the palladium(II) and platinum(II) complexes were studied by infrared and ^{1}H NMR spectroscopy; where necessary these complexes were purified by PLC or flash chromatography. Numerous attempts to obtain crystals of various complexes, suitable for X-ray crystallographic analysis, proved unsuccessful. In most cases the stoichiometry of the complexes was assumed to be 1:1, as equal amounts of metal and ligand were reacted, or, in the solvent extraction experiments, approximately one equivalent of metal was extracted by the ligand. In future work, fast atom bombardment (FAB) mass spectrometry and electro spray (ES) mass spectrometry should be useful in determining whether the complexes are monomeric, dimeric, trimeric *etc.*

3.3.2 Data for isolated complexes

1,*2-Bis(benzylthio)ethane* (**200**)-*palladium(II) complex* **201**:- The bright yellow organic phase was separated from the acidic aqueous phase and dried (anhyd. $MgSO_4$). The solvent (toluene) was evaporated *in vacuo* and the residue was shown, by TLC, to contain one component, which was purified by PLC [elution with MeOH-$CHCl_3$ (1:9)] to afford the *syn*- and *anti*-isomers of complex **201**; δ_H(400MHz; $CDCl_3$) 2.53-2.62 and 2.77-2.83 (4H, 2 x m, SCH_2CH_2S), 4.17 (dd, *J* 13.7 and 54.6 Hz, $ArCH_2S$), 4.48 (dd, *J* 13.6 and 86.7 Hz, $ArCH_2S$) and 7.13-7.49 (10H, m,

ArH).

N-*[2-(Benzylthio)ethanoyl]-2-(5-phenyl-1,4-dithiapentyl)aniline* (**159**)-*palladium(II) complex* **202**.- After the solvent extraction experiment, the loaded toluene organic phase was dried (anhyd. $MgSO_4$) and the toluene evaporated *in vacuo* leaving a brown residue (16 mg). Three components were separated by PLC [elution with MeOH-$CHCl_3$ (1:19)], *viz.*,

i) the *syn-* and *anti*-isomers of complex **202** (6 mg) (R_F 0.72); ν_{max}(KBr)/cm^{-1} 1620 (CO) (NH absorption absent); δ_H(400 MHz; $CDCl_3$) 2.55-2.62 (m, CH_2S), 2.97-3.16 (m, CH_2S), 3.28-3.41 (m, CH_2S), 3.52 (d, $CO.CH_2S$), 3.69-3.79 (m, $ArCH_2S$ and $CO.CH_2S$), 4.15 (dd, *J* 13.6 and 31.7 Hz, $ArCH_2S$), 4.32 (s, $ArCH_2S$), 6.98-7.50 (14H, m, ArH) and 8.76 (1H, dd, 6-H).

ii) a yellow complex (1.5 mg) (R_F 0.34), which did not exhibit an amide hydrogen signal in the ^1H NMR spectrum.

iii) a yellow complex (1.5 mg) (R_F 0.29), which exhibited an amide hydrogen signal in the ^1H NMR spectrum.

*2-Mercapto-*N-*(2-methylthiophenyl)ethanamide* (**151a**)-*palladium(II) complex*:- Evaporation of the solvent (toluene) *in vacuo* afforded an orange residue, TLC of which indicated the presence of only one component, with a retention time similar to that of the free ligand; ν_{max}(KBr)/cm^{-1} 1610 (CO) (NH and SH absorptions absent). The ^1H NMR spectrum contained complex signals.

*2-Mercapto-*N-*phenylethanamide* (**140a**)-*palladium(II) complex*:- An orange precipitate formed in the organic phase during the solvent extraction experiment. The phases were separated and the organic phase was concentrated by evaporation of toluene *in vacuo* and then introduced onto a 1 cm flash column [elution with MeOH-$CHCl_3$ (1:19)]. The major component was an insoluble precipitate, which did not move from the base line [ν_{max}(KBr)/cm^{-1} 3290 (NH),

1655 (CO) (SH absorption absent); the ^{1}H NMR spectrum contained very broad peaks, indicative of polymer formation].

N,N'-*Diphenyl-3,6-dithiaoctanediamide* (**107a**)-*palladium(II) complex* **206a**:-

Method 1

After the solvent extraction with $CHCl_3$, the phases were separated and the organic phase was diluted with $CHCl_3$ to dissolve most of the precipitate before drying (anhyd. $MgSO_4$) and evaporation of the $CHCl_3$ *in vacuo*. The yellow, solid residue was dried *in vacuo* with moderate heating (50-60 °C) to afford the *syn*- and *anti*-isomers of complex **206a**; ν_{max}(KBr)/cm^{-1} 3300 (NH) and 1665 (CO); δ_H(400 MHz; DMSO-d_6) 3.34 and 3.51-3.68 (4H, 2 x m, SCH_2CH_2S), 4.07-4.18 and 4.35-4.43 (4H, 2 x m, $CO.CH_2S$), 7.10 (2H, m, ArH), 7.34 (4H, m, ArH), 7.53-7.62 (4H, m, ArH) and 10.46 and 10.50 (2H, 2 x br s, NH).

Method 2

The yellow precipitate that formed in the organic phase during the solvent extraction with toluene was collected by filtration, washed with MeOH and then dried *in vacuo* to afford complex **206a**.

Method 3

N,N'-Diphenyl-3,6-dithiaoctanediamide **107a** (7.2 mg, 0.020 mmol) in MeOH (80 mL) was added to a 0.001 **M**-$PdCl_2$ solution in 1 **M**-HCl (20 mL). The clear yellow solution was stirred for several hours and then left to stand for 2 days. Upon evaporation of the MeOH *in vacuo*, a yellow precipitate formed which was collected by filtration and dried *in vacuo* with moderate heating to afford complex **206a**.

N,N'-*Bis(4-methoxyphenyl)-3,6-dithiaoctanediamide* (**107b**)-*palladium(II) complex* **206b**.-

Method 1

During the solvent extraction experiment with MIBK, a precipitate formed in the organic phase.

The precipitate was filtered off and dried *in vacuo* with moderate heating (50 °C) to afford the *syn-* and *anti*-isomers of complex **206b**; ν_{max}(KBr)/cm^{-1} 3305 (NH) and 1660 (CO); δ_H(400 MHz; DMSO-d_6) 3.36 and 3.51-3.67 (4H, 2 x m, SCH_2CH_2S), 3.73 (6H, m, OCH_3), 4.01-4.13 and 4.31-4.38 (4H, 2 x m, $CO.CH_2S$), 6.84-6.95 (4H, m, ArH), 7.44-7.53 (4H, m, ArH) and 10.32 and 10.36 (2H, 2 x br s, NH).

Method 2

The experimental procedure described in method 3 for the synthesis of complex **206a** was followed, using *N,N'*-bis(4-methoxyphenyl)-3,6-dithiaoctanediamide **107b** (8.4 mg, 0.020 mmol) in MeOH (80 mL) and a 0.001 **M**-$PdCl_2$ solution in 1 **M**-HCl (20 mL). Within 5 minutes of mixing the solutions a yellow precipitate had formed. The MeOH was evaporated *in vacuo* and the yellow precipitate was filtered and dried *in vacuo* with moderate heating to afford complex **206b**.

N,N'-*Bis(3-chlorophenyl)-3,6-dithiaoctanediamide* (**107c**)-*palladium(II) complex* **206c**.-

Method 1

No precipitate formed during the solvent extraction experiment with MIBK and, upon removal of the organic solvent *in vacuo*, a viscous yellow-red oil was obtained, which was dried *in vacuo* with moderate heating to afford the *syn-* and *anti*-isomers of complex **206c**; ν_{max}(KBr)/cm^{-1} 3300 (NH) and 1685 (CO); δ_H(400 MHz; DMSO-d_6) 3.35 and 3.50-3.67 (4H, 2 x m, SCH_2CH_2S), 4.05-4.24 and 4.36-4.43 (4H, 2 x m, $CO.CH_2S$), 7.12-7.20 (2H, m, ArH), 7.31-7.48 (4H, m, ArH), 7.79 (2H, s, ArH) and 10.65 and 10.68 (2H, 2 x br s, NH).

Method 2

Repeating the solvent extraction experiment with $CHCl_3$ or toluene as the solvent also resulted in the formation of complex **206c**.

N,N'-*Bis(2-chlorophenyl)-3,6-dithiaoctanediamide* (**107d**)-*palladium(II) complex* **206d**.- During the solvent extraction experiment with toluene and MIBK a precipitate formed, which was filtered off and dried *in vacuo* with moderate heating (50 °C) to afford the *syn*- and *anti*-isomers of complex **206d**; ν_{max}(KBr)/cm^{-1} 3310 (NH) and 1680 (CO); δ_H(400 MHz; DMSO-d_6) 3.37 and 3.52-3.67 (4H, 2 x m, SCH_2CH_2S), 4.09-4.23 and 4.32-4.44 (4H, 2 x m, $CO.CH_2S$), 7.10-7.24 (6H, m, ArH), 7.39-7.43 (2H, m, ArH) and 9.82 and 9.89 (2H, 2 x br s, NH).

N,N'-*Bis(2-methylphenyl)-3,6-dithiaoctanediamide* (**107e**)-*palladium(II) complex* **206e**:- During the solvent extraction experiment with MIBK, a precipitate formed which was collected by filtration and dried *in vacuo* with moderate heating (50 °C) to afford the *syn*- and *anti*-isomers of complex **206e**; ν_{max}(KBr)/cm^{-1} 3260 (NH) and 1660 (CO); δ_H(400 MHz; DMSO-d_6) 2.50 (6H, m, CH_3), 3.37 and 3.45-3.68 (4H, 2 x m, SCH_2CH_2S), 4.16-4.28 and 4.41-4.49 (4H, 2 x m, $CO.CH_2S$), 7.25 (2H, m, ArH), 7.36 (2H, m, ArH), 7.52 (2H, m, ArH), 7.70 (2H, m, ArH) and 10.14 and 10.20 (2H, 2 x br s, NH).

N,N'-*Bis(2-methoxyphenyl)-3,6-dithiaoctanediamide* (**107f**)-*palladium(II) complex* **206f**.- After the solvent extraction experiment with $CHCl_3$, MIBK and toluene, the organic phase was separated and dried (anhyd. $MgSO_4$), and the solvent was removed *in vacuo* to afford a yellow precipitate, which was dried *in vacuo* with moderate heating (50 °C) to afford the *syn*- and *anti*-isomers of complex **206f**; ν_{max}(KBr)/cm^{-1} 3330 (NH) and 1690 (CO); δ_H(400 MHz; CD_3CN) 3.42-3.68 (4H, m, SCH_2CH_2S), 3.84 (6H, s, OCH_3), 4.14-4.50 (4H, m, $CO.CH_2S$), 6.93 (2H, m, ArH), 7.03-7.17 (4H, m, ArH), 7.84-7.93 (2H, m, ArH) and 9.79 and 9.83 (2H, 2 x br s, NH).

3.4 SYNTHETIC PROCEDURES FOR THE COMPLEXATION OF SELECTED LIGANDS WITH PALLADIUM(II) AND PLATINUM(II)

N,N'-*Diphenyl-3,6-dithiaoctanediamide* (**107a**)-*palladium(II) complex* **208a**.-
A solution of *N,N'*-diphenyl-3,6-dithiaoctanediamide **107a** (7.2 mg, 0.020 mmol) in MeOH (80 mL) was added to a 0.001 **M**-$PdCl_2$ solution in 1 **M**-HCl (20 mL). The clear yellow mixture was stirred for 1 h before basifying (pH 9) with a solution of Na_2CO_3 in 20% aqueous MeOH. The solution was allowed to stand for 2 days. Upon removal of the MeOH *in vacuo,* an orange precipitate formed, which was filtered off and dried *in vacuo* to afford complex **208a**; ν_{max}(KBr)/cm^{-1} 1680 (CO) (NH absorption absent); δ_H(400 MHz; DMSO-d_6) 3.15-4.49 (m, SCH_2), 6.80-7.71 (m, ArH) and 10.08, 10.48 and 10.54 (small NH resonances).

N,N'-*Diphenyl-3,6-dithiaoctanediamide* (**107a**)-*platinum(II) complex* **210a**.- A solution of K_2PtCl_4 (0.10 g, 0.24 mmol) in H_2O (10 mL) was added to a stirred solution of *N,N'*-diphenyl-4,7-dithiaoctanediamide **107a** (0.087 g, 0.24 mmol) in MeOH (25 mL). A precipitate formed, and MeOH (20 mL) and acetone (10 mL) were added in unsuccessful attempts to dissolve this precipitate. Addition of H_2O (10 mL) did dissolve the precipitate. A solution of K_2CO_3 (16.6 mg, 0.120 mmol) in H_2O (10 mL) was then added and the solution was stirred for a further 24 h, during which time a precipitate formed. The precipitate was filtered off and recrystallised from $CHCl_3$-acetone to afford light green crystals of complex **210a**; ν_{max}(KBr)/cm^{-1} 1607 (CO) (NH absorption absent); δ_H(400 MHz; DMSO-d_6) 2.90-4.68 (m, SCH_2), 6.50-7.66 (m, ArH) and 10.17, 10.28, 10.46, 10.49 and 10.51 (small NH resonances).

The macrocyclic ligand (**182a**)-*palladium(II) complex* **211a**.- A 0.001 **M**-$PdCl_2$ solution in 1 **M**-HCl (20 mL) was added to a stirred solution of the macrocyclic ligand **182a** (5.7 mg, 0.020 mmol) in MeOH (80 mL) and acetone (40 mL). The resulting clear yellow solution was stirred

for 2 h before it was basified (pH~9) with a solution of K_2CO_3 in 50% aqueous MeOH. The basic solution was stirred for 1 h before removing the MeOH *in vacuo*. The orange precipitate which formed was too fine to filter and was consequently extracted into $CHCl_3$. The combined $CHCl_3$ extract was washed (satd. brine) and dried (anhyd. $MgSO_4$) and the $CHCl_3$ evaporated *in vacuo* to afford an orange residue of complex **211a**; ν_{max}(KBr)/cm^{-1} 1605 (CO) (NH absorption absent); δ_H(400 MHz; $CDCl_3$) 2.59-3.72 (m, SCH_2), 4.20 (dd, SCH_2), 6.95-7.43 (m, ArH) and 8.93 and 8.98 (2 x d, 6-H).

The macrocyclic ligand (**182a**)*-platinum(II) complex* **211b**.-

A 0.001 **M**-K_2PtCl_4 solution in 1 **M**-HCl (20 mL) was added to a stirred solution of the macrocyclic ligand **182a** (5.7 mg, 0.020 mmol) in MeOH (80 mL) and acetone (40 mL). The mixture was stirred for 2 h at room temperature before basifying (pH 9) by the addition of a solution of K_2CO_3 in 50% aqueous MeOH. The basic solution was stirred overnight and, upon removal of the MeOH and acetone *in vacuo*, a light green precipitate formed, which was extracted into $CHCl_3$. The $CHCl_3$ extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$) and the $CHCl_3$ evaporated *in vacuo* to afford, as a light green precipitate, complex **211b**; ν_{max}(KBr)/cm^{-1} 1615 (CO) (NH absorption absent); δ_H(400 MHz; $CDCl_3$) 2.6-4.4 (m, SCH_2), 6.7-7.7 (m, ArH) and 8.99 (m, ArH).

3.5 SYNTHETIC PROCEDURES FOR THE COORDINATION OF SELECTED LIGANDS WITH TETRACHLOROPLATINATE AND CISPLATIN

All these reactions were conducted at room temperature and, generally, in 80% aqueous MeOH; in some cases, acetone was added to ensure homogeneity. *N,N*-Diethylaniline (pK_a 6.56) and aqueous 0.0974 **M**-HCl were used to buffer the reaction solutions. The proportions of *N,N*-diethylaniline and HCl were such that one quarter or one half of the *N,N*-diethylaniline was protonated upon mixing the two solutions, thus providing a pH of *ca.* 7.0 or 6.6 respectively. The *N,N*-diethylaniline was distilled before use. A stock solution of tetrachloroplatinate was made up by dissolving $K_2[PtCl_4]$ (0.10 g, 0.25 mmol) in 0.0974 **M**-HCl (10 mL), this solution was used for all the reactions.

Reaction of N-*(2-methylthiophenyl)acetamide* **150a** *with* $[PtCl_4]^{2-}$.- A stock solution of *N*-(2-methylthiophenyl)ethanamide **150a** (0.052g, 0.31 mmol) and *N,N*-diethylaniline (0.37 g, 2.5 mmol) was made up in MeOH (25 mL). This ligand-buffer solution was added to the $[PtCl_4]^{2-}$ solution (2 mL) and the mixture was stirred at room temperature for 24 h. The MeOH was removed *in vacuo,* and the aqueous residue was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed (satd. brine) and dried (anhyd. $MgSO_4$), and the $CHCl_3$ evaporated *in vacuo.* The residue was purified by flash chromatography [elution with MeOH-$CHCl_3$ (1:9), using a 1 cm diameter column] to afford, as a viscous yellow oil, the platinum complex; ν_{max}(KBr)/cm^{-1} 3290 (NH) and 1690 (CO); δ_H(400 MHz; $CDCl_3$) 2.09 (3H, s, $CO.CH_3$), 2.66 (3H, s, SCH_3), 6.68-7.66 (m, ArH), 8.07 (1H, d, 6-H), 8.59 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 12.4 and 19.5 (SCH_3 and $COCH_3$), 124.9, 125.6, 129.3, 131.0, 131.5 and 137.2 (ArC) and 169.0 (CO).

*Reaction of 2-mercapto-*N*-(2-methylthiophenyl)ethanamide* **151a** *with* $[PtCl_4]^{2-}$.- A stock solution was made up by dissolving 2-mercapto-*N*-(2-methylthiophenyl)ethanamide **151a** (0.033 g, 0.16 mmol) and *N,N*-diethylaniline (0.37g, 2.5 mmol) in MeOH (25 mL). The ligand-buffer solution (8 mL) was added to the $[PtCl_4]^{2-}$ stock solution (2 mL), and the resulting mixture was stirred at room temperature. Within 10 minutes, a yellow precipitate formed which did not dissolve upon addition of acetone (4 mL). After stirring for 2 h, the precipitate was allowed to settle and the liquid was carefully drawn off with a Pasteur pipette. The precipitate was then washed with MeOH, which was also carefully removed using a Pasteur pipette. The precipitate was dried *in vacuo* to afford the platinum complex (0.012 g); ν_{max}(KBr)/cm^{-1} 1680 and 1610 (CO) (NH and SH absorptions absent); δ_H(400 MHz; $CDCl_3$) 2.15-2.40 (br m), 6.8-7.7 (br m, ArH), 8.6-8.95 (br m, ArH) and 9.20-9.70 (br m).

Reaction of N*-(2-Mercaptoethanoyl)-2-(2-mercaptoethyl)thio-4-methoxyaniline* **172b** *with* $[PtCl_4]^{2-}$.- A stock solution was made up by dissolving *N*-(2-mercaptoethanoyl)-2-(2-mercaptoethyl)thio-4-methoxyaniline **172b** (0.0452g, 0.156 mmol) and *N,N*-diethylaniline (0.37 g, 2.5 mmol) in MeOH (25 mL). This ligand-buffer solution (8 mL) was added to the $[PtCl_4]^{2-}$ solution (2 mL) and, within 5 minutes of mixing, a yellow precipitate had formed. The solution was stirred for 12 h and then the yellow precipitate was allowed to settle. The aqueous methanol was removed with a Pasteur pipette, and the precipitate was washed with MeOH. After the precipitate had settled, the MeOH washings were drawn off with a Pasteur pipette, and the precipitate was dried *in vacuo* to give the polymeric complex; ν_{max}(KBr)/cm^{-1} 1650 (CO) (NH and SH absorptions absent); δ_H(400 MHz; DMSO-d_6) 2.0-4.10 (br m, SCH_2), 6.41-7.6 (br m, ArH) and 9.36, 9.46 and 9.63 (3 x s, NH).

Reaction of the macrocyclic ligand **182a** *with* $[PtCl_4]^{2-}$.- A ligand-buffer stock solution was made up by dissolving the macrocyclic ligand **182a** (0.018 g, 0.063 mmol) and *N,N*-

diethylaniline (0.15 g, 1.0 mmol) in acetone (10 mL) and MeOH (15 mL). The ligand-buffer solution (10 mL) was added to the $[PtCl_4]^{2-}$ solution (1 mL). Within 5 minutes, a yellow precipitate had formed, but the reaction solution remained a yellow colour. TLC [elution with MeOH-$CHCl_3$ (1:19)] showed that all of the free ligand had been consumed in the reaction and that an elutable complex remained in solution. The clear yellow solution was carefully drawn off with a Pasteur pipette, leaving the precipitate, which was rinsed with MeOH and dried *in vacuo*. The ^1H NMR spectrum of the yellow precipitate indicated a mixture containing the complex **212**; [δ_H(400 MHz; DMSO-d_6) 3.0-4.5 (m, SCH_2), 6.75-7.8 9 (m, ArH), 8.25, 8.91 and 9.00 (3 x d, 6-H) and 10.52 (s, NH)]. The solvents were evaporated *in vacuo* from the yellow solution, and the aqueous residue was extracted with $CHCl_3$. The $CHCl_3$ extracts were dried (anhyd. $MgSO_4$), concentrated *in vacuo* and subjected to flash chromatography [elution with MeOH:$CHCl_3$ (1:9)] to afford complex **211b**; ν_{max}(KBr)/cm^{-1} 1620 (CO) (NH absorption absent); δ_H(400 MHz; $CDCl_3$) 2.5-4.3 (m, SCH_2), 6.6-7.6 (m, ArH) and 9.00 and 9.06 (2 x d, 6-H).

Reaction of N,N'-*diphenyl-3,6-dithiaoctanediamide* **107a** *with* $[PtCl_4]^{2-}$.- A stock solution was made up by dissolving *N,N'*-diphenyl-3,6-dithiaoctanediamide **107a** (0.056 g, 0.16 mmol) and *N,N*-diethylaniline (0.37 g, 2.5 mmol) in MeOH (25 mL). This ligand-buffer solution (8 mL) was added to the $[PtCl_4]^{2-}$ solution (2 mL), and the resulting mixture was stirred for 2 h, during which time a light yellow precipitate formed. TLC showed that, after 2 h, almost all the ligand had been consumed. The precipitate was allowed to settle and the liquid was drawn off with a Pasteur pipette. The precipitate was rinsed twice with MeOH and then dried *in vacuo* with moderate heating (50-60 °C) to afford the *syn*- and *anti*-isomers of the platinum sulfur-sulfur chelate **209a**; δ_H(400 MHz; DMSO-d_6) 3.02-3.76 (m, SCH_2), 4.11 (dd, *J* 15.4 and 139 Hz, SCH_2CO), 4.30 (dd, *J* 15.4 and 108 Hz, SCH_2CO), 7.12 (m, ArH), 7.34 (m, ArH), 7.58 (m, ArH) and 10.46 and 10.53 (2 x s, NH).

Reaction of N,N'-*bis(2-chlorophenyl)-3,6-dithiaoctanediamide* **107d** *with* $[PtCl_4]^{2-}$.- The experimental procedure employed for the reaction of *N,N'*-diphenyl-3,6-dithiaoctanediamide **107a** with $[PtCl_4]^{2-}$ was followed, using *N,N'*-bis(2-chlorophenyl)-3,6-dithiaoctanediamide **107d** (0.067g, 0.16 mmol) and *N,N*-diethylaniline (0.37 g, 2.5 mmol) in acetone-methanol (1:1) (50 mL). The ligand-buffer solution (16 mL) was added to the $[PtCl_4]^{2-}$ solution (2 mL). From the resulting mixture was precipitated, as a light yellow solid, the platinum sulfur-sulfur chelate; δ_H(400 MHz; DMSO-d_6) 3.1-3.5 (4H, m, SCH_2), 4.0-4.5 (4H, m, $COCH_2S$), 7.17-7.77 (8H, m, ArH) and 10.12 and 10.19 (2H, 2 x s, NH).

Reaction of N,N'-*diphenyl-3,6-dithiaoctanediamide* **107a** *with cisplatin.*- A cisplatin stock solution was made up by dissolving cisplatin (0.022 g, 7.3×10^{-5} mol) and NaCl (0.088 g, 1.5 mmol) in 0.0974 **M**-HCl (20 mL) and MeOH (30 mL). A solution *N,N'*-diphenyl-3,6-dithiaoctanediamide **107a** (0.0132 g, 3.65×10^{-5} mol) and *N,N*-diethylaniline (0.58 g, 3.9×10^{-3} mol) in MeOH (25 mL) was added to the cisplatin solution (25 mL), and the resulting mixture was stirred for 24 h. The MeOH was removed *in vacuo* and the aqueous residue was extracted with $CHCl_3$. The combined $CHCl_3$ extract was washed (satd. brine) and dried ($MgSO_4$) and the $CHCl_3$ evaporated *in vacuo.* Purification of the residue by PLC afforded the starting material **107a** quantitatively.

Reaction of N-*(2-mercaptoethanoyl)-2-(2-mercaptoethyl)thio-4-methoxyaniline* **172b** *with cisplatin.*- A solution of *N*-(2-mercaptoethanoyl)-2-(2-mercaptoethyl)thio-4-methoxyaniline **172b** (0.0106 g, 3.65×10^{-5} mol) and *N,N*-diethylaniline (0.37 g, 2.5 mmol) in MeOH (25 mL) was added to the cisplatin stock solution (25 mL) (preparation described in the previous procedure), and the resulting mixture was stirred overnight, during which time a fine precipitate formed. The methanol was evaporated *in vacuo* and the aqueous residue was extracted with $CHCl_3$. The organic solution was dried (anhyd. $MgSO_4$), concentrated *in vacuo* and subjected

to PLC [elution with EtOAc-hexane (4:6)] to afford two fractions, *viz.*,

i) a uv-active component, which was not eluted from the baseline; δ_H(400 MHz; $CDCl_3$), 1.65 (br s, NH_3), 3.31 (br s, CH_2S), 3.66 (br s, OMe), 7.51 (br s, ArH), 7.70 (br s, ArH) and 13.68 (br s, NH) (The broad peaks in the ^1H NMR spectrum are suggestive of polymer formation).

ii) a uv-active elutable component **213** (R_F 0.06); The ^1H NMR (400 MHz; $CDCl_3$) spectrum of which contains peaks corresponding to the free ligand as well as peaks at 1.58 (6H, br s, NH_3), 2.7-3.2 (4H, m, SCH_2), 3.34 (2H, dd, $COCH_2S$), 3.79 (3H, s, OCH_3), 6.65-7.21 (3H, m, ArH) and 9.48 (1H, br s, CO.NH).

Reaction of the macrocyclic ligand **182a** *with cisplatin.*- A solution of the macrocyclic ligand **182a** (0.0057 g, 2.0 x 10^{-5} mol) and *N,N*-diethylaniline (0.58 g, 3.9 x 10^{-3} mol) in MeOH (80 mL) was added to a solution of cisplatin (0.0060 g, 3.0 x 10^{-5} mol) in 0.1 **M**-HCl (20 mL) and H_2O (60 mL). The mixture was stirred for 24 h, and the MeOH was then removed *in vacuo*. The aqueous residue was extracted with $CHCl_3$. The combined extracts were dried (anhyd. $MgSO_4$) and the solvent evaporated *in vacuo*. TLC suggested that a small amount of the platinum complex **211b** had formed. Separation of this complex, by PLC, from the relatively large amounts of *N,N*-diethylaniline present was not successful.

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