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**SYNTHESIS OF *N*-ALKYL- AND *N,N*-DIALKYL-*N'*-ACYL-
AND *N'*-AROYLTHIOUREAS,
AND ASPECTS OF THEIR CO-ORDINATION
CHEMISTRY WITH Pt(II) AND Pd(II)**

A thesis submitted to the
UNIVERSITY OF CAPE TOWN
in fulfilment of the requirements for the degree of
DOCTOR OF PHILOSOPHY

by

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June 2000

*This thesis is dedicated to my parents, Roy and Mara Miller, and to my wife Adrienne.
Thank you for your unselfish love and constant moral support, and for your patience
and encouragement throughout this project.*

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to Professor Klaus Koch, my project supervisor, for giving me the opportunity to undertake this research, and for the enthusiastic assistance and guidance he provided throughout this project. I would also like to thank Professor Roger Hunter for the active interest he showed in this work, and for the valuable advice he constantly provided.

My appreciation is also extended to the following people:

Dr Cheryl Sacht and Dr Tarron Grimbacher for the guidance they provided during the early stages of this research;

Professor Tom Modro for valuable comments and insights provided into a number of experimental results;

Dr Achim Lienke for carrying out the computational calculations discussed in this work;

Dr Susan Bourne, Dr John Bacsá and Dr Anita Coetzee for determining the crystal structures described in this work;

Ms Claire Lawrence for her help and friendly encouragement, and for proof reading this thesis;

Mr Noel Hendriks, Dr Krassi Dimitrova and Mr Piero Benincasa for the efficient NMR and elemental microanalytical services they provided;

Mr Roger Wilson, Mr Arthur Joseph and Mr Andre de Jager for preparing and repairing laboratory equipment;

Past and present friends and colleagues in the Platinum Metals Research Group for their friendly help and encouragement and for providing a very pleasant working environment.

Finally, I would like to thank Ranger Oil, Sasol, TUCSIN of Namibia, and Professor Klaus Koch for the generous financial support that was provided to me throughout this project.

ABSTRACT

The synthesis of simple, and also bipodal *N*-substituted *N'*-acyl- and *N'*-aroylthiourea ligands has been investigated, along with aspects of their co-ordination chemistry to Pt(II) and Pd(II).

The ligands are commonly produced by reacting a secondary or primary amine with an acyl or aroyl isothiocyanate. This synthesis requires nucleophilic addition of the amine to the thiocarbonyl carbon of the acyl or aroyl isothiocyanate. However, a competitive side-reaction frequently occurs because the amine nucleophile can attack the carbonyl carbon of the isothiocyanate reagent instead. This leads to substitution of the isothiocyanate moiety and the formation of an *N*-substituted amide.

From a series of reactions between *acyl* isothiocyanates and amines, it has been established that the carbonyl carbon, and not the thiocarbonyl carbon of an acyl isothiocyanate is the more reactive electrophilic centre, and that the *N*-substituted amides are often the dominant products from these reactions. However, because the *sp* hybridised thiocarbonyl carbon is sterically more exposed than the *sp*² hybridised carbonyl carbon, the regioselectivity between the two centres is also markedly dependent on the steric properties of both the amine nucleophile, and the aliphatic R' substituent of the acyl isothiocyanate. For amines in which the nitrogen occurs at a molecular apex (i.e. the cyclic secondary amines and dimethylamine), or where the nitrogen is found at the end of a single alkyl chain (i.e. the primary amines), the predominant reaction pathway is the substitution at the *carbonyl* carbon. However, diethylamine and longer chain dialkylamines react predominantly at the *thiocarbonyl* carbon to give the desired *N,N*-dialkyl-*N'*-acylthioureas. The difference in regioselectivity between the two groups of amines is attributed to the fact that the nitrogen nucleophile in the dialkylamines is afforded 'Front Strain' steric protection by the β methylene hydrogens of the alkyl chains. Nucleophilic attack at the acyl isothiocyanate's sterically more exposed thiocarbonyl carbon is therefore favoured by these particular amines.

The aliphatic R' group on an acyl isothiocyanate also influences the outcome of the amine – acyl isothiocyanate reaction, because this substituent may restrict the amine nucleophile's access to the carbonyl carbon. With a tertiary butyl R' group, for example, access to the carbonyl carbon is hindered to such a degree that even the cyclic amines and dimethylamine predominantly react at the thiocarbonyl carbon.

Due to the resonance interaction between the carbonyl carbon and an aromatic R' group, the problem of amide side-product formation is significantly less pronounced in reactions between *aroyl* isothiocyanates and amines. This has been established from a series of reactions between amines and various *para* substituted benzoyl isothiocyanates. In most of these reactions the desired *N*-substituted *N'*-benzoylthioureas were the dominant products. Major fractions of the amidic products were only isolated from the reactions between cyclic amines and benzoyl isothiocyanates with resonance withdrawing *para*-substituents. Diethylamine and the longer chain dialkylamines, however, again reacted with a very high degree of selectivity at the thiocarbonyl carbon of benzoyl isothiocyanates, regardless of whether the latter had electron releasing or electron withdrawing groups as *para*-substituents on the phenyl ring. This

indicates that 'Front Strain' steric shielding of the nitrogen nucleophile also plays an important role in determining the outcome of the aroyl isothiocyanate – amine reactions. It has also been found from the benzoyl isothiocyanate – amine reactions that amide side-product formation is less prevalent in reactions with moderately basic amines than it is in reactions with strongly basic amines.

Three alternative procedures for the synthesis of *N*-substituted *N'*-acyl and *N'*-aroylthioureas have also been studied. The most successful of these methods is based on the reaction between an acyl chloride and a *N*-substituted thiourea. In the presence of triethylamine base, this reaction proceeds via the formation of a *S*-substituted thiourea intermediate, which subsequently rearranges to the *N*-substituted *N'*-acyl or *N'*-aroylthiourea. By following this procedure, a variety of *N*-substituted *N'*-acylthioureas were synthesised in yields ranging between 60 and 90%.

The $-\text{C}(\text{O})-\text{NH}-\text{C}(\text{S})-$ moiety of the *N,N*-disubstituted *N'*-acyl and *N'*-aroylthiourea ligands (HL) can act as a bidentate chelating moiety that coordinates to a transition metal ion via the oxygen and sulphur atoms once the acidic NH proton is dissociated. It has been determined that the simple *N,N*-disubstituted *N'*-acylthioureas, like the analogous *N'*-aroylthioureas, will readily co-ordinate to Pt(II) in this fashion to give neutral square planar complexes with 2:1 ligand to metal stoichiometry i.e. $[\text{Pt}(\text{L}-\text{S},\text{O})_2]$. ^{195}Pt NMR spectroscopy and X-ray crystallography show that the four donor atoms virtually exclusively adopt the *cis* conformation at the metal centre of these complexes. Minor amounts (i.e. < 10%) of *trans*- $[\text{Pt}(\text{L}-\text{S},\text{O})_2]$ complex could, however, be detected in two instances when electron rich *N'*-(3,4,5-trimethoxybenzoyl)thioureas were used as ligands.

The $-\text{C}(\text{O})-\text{NH}-\text{C}(\text{S})-$ moiety of *N*-monosubstituted *N'*-acyl- and *N'*-aroylthioureas (H_2L) does not participate in bidentate *S,O* coordination because the oxygen atom of the ligand is locked into a stable intermolecular hydrogen bond. In HCl solutions these ligands will coordinate to Pt(II) or Pd(II), but only via their sulphur atoms, and without dissociation of the NH hydrogens. Under these conditions the complexes formed are usually of the type $[\text{M}(\text{H}_2\text{L})_2\text{Cl}_2]$. However, it is shown that with a *N*-propyl-*N'*-butanoylthiourea it is possible to induce an unusual form of *trans N,S* bidentate coordination to Pt(II) once the ligand is deprotonated. The resulting complex is a distorted square planar compound with 2:1 ligand to metal stoichiometry i.e. *trans*- $[\text{Pt}(\text{HL}-\text{N},\text{S})_2]$.

The bipodal *N'*-acyl- and *N'*-aroylthioureas (H_2L) are ligands which have two $-\text{C}(\text{O})-\text{NH}-\text{C}(\text{S})-$ moieties linked to each other with an aliphatic or aromatic spacer group. Although these ligands also co-ordinate in *cis* bidentate *S,O* chelating fashion to Pt(II) and Pd(II), the overall metal to ligand stoichiometry is 1:1. Furthermore, with rigid or short chain spacer groups, the two chelating moieties of a bipodal ligand molecule co-ordinate to different metal centres. The resulting complexes may thus be in the form metal – ligand co-ordination polymers (i.e. $[\text{M}(\text{L}-\text{S},\text{O})]_x$), or metallamacrocycles consisting of two or more metal centres linked into a macrocycle by an equal number of ligands (i.e. $[\text{M}(\text{L}-\text{S},\text{O})]_{2,3,\dots}$). Bipodal ligands with a phenyl ring spacer reacted with Pt(II) and Pd(II) to produce either 2:2 or 3:3 metallamacrocycles ($[\text{M}(\text{L}-\text{S},\text{O})]_2$ and $[\text{M}(\text{L}-\text{S},\text{O})]_3$), depending on whether the two chelating moieties of the ligand were in *meta* or in

para positions with respect to each other on the phenyl ring spacer. The bipodal ligands with aliphatic spacer groups also reacted with Pt(II) and Pd(II) to produce $[M(L-S,O)]_x$ type complexes. However, it has not been determined with certainty whether these compounds were in the form of metallamacrocycles, or whether they had formed metal – ligand co-ordination polymers.

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LIST OF SYMBOLS AND ABBREVIATIONS

Å	angstrom unit, 10^{-10} m
Hz	hertz, s^{-1}
mp	melting point in $^{\circ}\text{C}$
δ	NMR chemical shift
ppm	parts per million (NMR)
lit.	literature
R_f	sample to solvent front mobility ratio on thin layer chromatogram
CDCl_3	deuterated chloroform
CD_2Cl_2	deuterated methylene chloride
DMF	dimethylformamide
DMSO	dimethylsulfoxide
$\text{DMSO-}d_6$	deuterated dimethylsulfoxide
THF	tetrahydrofuran
M^{n+}	metal cation
X	halogen
HL	N,N-disubstituted-N'-acyl- or N'-aroylthiourea
H_2L (in chapter 5)	N-monosubstituted-N'-acyl- or N'-aroylthiourea
H_2L (in chapter 6)	bipodal N'-acyl- or N'-aroylthiourea

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CHAPTER 1

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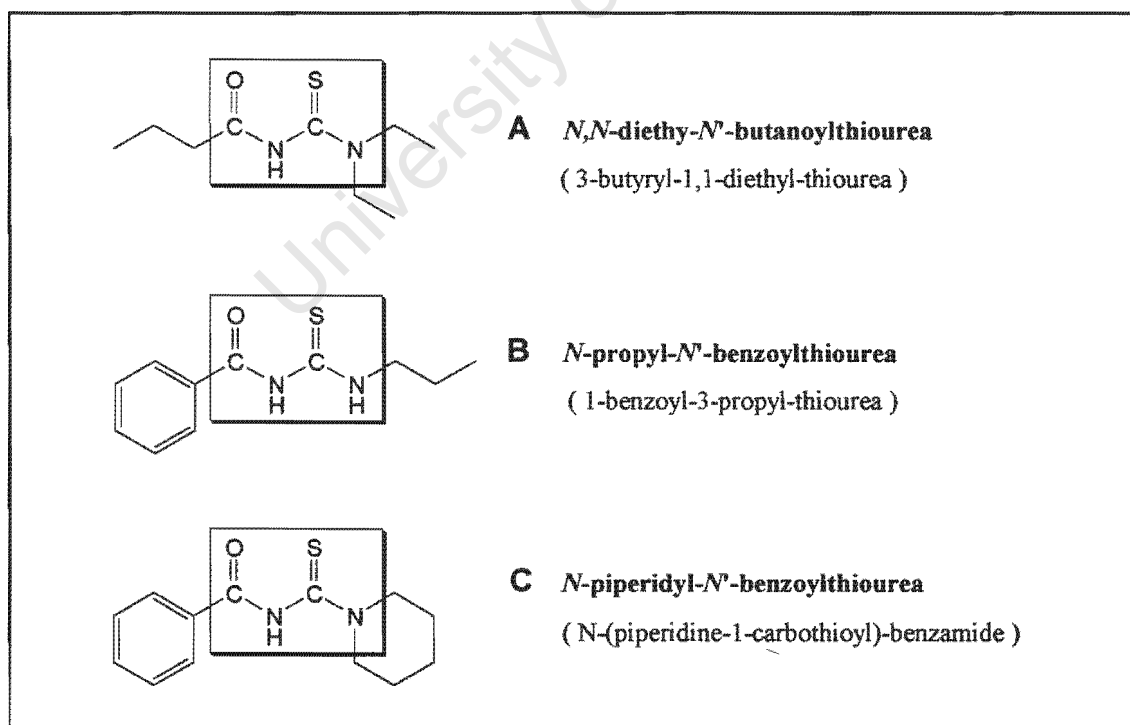
Introduction

1.1 About *N*-alkyl and *N,N*-dialkyl-*N'*-acyl- and *N'*-aroylthioureas

The names *N'*-acylthiourea and *N'*-aroylthiourea are collective terms, commonly used to describe a group of asymmetrically substituted thioureas which have one of the thiourea nitrogens (*N'*) linked to a single acyl or aroyl group. Thus, characteristic of this group of compounds is a central motif composed of thiocarbonyl and carbonyl carbons linked via a protonated nitrogen (see figure 1.1). Variation within this group depends entirely on the substituents found on either the carbonyl carbon (i.e. the *R'* substituent) or on the second nitrogen atom (*N*) of the thiourea (i.e. the *R* substituents). Should the carbonyl carbon be linked to an alkyl *R'* group, the molecule is referred to as an *acylthiourea* (**A**, figure 1.1). If, on the other hand it is linked to an aromatic *R'* group, the compound is an *aroylthiourea* (**B** and **C**, figure 1.1). The distinction between acyl and aroylthioureas is important for purposes of this work, even though the term *acylthiourea* is frequently used to collectively describe both *N'*-acyl- and *N'*-aroylthioureas in the literature.

The *N* nitrogen of the thiourea may be linked to one or two alkyl substituents to give either *N*-alkyl or *N,N*-dialkyl substituted compounds. Alternatively, it may also form the heteroatom bridge of a cyclic alkyl group (**C**, figure 1.1). Of course the substituents on this nitrogen need not necessarily be alkyl groups, but

Figure 1.1 Schematic representation* of some *N*-alkyl and *N,N*-dialkyl-*N'*-acyl- and *N'*-aroylthioureas (the formal IUPAC^{1,2} names are listed in parentheses)



* For illustration of the central thiourea motif and the carbonyl group, the diagrams show the compounds in *Z,Z'* conformation. In practice the preferred conformation is *E,Z'*, where the carbonyl and thiocarbonyl groups are essentially projected in opposite directions³.

could include aromatic and other unsaturated groups as well. While no such compounds were prepared in the course of this research, the more general term *N*-substituted *N'*-acyl or *N'*-aroylthiourea is occasionally used in the discussions that follow (i.e. the term is applied collectively to include references to the compounds with *N*-alkyl, *N,N*-dialkyl and cyclic substituents, and to the *N'*-acyl- and *N'*-aroylthioureas with the other possible *N* substituents).

The convention of distinguishing the two thiourea nitrogens of acyl- and aroylthioureas as *N* and *N'* has been adopted for this thesis since it appears to be common practice in the more recent literature. However, it must be added that it is not unusual to find them distinguished as nitrogens 1 and 3 instead. According to this system, an *N,N*-dialkyl-*N'*-acylthiourea is named as 1,1-dialkyl-3-acyl-thiourea. Although the latter seems to conform more closely to IUPAC nomenclature^{1,2}, the correct IUPAC system of naming these compounds is rarely, if ever, strictly applied in the relevant literature. This is not surprising, since the IUPAC names are awkward to use in a general discussion and may cause confusion. For example, an *N'*-benzoylthiourea is formally named as 1-benzoyl-3-methyl-thiourea when it has only one methyl group on the *N* nitrogen, and as 3-benzoyl-1,1-dimethyl-thiourea when there are two methyl groups on the *N* nitrogen. Furthermore, compounds where the *N* nitrogen forms the bridge of a cyclic alkyl group are not even classed as thioureas, but as amides with cyclic amine – carbothioyl substituents. (IUPAC names for the *N'*-acyl and *N'*-aroylthioureas in figure 1.1 are included in parentheses in the diagram. A more comprehensive list of representative IUPAC names for *N'*-acyl- and *N'*-aroylthioureas can be found in Appendix 8).

N-substituted-*N'*-acyl- and *N'*-aroylthioureas are not a new class of compounds. They were first synthesized and described by Neuki⁴ in 1873. This early work was extended significantly a few years later by Doran, Dixon, Hawthorne and Taylor^{5a-p}. Working in collaboration, they systematically studied the reactivity of a number of new acyl and aroyl isothiocyanate reagents. In the process, they produced more than seventy-five new *N*-substituted *N'*-acyl- and *N'*-aroylthioureas. However, this early research was followed by a period during which the interest in these compounds can best be described as sporadic. While a large variety of thiourea derivatives were known and had been utilized in almost every branch of chemistry by 1955⁶, a practical application for the *N'*-acyl- and *N'*-aroylthioureas seems to have remained elusive until the late 1970s. This is surprising, considering that the simple one-pot synthesis that is used almost exclusively today to produce these compounds was published as early as 1934 by Douglass and Dains⁷. This method is a modification of the procedure first outlined by Dixon^{5a-c} and is based on the reaction of an amine and an acyl or aroyl isothiocyanate*. Although the laboratory procedure is simple, it also allows for considerable variation of the R and R' substituents on the central *N'*-acyl- or *N'*-aroylthiourea motif.

* The amine – acyl/aroyl isothiocyanate synthesis of an *N'*-acyl- or *N'*-aroylthiourea is frequently referred to as the Douglass and Dains synthesis throughout this thesis. The reference to the relevant paper by these authors is, however, only included in the reference list at the end of this chapter (reference 7), and is not repeated in any of the reference lists of the other chapters.

Concerted interest in *N*-substituted *N'*-acyl- and *N'*-aroylthioureas was rekindled in 1975, by the pioneering work of Beyer and Hoyer⁸. They recognised in these molecules the aza analogues of monothio- β -diketones, compounds which were known to form stable chelates with transition metal ions. They found that *N,N*-dialkyl substituted *N'*-acyl- and *N'*-aroylthioureas behaved in similar fashion, acting as bidentate ligands that co-ordinate, via the oxygen and sulphur atoms, with mono-, di- and trivalent transition metal ions. In addition they established that the ligand properties were pH dependant and that with pH control they could achieve the selective precipitation, extraction and separation of transition metal ions. Since these compounds exhibited unusual stability to oxidation and hydrolysis when compared to other sulphur containing ligands⁹, their potential for practical application was soon also noticed by others. In particular, Schuster^{10,11}, discovered that the *N,N*-dialkyl substituted *N'*-aroylthioureas exhibited a remarkable affinity for the platinum group metals. He established that these ligands could be used under conditions of low pH to quantitatively separate platinum group metals, even from strongly interfering matrices. Based on this finding, he has developed several novel analytical procedures for the trace analysis of these metals¹²⁻¹⁴. The mechanism of co-ordination of *N*-alkyl and *N,N*-dialkyl-*N'*-aroylthioureas to platinum group metals has also been studied in detail by Koch¹⁵⁻¹⁸. He has shown that the mode of co-ordination is noticeably influenced by factors such as solution pH, the nature of the anions present in the solution, and by the substituents found on the ligand itself.

The renewed interest in *N'*-acyl- and *N'*-aroylthioureas has not only been restricted to the field of co-ordination chemistry and its analytical application. The Douglass and Dains⁷ synthesis has been used to produce *N'*-acyl- and *N'*-aroylthioureas as convenient starting materials for the synthesis of other new compounds^{19,20}. Furthermore, with suitable substituents, Grimbacher²¹ was able to synthesize a number of *N'*-aroylthioureas that exhibited liquid crystalline behaviour. This work has subsequently been extended by Wang²², to include metallomesogens based on the *N'*-aroylthiourea motif. *N'*-benzoylthioureas have also been immobilised on silica stationary phases²³. These have been used to separate linear and branched alkenes, and aromatic and cyclic hydrocarbons by gas chromatography. To date, it has been possible, using the Douglass and Dains⁷ synthesis, to produce *N'*-acyl- and aroylthioureas with substituents as diverse as aza-crown ethers²¹, ferrocenes²⁴, and even rim modified calixarenes²⁵.

1.2 About this thesis

Despite the considerable potential for wider application of *N*-substituted *N'*-acyl- and *N'*-aroylthioureas, their utilisation as selective ligands in platinum group metal recovery and analysis remains exciting. It is an area of research that has by no means been exhausted, and since South Africa continues to be the world's largest supplier of platinum group metals²⁶, it is of particular relevance. Such considerations provided the incentive for some of the early work conducted in the course of this project. Introductory goals were to use the established Douglass and Dains⁷ methodology to produce some novel *bipodal* *N'*-acyl- and *N'*-aroylthioureas. These are compounds with two acyl- or aroylthiourea chelating moieties (i.e. $-(O)C-NH-C(S)-$) on either end of a linking R' or R group. The aim was to test these compounds as

selective ligands for the recovery of platinum and palladium (and the eventually the other platinum group metals) from synthetic solutions, and from real refinery effluents. However, in the earliest stages of the project, the Douglass and Dains⁷ synthesis provided for several unexpected hurdles, and as a result, the course and emphasis of the experimental research changed significantly.

The unforeseen problems with the Douglass and Dains⁷ synthesis were first encountered during attempts to produce a series of bipodal adipoylthioureas. As a first step in these reactions, adipoyl chloride, a reagent with two acyl chloride moieties linked by a four carbon *n*-alkyl chain, was converted to the difunctional adipoyl isothiocyanate. This was followed by the acyl isothiocyanate - amine reaction step, which in these cases required the addition of two equivalents of secondary amine. Although this step was anticipated to yield the desired adipoylthiourea as the dominant product, its outcome was found, quite unexpectedly, to be critically dependant on the particular amine used for the reaction. With diethylamine and dibutylamine, for example, the reaction proceeded as intended, giving satisfactory yields (i.e. > 50%) of the targeted adipoylthioureas. However, neither of the targeted ligands were obtained when analogous reactions were carried out with piperidine and pyrrolidine. Instead, these two reactions produced products of an amidic nature. In subsequent work with other isothiocyanate and amine reagents, it became evident that these were not isolated cases and, that indeed *N*-substituted amides were frequently formed as side-products, and occasionally, even as the dominant compounds. It was also established early on, that the outcome did not only depend on the type of amine used, but was also influenced by the type of acyl or aroyl isothiocyanate employed in the reaction.

A comprehensive review of the relevant literature did little to provide clarification. Although some isolated reports alluded to similar difficulties in the synthesis of certain *N'*-acyl- and *N'*-aroylthioureas^{5,19,27}, the phenomenon was in no instances satisfactorily explained. With this realisation, efforts were re-directed from the bipodal ligands and their application, and devoted to a more detailed scrutiny of the Douglass and Dains⁷ procedure itself. Indeed, a large proportion of the work presented in this thesis just deals with reactions between simple amines and acyl or aroyl isothiocyanates, in order to explain why in some cases the thioureas are formed, while in other instances the reactions produce *N*-substituted amides as the dominant products. The bulk of these results are presented and discussed in chapter 2 and chapter 3.

The fact that a number of *N'*-acylthioureas and certain *N'*-aroylthioureas could not be obtained in satisfactory yields by the Douglass and Dains⁷ procedure, also prompted a brief investigation to determine whether these compounds could be produced by other simple and convenient methods. Three possible alternatives were tested in the course of this project and the results of this particular work are presented and discussed in chapter 4.

Despite the desire to understand the fundamental aspects that affected the synthesis of these compounds, the potential for their application in platinum group metal recovery was not ignored completely. A significant number of new *N'*-acylthioureas, and some less common *N'*-aroylthioureas were synthesised in the course of the investigations outlined above. Accordingly, many of these compounds were also tested as ligands for

co-ordination to platinum. This work, which is described in chapter 5, is intended to complement, and provide comparison to the existing data on the co-ordination chemistry of this group of thioureas.

The final chapter of this thesis is devoted to the work carried out on the bipodal *N*-acyl- and *N*-aroylthioureas. Although the initial work on these compounds was interrupted for the investigation of the Douglass and Dains⁷ procedure, it was continued once the factors affecting this synthesis were better understood. The chapter is divided into parts A and B. Part A deals with a systematic investigation into the synthesis of several bipodal ligands. This involved evaluating, as linking reagents, various difunctional acyl or aroyl isothiocyanates in reactions with simple amines, and diamines in reactions with simple acyl or aroyl isothiocyanates. In effect, the work in this part can be regarded as an extension of the investigations described in chapters 2 and 3. Although none of the bipodal ligands were tested in any practical applications as originally intended, their coordination chemistry with Pt(II) and Pd(II) was also investigated on a limited scale. A number of interesting complexes were prepared in the process, and these and other pertinent findings are discussed in part B of the chapter.

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CHAPTER 2

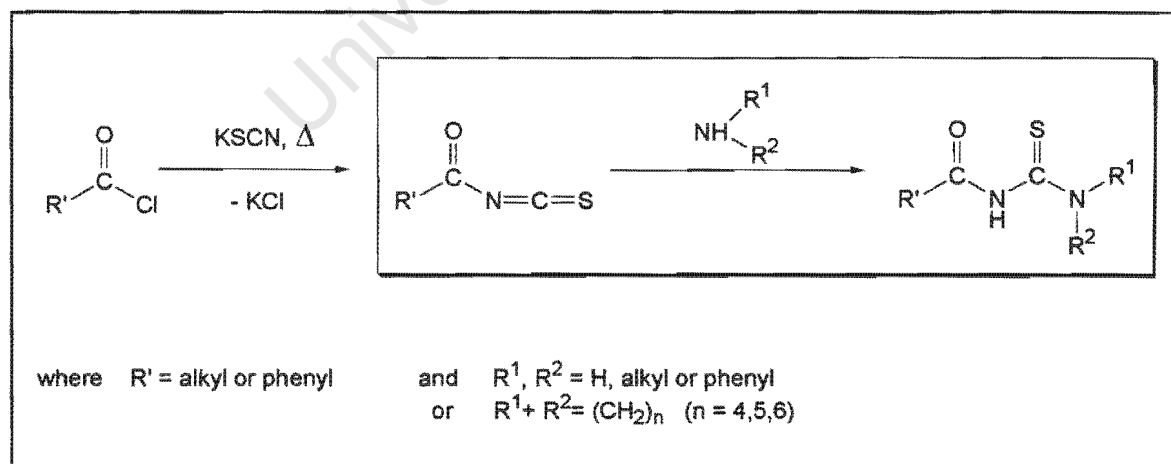
University of Cape Town

Synthesis of *N*-substituted *N'*-acylthioureas: Factors affecting the reaction between acyl isothiocyanates and aliphatic amines

2.1 Introduction

In recent years, almost all *N*-substituted *N'*-acyl- and *N'*-aroylthioureas have been synthesized according to the procedure described by Douglass and Dains. However, as was pointed out in chapter 1, this process is essentially based on a synthesis first outlined by Dixon¹ in 1895. Using anhydrous benzene as a solvent, he added a slight excess of lead thiocyanate to an acyl or aroyl chloride. This mixture was refluxed for fifteen minutes to produce the acyl or aroyl isothiocyanate. (Acyl and aroyl thiocyanate are also formed initially, but these are rapidly transformed to the isothiocyanate as well²). Unwanted lead chloride salt, that was a byproduct of the process, was removed by filtration. A primary or secondary amine was then added to the isothiocyanate solution. This was to react additively with the isothiocyanate to give the desired *N*-substituted *N'*-acyl- or *N'*-aroylthiourea. In their modification of this procedure, Douglass and Dains used anhydrous acetone as a solvent, and ammonium or potassium thiocyanate instead of lead thiocyanate. They also simplified the method to a 'one pot' synthesis, by proceeding to add the amine without prior filtration of the chloride salts. Although the synthesis is commonly attributed to Douglass and Dains, and is referred to as the 'Douglass and Dains procedure' in this thesis, it should be noted that their modifications affected only practical aspects of the synthesis. The key element of Dixon's¹ original procedure remains unchanged to this day: the addition of an amine to an acyl or aroyl isothiocyanate.

Figure 2.1 Reaction scheme used by Dixon¹ and Douglass and Dains to synthesise *N*-substituted *N'*-acyl and *N'*-aroylthioureas



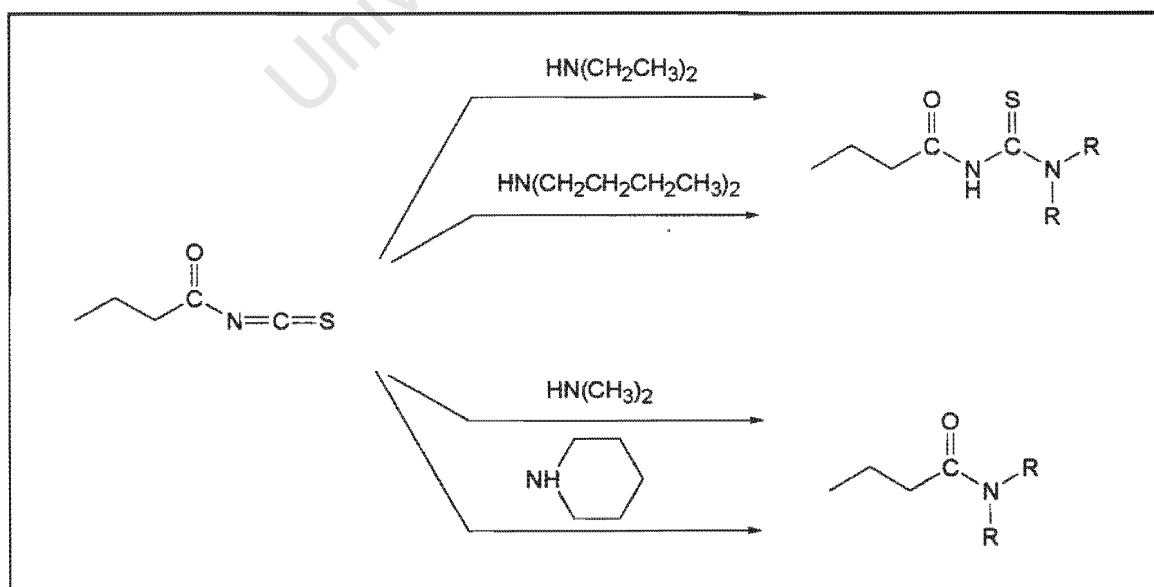
From the relevant literature following the work of Dixon¹ and of Douglass and Dains, it is evident that by far the majority of the reported compounds are *N'*-aroylthioureas, usually *N*-substituted *N'*-benzoylthioureas. True *N'*-acylthioureas, with aliphatic R' substituents on the carbonyl carbon, have been synthesized and

described far less frequently. To the uninitiated, this may appear surprising as there is no shortage of commercially available acyl halides that could serve as starting materials for such derivatives. However, the lack of data on *N'*-acylthioureas is not due to mere oversight.

Doran, Dixon and Hawthorne^{3a-o} found that several acyl isothiocyanates, including acetyl, propanoyl, and 2-methylpropanoyl isothiocyanate, produced satisfactory yields of *N'*-acylthioureas when reacted with aniline, toluidine and other aryl amines. However, they also reported that the same isothiocyanates gave poor yields of *N'*-acylthioureas when ammonia, benzylamine and piperidine were added instead. These amines tended to produce *N*-substituted amides by substituting the isothiocyanate moiety of the acyl isothiocyanate. The fact that other primary and secondary amines may react with acyl isothiocyanates in this manner has subsequently also been confirmed by others^{4,5}.

As was pointed out in chapter 1, quite varied results from the combination of amines and acyl isothiocyanates were also obtained during the course of this research (see figure 2.2). After the surprising results were recorded with the difunctional reagents, a number of reactions were carried out with simple acyl isothiocyanates. Butanoyl isothiocyanate, for example, was added to a variety of secondary amines. With dibutylamine it reacted, as required, to give *N,N*-dibutyl-*N'*-butanoylthiourea. Under similar conditions, however, it combined with piperidine to produce the piperidyl substituted butyramide. Substituted amide was also the dominant product isolated from the reaction when dimethylamine was used, while contrastingly good yields of the desired *N'*-acylthiourea were isolated from a reaction with diethylamine. Interestingly, however, when 2,2-dimethylpropanoyl isothiocyanate was used instead of butanoyl isothiocyanate, reactions with all four amines gave virtually quantitative yields of the *N*-substituted *N'*-acylthiourea.

Figure 2.2 Inconsistent results from reactions of butanoyl isothiocyanate: *N*-substituted *N'*-butanoylthioureas from reactions with diethyl- and dibutylamine, and *N*-substituted butyramides from reactions with dimethylamine and piperidine



Although this variable behaviour has been documented, there is no information in the literature to explain its origin. The reactions of acyl isothiocyanates and amines have not yet been studied on a systematic basis and certainly, the factors which determine the outcome of these combinations are not clearly understood. Even today, more than a hundred years after the early work of Doran and Dixon^{1,3a-c}, the synthesis of new *N*-substituted *N'*-acylthioureas appears to be based on a process of trial and error. The work described in this chapter is a qualitative investigation intended to address this shortcoming. Selected acyl isothiocyanates have been added to a series of primary and secondary amines. The major products of each reaction have been carefully isolated and characterised. The resulting data has been collated to highlight the factors which influence these reactions, and it is hoped that it may serve to make the synthesis of new *N*-substituted *N'*-acylthioureas a more predictable process.

2.2 Experimental Approach

The experimental investigations were based on the 'one pot' procedure of Douglass and Dains. This was done because it is currently the most popular procedure for the synthesis of *N'*-acyl- and *N'*-aroylthioureas, and because acetone, rather than benzene, is used as the reaction solvent. All the reagents and important reaction intermediates are readily soluble in acetone, and it is a cheap and less harmful solvent than benzene.

Acyl isothiocyanates were formed by refluxing acyl chloride and potassium thiocyanate in anhydrous acetone for 45 minutes. This mixture was allowed to cool to 20°C. The amine, also dissolved in anhydrous acetone, was then slowly added over a period of ten minutes. The mixture was stirred for a further 10 minutes and then boiled under reflux for one hour to ensure complete reaction. After the refluxing, the reaction solution was poured into a small volume of water and left to stand. This allowed for slow precipitation of some products as the acetone evaporated. Single product precipitates were recrystallised, while mixed precipitates were separated and purified by column chromatography. Oils and more soluble products were extracted and also purified by column chromatography.

Only fresh, commercially available acyl chlorides were used in the reactions. Since these reagents and acyl isothiocyanates are moisture sensitive, reactions were carried out under nitrogen, and, particular care was taken to ensure that solvent and reagents were thoroughly dried immediately prior to use. Further experimental details can be found in section 2.6.

The main isothiocyanates chosen for these investigations included butanoyl (**IA**), 2-methylpropanoyl (**IB**) and 2,2-dimethylpropanoyl isothiocyanate (**IC**). Significant within this selection was the variation of aliphatic substituents from a simple linear propyl chain (**IA**), to the branched and bulky tertiary butyl group (**IC**). The set of amines (**a – i**) selected for these reactions included secondary and primary aliphatic amines. Rather than carrying out each reaction in duplicate, the amine series were extended to include at least two similar examples of secondary cyclic amines, secondary dialkyl amines and primary alkyl amines. Nevertheless, to confirm certain results, a number of reactions were repeated.

2.3 Results

The dominant products from all the reactions investigated were, as expected, either *N*-substituted *N'*-acylthioureas (**II**) or *N*-substituted amides (**III**). In almost all cases, the combined yields of these two products accounted for at least 80% of the starting materials employed.

The *N'*-acylthiourea and amide yields from the reactions of butanoyl isothiocyanate (**IA**) with secondary amines are listed in table 2.1. A significant division is clearly distinguishable within this set of results. Diethylamine (**a**), dibutylamine (**b**), and cis-2,6-dimethylpiperidine (**c**), for convenience called 'group 1' amines, reacted with butanoyl isothiocyanate to produce *N,N*-disubstituted *N'*-butanoylthioureas in yields above 85%. Amide yields from these reactions did not exceed 10%. 'Group 2' amines, piperidine (**d**), pyrrolidine (**e**), morpholine (**f**), and dimethylamine (**g**), by contrast, reacted predominantly to form *N*-substituted butyramides in yields ranging between 60% and 80%. Yields of butanoylthioureas from this group of reactions did not exceed 20%. (For reactions that were repeated, only the average yields have been given since relative standard deviations for these values were all below 3%).

Results from the reactions of 2-methylpropanoyl isothiocyanate (**IB**) with dibutylamine and piperidine are also included in table 2.1. As in reactions with butanoyl isothiocyanate, dibutylamine combined to form the *N*-substituted *N'*-acylthiourea. Once again, piperidine reacted as a group 2 amine to produce the amide as the dominant product. The yield of acylthiourea from this reaction was, however, somewhat higher (26.1%) than the values recorded for the other group 2 amine reactions.

In contrast to the results listed in table 2.1, it is evident that secondary amines behave quite uniformly when added to 2,2-dimethylpropanoyl isothiocyanate (**IC**). Results of these reactions are summarised in table 2.2 and show that both group 1 and group 2 amines reacted to produce almost quantitative yields of *N*-substituted *N'*-(2,2-dimethylpropanoyl)thioureas.

Data from the reactions of propyl- (**h**) and butylamine (**i**) with various acyl isothiocyanates can be found in table 2.3. With butanoyl (**IA**) and decanoyl isothiocyanate (**ID**) these primary amines react to produce *N*-substituted amides as major products. As in the reactions of the group 2 secondary amines with butanoyl isothiocyanate, the yields of *N'*-acylthioureas did not exceed 20%. A surprisingly even product distribution is however obtained when these primary amines are added to 2,2-dimethylpropanoyl isothiocyanate (**IC**). Typically these combinations gave mixtures containing 30% yields of *N*-acylthiourea and 40% yields of the corresponding amide.

Table 2.1 Product yields from the reactions of butanoyl isothiocyanate and 2-methylpropanoyl isothiocyanate with secondary aliphatic amines

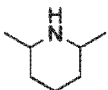
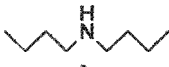
Acyl isothiocyanate	Secondary amine	Yield acylthiourea (%)	Yield amide (%)	Product ratio (P _r)
$\text{R}'-\overset{\text{O}}{\underset{\text{NCS}}{\text{C}}}$	$\text{HNR}_2 \text{ or } \text{HN}(\text{CH}_2)_n$	$\text{R}'-\overset{\text{O}}{\underset{\text{H}}{\text{N}}}-\overset{\text{S}}{\underset{\text{NR}_2}{\text{C}}}$	$\text{R}'-\overset{\text{O}}{\text{C}}-\text{NR}_2$	$\frac{\text{Yield III}}{\text{Yield II}}$
I		II	III	
$\text{CH}_3\text{CH}_2\text{CH}_2\overset{\text{O}}{\underset{\text{NCS}}{\text{C}}} +$ IA	 a	85.7	7.9	0.09
	 b	86.4	9.3	0.11
	 c	89.2	-	< 0.11
	 d	8.5	64.4	7.58
	 e	3.6	68.9	19.1
	 f	17.8	76.1	4.28
	 g	10.7	76.1	7.11
$\text{CH}_3\text{CH}(\text{CH}_3)\overset{\text{O}}{\underset{\text{NCS}}{\text{C}}} +$ IB	 b	97.0	-	< 0.10
	 c	26.1	73.1	2.80

Table 2.2 Product yields from the reactions of 2,2-dimethylpropanoyl isothiocyanate with secondary aliphatic amines

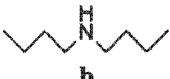
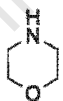
Acyl isothiocyanate	Secondary amine	Yield acylthiourea (%)	Yield amide (%)	Product ratio (P _r)
$\text{R}'-\overset{\text{O}}{\underset{\text{NCS}}{\text{C}}}$	$\text{HNR}_2 \text{ or } \text{HN}(\text{CH}_2)_n$	$\text{R}'-\overset{\text{O}}{\underset{\text{H}}{\text{N}}}=\text{S}-\text{NR}_2$	$\text{R}'-\overset{\text{O}}{\text{C}}-\text{NR}_2$	$\frac{\text{Yield III}}{\text{Yield II}}$
I		II	III	
$\text{IC} \quad \text{+}$	 a	98.0	-	< 0.10
	 b	97.6	-	< 0.10
	 d	96.1	1.1	0.01
	 e	90.1	-	< 0.10
	 f	97.2	-	< 0.10
	 g	99.0	-	< 0.10

Table 2.3 Product yields from the reactions of various acyl isothiocyanates with primary aliphatic amines

Acyl isothiocyanate	Secondary amine	Yield acylthiourea (%)	Yield amide (%)	Product ratio (P _r)
$\text{R}'-\overset{\text{O}}{\underset{\text{NCS}}{\text{C}}}$	H_2NR	$\text{R}'-\overset{\text{O}}{\underset{\text{H}}{\text{N}}}=\overset{\text{S}}{\text{C}}-\text{NHR}$	$\text{R}'-\overset{\text{O}}{\text{C}}-\text{NHR}$	$\frac{\text{Yield III}}{\text{Yield II}}$
I		II	III	
$\text{CH}_3\text{CH}_2\text{CH}_2\overset{\text{O}}{\underset{\text{NCS}}{\text{C}}} +$	$\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_3$ h	14.3	74.9	5.24
IA	$\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ i	10.4	64.0	6.15
$\text{CH}_3(\text{CH}_2)_6\overset{\text{O}}{\underset{\text{NCS}}{\text{C}}} +$	$\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_3$ h	8.8	56.5	6.42
ID				
$(\text{CH}_3)_3\text{C}\overset{\text{O}}{\underset{\text{NCS}}{\text{C}}} +$	$\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_3$ h	30.2	39.0	1.29
IC	$\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ i	25.3	40.5	1.60

2.4 Discussion

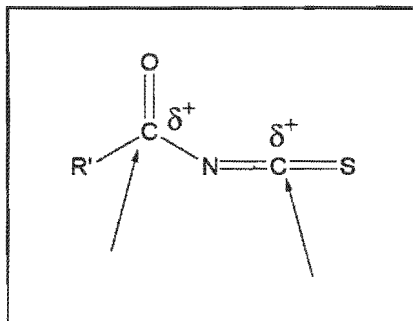
The outcome of a reaction between an acyl isothiocyanate and an aliphatic amine is clearly dependant on the substituents of both reagents. This is evident in all the results listed on the previous pages. Both the acyl R' group of the isothiocyanate, and the alkyl R substituents of the amine, primarily direct the course of the reaction by steric means. In the case of the amine, the steric bulk of the alkyl groups influence the accessibility of the nitrogen nucleophile and drive its selectivity towards those electrophilic sites with more accomodating geometry. This is important, because there are two electrophilic sites to be found on acyl isothiocyanates. Although one of these appears to be significantly more reactive towards amine nucleophiles, its reactivity is dramatically reduced by steric crowding from a bulky acyl R' group. These aspects will be explained in the discussion below.

Other interpretations of the above data have also been considered. Some of the early results from this work seemed to indicate that only amine basicity dictated the outcome of these reactions and that amide formation occurred via a ketene intermediate. Doran, Dixon and Hawthorne^{3k-m.o}, on the other hand, believed that reactions of acyl isothiocyanate were dependent on an acyl isothiocyanate – acyl thiocyanate equilibrium and that temperature also played an important role. The pertinence of these explanations will also be discussed at the end of this chapter.

2.4.1 Acyl isothiocyanates: reagents with two competing electrophilic centres

Nucleophilic attack on acyl isothiocyanates is complicated by the presence of both carbonyl (C=O) and thiocarbonyl carbon (C=S) electrophilic centres. In the context of the synthesis of *N*-substituted *N'*-acylthioureas, this was first pointed out by Elmore and Ogle⁴.

Figure 2.3 The carbonyl and thiocarbonyl electrophilic centres of acyl isothiocyanates

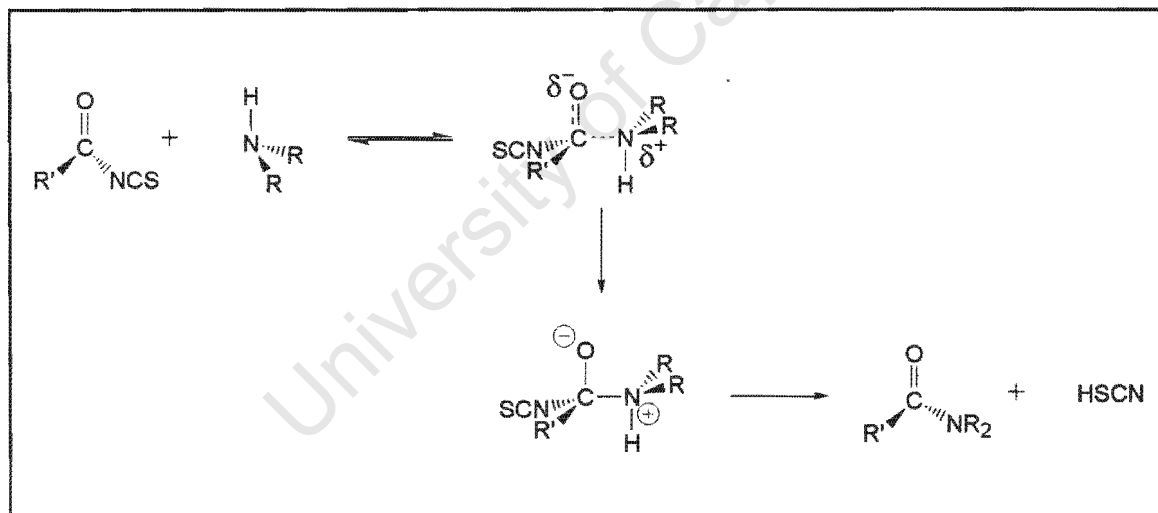


The Douglass and Dains procedure requires that attack by the amine is restricted to the thiocarbonyl carbon. Reaction at this site is the nucleophilic addition that will produce the desired *N'*-acylthiourea. Unfortunately, nucleophilic attack by the amine can also occur at the carbonyl carbon. Reaction at this site leads to elimination of the isothiocyanate moiety and formation of *N*-substituted amides. From the early reports

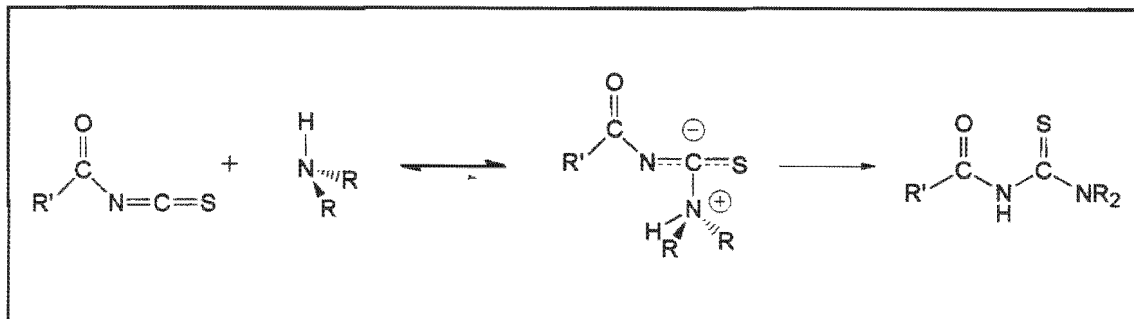
previously mentioned (section 2.1^{3a-o, 4, 5}) and from the variable results listed in table 2.1 it is evident that both centres are in active competition for the amine. To understand the factors that govern regioselectivity between the two centres it is important to compare their properties and reactions that take place at each site.

The carbonyl carbon of an acyl isothiocyanate is a trigonal sp^2 -hybridised centre with a significant partial positive charge. According to Pearson's HSAB principle, this centre is considered to be a hard Lewis acid and it is thus not surprising that it will react readily with hard bases like amines^{7,8}. The reaction is a substitution process that can occur via a concerted S_N2 mechanism or via a stepwise addition – elimination pathway. When these reactions are carried out in organic solvents, however, or with strong bases like aliphatic amines, the latter is the more likely process¹¹⁻¹⁴. It is initiated by nucleophilic attack of the amine (figure 2.4) and gives rise to an intermediate where the carbon, now a tetrahedral sp^3 centre, is bonded to the amine nitrogen, itself also in tetrahedral sp^3 form. With strongly basic nucleophiles, formation of this intermediate also represents the rate determining step⁹⁻¹⁴. The trigonal carbonyl carbon is restored, and the reaction completed, by the subsequent elimination of the isothiocyanate group. The final product is an *N*-substituted amide.

Figure 2.4 Nucleophilic attack at the carbonyl carbon of the acyl isothiocyanate: formation of *N*-substituted amide



Unlike the carbonyl carbon, the thiocarbonyl carbon is an sp -hybridised centre. Analogous reactions of *p*-nitrophenyl isothiocyanates have revealed that nucleophilic addition of an amine at such a carbon occurs via the formation of a trigonal zwitterionic intermediate^{15,16} (figure 2.5). At this intermediate stage, the thiocarbonyl carbon is an sp^2 centre, that is bonded to the now tetrahedral amine nitrogen. Again, with strongly basic amines, this step is the rate determining step^{15,16}. Formation of the *N*-(*p*-nitrophenyl)thiourea product is then completed by a proton transfer to the nitrogen of the isothiocyanate moiety.

Figure 2.5 Nucleophilic attack at the thiocarbonyl carbon of the acyl isothiocyanate: formation of *N*-substituted *N'*-acylthiourea via a trigonal zwitterionic intermediate

In terms of Pearson's HSAB principle, it is not easy to compare the thiocarbonyl carbon of isothiocyanates with the acyl carbonyl carbon. Certainly, in β -ketothiones, the thiocarbonyl is much softer than the carbonyl group⁷ and less vulnerable to amine attack. The pertinence of this example is, however, limited in the case of acyl isothiocyanates. Here the thiocarbonyl carbon is sp , rather than sp^2 hybridised, and it is linked to nitrogen. Both are factors which might be expected to increase the hardness of this centre⁷.

However, direct comparison of the reactions at each site is quite possible, due to the fact that both reactions are second order, irreversible processes, with nucleophilic attack as the rate determining step. Furthermore, each gives rise to thermodynamically stable products under the reaction conditions employed. These aspects are particularly convenient when comparing such competing reactions since it means that the ratio of their rate constants ($k_{C=O}/k_{C=S}$) is directly reflected by the ratio of their product yields, P_r ¹⁸:

$$k_{C=O}/k_{C=S} = \frac{[\text{amide}]}{[\text{acylthiourea}]} = P_r$$

Thus, for the Douglass and Dains synthesis, the final proportion of *N*-substituted amide and *N'*-acylthiourea is a direct measure of the extent to which amine substitution at the carbonyl carbon competes with amine addition at the thiocarbonyl carbon. Furthermore, by comparing P_r values from the combination of different acyl isothiocyanates and amines it becomes possible to establish which structure – activity relationships influence this competition.

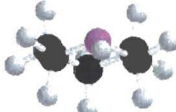
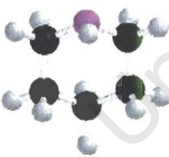
2.4.2 Secondary aliphatic amines: the link between shape and reactivity

In the context of this work, the reactions of the secondary aliphatic amines with butanoyl isothiocyanate produced one of the most important set of results (see table 2.1). The amide : acylthiourea product ratios (P_r) in table 2.1 show that the reactivity of these amines is sharply divided. Amines **a** to **c** (group 1) favoured the thiocarbonyl carbon as an addition site, while amines **d** to **g** (group 2) predominantly attacked the carbonyl carbon. This division is remarkable since secondary aliphatic amines are usually regarded as a group of closely related nucleophiles. Although the P_r values reflect close to a hundred fold change in reactivity, the

division does not correlate with any of the common properties usually associated with amines. With the exception of morpholine, secondary aliphatic amines are all regarded as strong bases. pK_a values for group 1 and group 2 amines overlap completely and fall within a narrow range between 10.7 and 11.3^{19,20}.

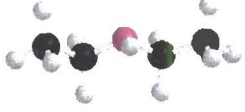
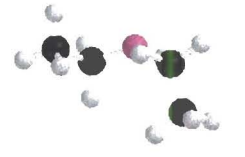
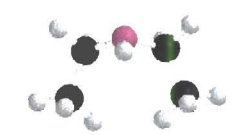
After considering several possibilities (see section 2.4.6), the contrasting regioselective behaviour of group 1 and group 2 amines was traced to one distinguishing steric feature. In heterocyclic amines like piperidine, the nitrogen nucleophile is situated at a molecular apex. Its lone pair of electrons is particularly exposed when the molecule adopts a conformation where the hydrogen on the nitrogen is in an axial position (conformer ii, table 2.4). (The alternative, where the hydrogen adopts the equatorial position (conformer i, table 2.4), is energetically only marginally less strained^{21,24}, so that population of the two states at 25°C is almost equivalent.).

Table 2.4 Strain energy differences between the conformers of piperidine²⁴. (All conformers are orientated with the N-H hydrogen toward the viewer and the lone pair of electrons vertically above the nitrogen atom.)

Conformers of Piperidine	Strain Energy	Energy Differences	Boltzmann Distribution
	E (kJ/mol)	ΔE (kJ/mol)	$(N_x/N_i)_{298K}$
i 	-	0.000	1.000
ii 	-	0.42	0.84

By comparison, the geometry of the dialkylamines is quite different. In its favoured, least strained conformation (conformer i, table 2.5), diethylamine essentially resembles a linear hydrocarbon chain^{22,23}. In this case the nitrogen nucleophile forms a relatively inconspicuous part of the carbon backbone, which itself is surrounded by a sheath of hydrogen atoms. The lone pair of the nitrogen is not nearly as exposed as in the axial conformer (ii, table 2.4) of piperidine. Although this chain is flexible and can adopt two geometries resembling piperidine, these conformers are sterically far more strained (conformers v and vi, table 2.5).

Table 2.5 Strain energy differences between the conformers of diethylamine ²⁴. (All conformers are orientated with the N-H hydrogen toward the viewer and the lone pair of electrons vertically above the nitrogen atom.)

Conformers of Diethylamine	Strain Energy	Energy Differences	Boltzmann Distribution
	E (kJ/mol)	ΔE (kJ/mol)	$(N_i/N_1)_{298K}$
i 	10.716	0.000	1.000
ii 	15.028	4.312	0.176
iii 	15.111	4.395	0.167
iv 	18.544	7.828	0.043
v 	25.367	14.651	0.003
vi 	26.330	15.614	0.002

The conformational strain energies for piperidine and diethylamine were determined in a conformational search using MM⁺ molecular mechanics calculations²⁴. This search, based on incremental rotation of the torsion angles around the skeletal N-C_α and N-C_β bonds, indicated that less than 0.2% of the diethylamine adopts the geometry of conformer vi where the nitrogen lone pair is almost as exposed as in the axial conformer (ii, table 2.4) of piperidine.

Although these differences are usually taken for granted and not specifically described in the literature, their effects are probably frequently overlooked. The shortened HN<R¹R² type notation that is usually used to represent secondary dialkylamines in mechanistic diagrams, obscures these differences. It creates the impression that the overall molecule is sharply bent rather than linear, and that the nitrogen nucleophile always forms an exposed bridging apex between the two alkyl substituents.

Compelling evidence that these particular steric differences were indeed of primary significance, was provided by the reactions of dimethylamine and *cis*-2,6-dimethylpiperidine (g and c, table 2.1). Dimethylamine (g, table 2.1) did not conform to the behaviour of the other dialkyl amines, and favoured the carbonyl carbon as a reaction site. As a consequence it had to be classified as a group 2 amine, along with the heterocyclic amines. This result, however, is not an anomalous one. The backbone of dimethylamine consists of two methyl carbons linked by the tetrahedral nitrogen. It is the only dialkyl amine where the nitrogen does actually form an exposed bridging apex between the alkyl groups. Its overall shape closely resembles the nitrogen-containing fragment of a heterocyclic amine (i.e. the -C6-N-C2- fragment of piperidine).

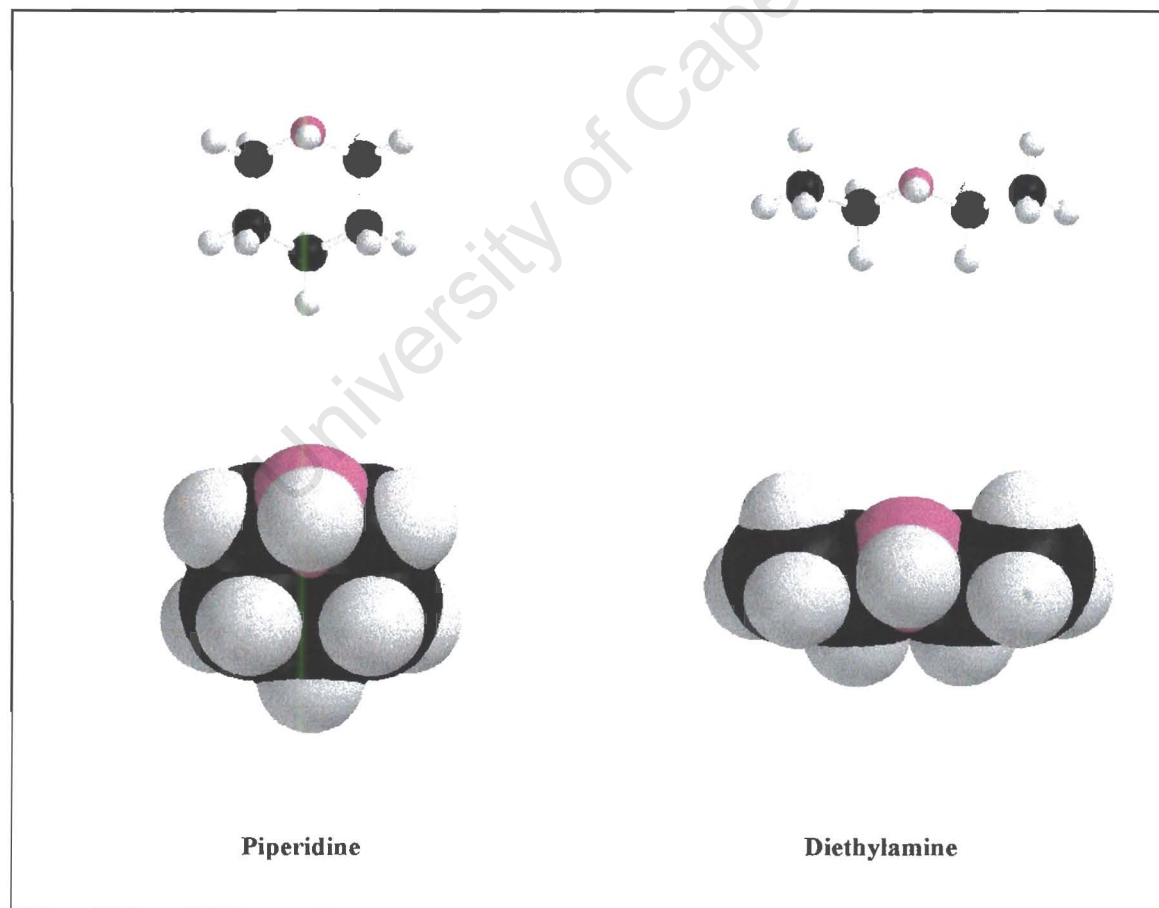
Another amine that also appears to behave abnormally is *cis*-2,6-dimethylpiperidine (c, table 2.1). Although heterocyclic, it favoured the pathway of addition at the thiocarbonyl carbon of butanoyl isothiocyanate and had to be grouped with the dialkylamines (group 1). Its behaviour is, however, also quite consistent with the observed trends. The two methyl groups of this amine can be regarded as β and β' substituents of the -C6-N-C2- fragment of the ring. In effect this fragment is extended into a linear chain that can be viewed as a rigidly held analogue of diethylamine. Thus, regioselective reaction of this heterocyclic amine at the thiocarbonyl carbon is to be expected.

The reactions of dimethylamine and *cis*-2,6-dimethylpiperidine, and the division between the group 1 and group 2 amines, highlight the important steric role of β methyl or methylene groups on reactivity of the amine nucleophile. The amines that favoured the carbonyl carbon as a reaction site (group 2), were either amines without β methyl or methylene groups (dimethyl amine, g), or amines where these groups were rigidly held by cyclisation, completely away from the side of the nitrogen lone pair (heterocyclic amines, d - f). The group 1 amines, all with 'free' β methyl or methylene groups, were restricted to reaction at the thiocarbonyl carbon.

The steric influences of these β groups can also be illustrated by comparing the ball and spoke, and the space-filled CPK models of diethylamine and piperidine in figure 2.6. These models were built up using the

minimised, least strained linear conformer of diethylamine and the minimised, axial N-H conformer of piperidine ²⁴. The ball and spoke model of diethylamine shows how one hydrogen atom on each β methyl group, protrudes above the C_{α} -N- $C_{\alpha'}$ apex (i.e. the β and β' hydrogens that are synclinal to the C_{α} -N and $C_{\alpha'}$ -N bonds). The corresponding space filled model shows how significantly these particular hydrogens add to the steric bulk contained in the immediate vicinity of the nitrogen nucleophile. To a degree they shield this nitrogen from an approaching electrophile and it is likely that some steric deformation will be required to allow an electrophilic centre to approach within bonding distance. Repulsion between these methyl groups and the substituents of the electrophile will certainly affect the conformation of the reaction intermediate. As far as the reactivity of this amine is concerned, these elements of steric strain represent additional activation energy and will influence the reaction rate with the electrophile ⁸. By comparison, the geometry of piperidine could be considered optimised for electrophilic attack. Since the β methylene groups are trapped in the ring, the nitrogen nucleophile is more accessible, and sterically easier to accommodate in the formation of an intermediate.

Figure 2.6 Graphic comparison of the the axial N-H conformer of piperidine and the lowest energy linear conformer of diethylamine using ball and spoke and space filled CPK models ²⁴



This type of steric influence from β methyl and methylene groups is typical of 'Front' or 'F' strain effects⁸. F strain is regarded as one of the principal factors affecting reactivity²⁶, and was first described by H.C. Brown²⁷. In terms of an addition reaction, it arises from the steric repulsion between the substituents of the two combining reagents. The magnitude of F strain depends on the size and shape of the substituents, and on the distance between them.

The F strain exerted by a wide variety of alkyl substituents has been compared by Beckhaus²⁶, who used molecular mechanics to calculate a series of steric repulsion or F strain constants ($\mathcal{S}_f$). With simple alkanes as models, he chose the methyl ($-\text{CH}_3$) and tertiary butyl ($-\text{C}(\text{CH}_3)_3$) alkyl groups to represent 'molecular cores' of high symmetry and to act as steric templates for the alkyl group (R) of interest. He determined the F strain constant ($\mathcal{S}_f$) by calculating the difference between the heats of formation of the two alkane derivatives, as follows:

$$\mathcal{S}_f(\text{R}) = \Delta H_f^\circ[\text{R}-\text{C}(\text{CH}_3)_3] - \Delta H_f^\circ[\text{R}-\text{CH}_3] + 8.87 \quad (10^4 \text{ J/mol})$$

The additive term in this equation appears on normalisation against $\mathcal{S}_f(\text{CH}_3)$. Some of these $\mathcal{S}_f$ values, are listed in table 2.6 below.

Table 2.6 Beckhaus' steric substituent constants for various alkyl groups²⁶

-R	$\mathcal{S}_f$ (10^4 J/mol)
$-\text{CH}_3$	0
$-\text{CH}_2\text{CH}_3$	0.86
$-\text{CH}_2\text{CH}_2\text{CH}_3$	0.89
$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	0.86
$-\text{CH}(\text{CH}_3)_2$	2.29
$-\text{C}(\text{CH}_3)_3$	3.82

Beckhaus' set of $\mathcal{S}_f$ constants is of particular interest, since it is a scale of steric parameters that accurately reflects the reactivities exhibited by dimethylamine, diethylamine and dibutylamine in table 2.1. The difference of 0.86×10^4 J/mol, between the $\mathcal{S}_f$ of methyl and ethyl R groups, is relatively large. It indicates the considerable steric effect of introducing a β methyl substituent on the α carbon, and in this work on butanoyl isothiocyanate – amine reactions, it correlates with the change in regioselectivity between

dimethyl- and diethylamine. The $\mathcal{S}_\text{F}$ values of ethyl and butyl groups, on the other hand, are identical. They are also very similar to the values listed for other linear alkyl groups. This confirms the dominant influence of the β group on F strain properties of linear alkyl substituents. Extending the chain beyond this group, has a negligible effect. In terms of the reactions with butanoyl isothiocyanate, $\mathcal{S}_\text{F}$ values dictate that dibutylamine and diethylamine should exhibit the same regioselective behaviour. This prediction is verified by the experimental result (table 2.1).

Beckhaus' studies were not the first to provide evidence of the relationship between β methyl groups and F strain. While examining the interaction of amine bases with borontrifluoride, H.C. Brown^{27,28} found that pyridine displaced 2,6-dimethylpyridine from the acid-base adduct even though the latter was a stronger base. Furthermore, with trimethylboron, a bulkier reference acid, 2,6-dimethylpiperidine exhibited no basic properties whatsoever. He attributed these results to the steric effects of the methyl groups on the ring and used them to illustrate the principle of F strain. Since pyridine and 2,6-dimethylpyridine are the aromatic analogues of piperidine (d) and *cis*-2,6-dimethylpiperidine (c), his examples are also of particular relevance to this work.

2.4.3 Steric and electronic influences on the reactivity of acyl isothiocyanates

As far as HSAB comparison of the electrophilic centres is concerned (see section 2.4.3), the results in table 2.1 show that, even in acyl isothiocyanates, the carbonyl carbon is the harder centre and hence the favoured site for amine attack. However, since addition at the thiocarbonyl carbon competes effectively when the nitrogen nucleophile of the amine is sterically hindered, the steric constraints associated with each centre must differ substantially. In this regard, it is important to recognise that a trigonal sp^2 carbonyl carbon is more congested than a linear sp thiocarbonyl carbon and thus less accommodating of steric bulk¹⁰. Amine attack at the former site leads to the formation of a crowded intermediate where the carbon and the amine nitrogen are both in tetrahedral form (section 2.4.3). By comparison, when an amine approaches the sp centre, steric congestion is less severe, and the trigonal zwitterion that is formed is not as crowded as the tetrahedral intermediate of the carbonyl carbon. In acyl isothiocyanates, these steric differences between the electrophilic centres are reflected by the regioselective behaviour of the amines. Those with exposed nitrogen nucleophiles were able to attack the more hindered carbonyl carbon, while only amines with the additional steric bulk of 'free' β groups, were more readily accommodated at the less congested thiocarbonyl carbon. As far as the Douglass and Dains synthesis of *N*-substituted *N'*-acylthioureas is concerned, this is a serious limitation.

Fortunately, however, with appropriate acyl substituents (R'), it seems possible to crowd the carbonyl carbon to such an extent, that the access of exposed nucleophiles is also restricted. In reactions with 2,2-dimethylpropanoyl isothiocyanate (table 2.2), even the unhindered heterocyclic amines and dimethylamine favoured the thiocarbonyl carbon as an addition site. This suggests that the bulky tertiary butyl group effectively reduces access to the carbonyl carbon. If the steric environment of the thiocarbonyl carbon is

relatively unaffected by this R' group, it may conceivably represent a more suitable addition site, even though it is the softer centre. These observations are quite consistent with the effects of F strain and it appears that bulky acyl R' groups protect the carbonyl carbon, in much the same way that bulky alkyl groups on the amine hindered reaction at the nitrogen nucleophile.

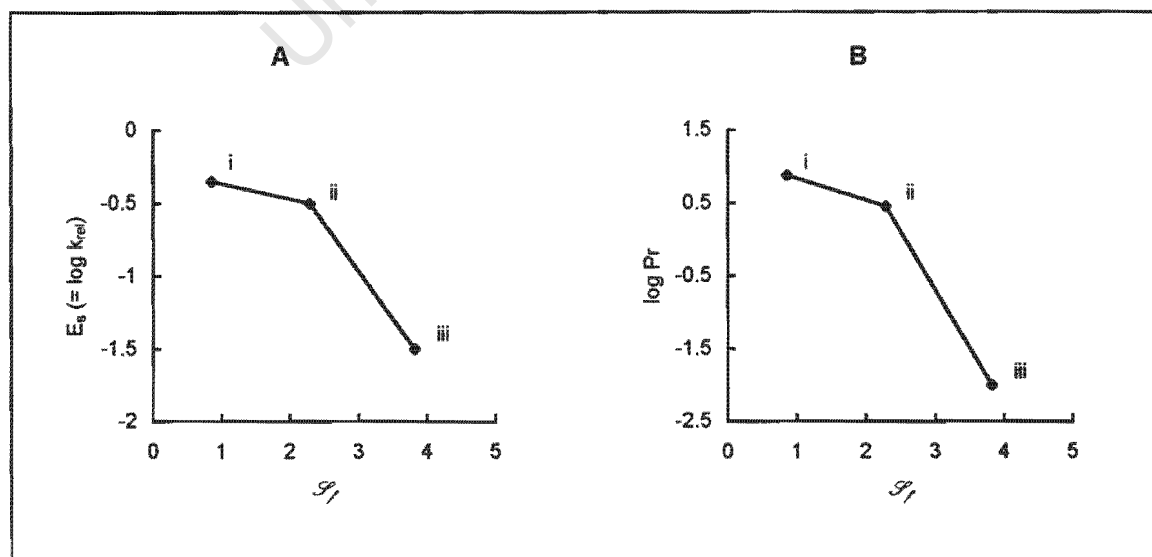
F strain effects from aliphatic acyl R' groups are known to be important influences in reactions at carbonyl carbon centres, and Beckhaus²⁶ showed that $\mathcal{S}_f$ constants are directly related to Taft's E_s ⁸ values. The latter are steric parameters that are traditionally determined from the rates of acid catalysed ester hydrolysis, and they essentially reflect the hindrance imposed by an R' group on a nucleophilic reaction at a carbonyl carbon. Since the electronic properties of aliphatic R' groups are believed to have little or no influence^{8,30,31} the E_s values are derived directly from the hydrolysis rate constants, k_{rel} , according to the equation

$$\log k_{rel} = \rho_s E_s$$

ρ_s is a steric susceptibility constant which for ester hydrolysis is set to 1.

The correlation of $\mathcal{S}_f$ and E_s parameters is of interest because it reveals some important parallels between the reactions of aliphatic esters²⁶ and acyl isothiocyanates. This can be seen in figure 2.7 where E_s and $\log P_r$ values (graph A and B) for the *n*-propyl, *iso*-propyl and tertiary butyl R' groups are plotted as functions of $\mathcal{S}_f$. The $\log P_r$ values are from the reactions of piperidine with butanoyl, 2-methylpropanoyl and 2,2-dimethylpropanoyl isothiocyanate (tables 2.1 and 2.2), and, except for a larger range, appear to duplicate the decreasing trend of the three E_s constants.

Figure 2.7 Comparing R' group F strain effects on acid catalysed hydrolysis of aliphatic esters²⁶ (graph A) and on reactions of piperidine with acyl isothiocyanates (graph B). R' groups include *n*-propyl (i), *iso*-propyl (ii) and *tert*-butyl (iii) groups

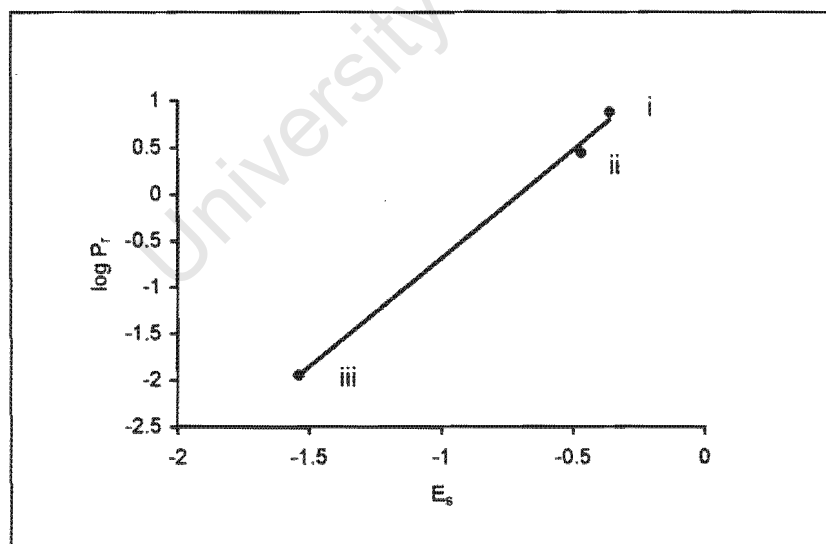


The comparison confirms that the reactivity of an acyl isothiocyanate is primarily influenced by the degree of F strain shielding from the acyl R' groups. Assuming that the correlation of such limited data is not coincidental, it also directs attention to the close association of E_s and $\log P_r$ values. This important relationship, which is near to linear for the three R' groups in question (see figure 2.8), further clarifies the role of the R' group, and the role of each electrophilic centre.

To begin with, the correlation between E_s and $\log P_r$ substantiates the premiss that the rate of amine addition at the thiocarbonyl carbon is not influenced by changing the acyl R' group. As in ester hydrolysis, the R' group only affects nucleophilic attack at the carbonyl carbon. (This aspect of the relationship is best understood by recalling that the product ratio P_r is equivalent to the ratio of the rate constants for the two competing reactions i.e. $P_r = k_{C=O}/k_{C=S}$ – see section 2.4.1). The link between E_s and $\log P_r$ also confirms that the R' group influence on the carbonyl carbon and hence on $k_{C=O}$ is of a steric nature.

From the linear correlation it is also evident that acyl isothiocyanate – amine reactions have a very low susceptibility to any electronic influences from the aliphatic R' groups. Although this result is not an unexpected one, it is reassuring that similar findings have been reported for uncatalysed aminolysis reactions of aliphatic *p*-nitrophenyl esters^{32,33}. Since these reactions also involve an amine nucleophile and proceed via the formation of a tetrahedral intermediate, they are reasonably similar to the reaction that takes place at the carbonyl carbon of an acyl isothiocyanate.

Figure 2.8 Graph of $\log P_r$ versus E_s for *n*-propyl (i), *iso*-propyl (ii) and *tert*-butyl (iii) R' groups



The slope of the graph in figure 2.8 indicates a steric susceptibility constant (ρ_s) of 2.3 (similar values were also calculated for dimethylamine and the other cyclic amines from their reactions with butanoyl and 2,2-dimethylpropanoyl isothiocyanate). This figure is very high when compared to the ρ_s of 0.99 that is reported for R' group variations in ester aminolysis^{32,33}. This comparison is, however, of limited value since the ester

aminolysis reactions were carried out using primary instead of secondary amines, and steric susceptibility also depends on the geometry of the nucleophile³³.

2.4.4 Reactions between primary aliphatic amines and acyl isothiocyanates

In many respects, *n*-propylamine and *n*-butylamine are similar nucleophiles to their secondary amine counterparts. Although their average pK_a values of around 10.6^{19,20} are marginally lower, they are also considered to be strongly basic, hard nucleophiles⁷. Unlike diethyl- and dibutylamine, however, they clearly favoured the carbonyl centres of butanoyl and decanoyl isothiocyanate (**IA** and **ID**, table 2.3) and produced only low yields of *N*-substituted acylthioureas ($\pm 10\%$). In terms of the F strain effects that have been discussed in this chapter, this is not surprising. Since the nitrogen nucleophile is at the end of a single alkyl chain, it is significantly more exposed. Even the bulky tertiary butyl group of 2,2-dimethylpropanoyl isothiocyanate was only partially effective in preventing these amines from reacting at the carbonyl carbon, and in these instances, the yields of acylthiourea showed just moderate improvements (25 – 30%). The reduced steric influence of the acyl *R'* group is also reflected in the ρ_s value of 0.51. This averaged figure was estimated by comparing the P_r ratios from the butanoyl and 2,2-dimethylpropanoyl isothiocyanate reactions, and is somewhat below the value of 0.99 reported for the ester aminolysis reactions^{32,33}. Despite the limited experimental data, it is tempting to suggest that the discrepancy would have been smaller if branched rather than linear primary amines had also been used in the acyl isothiocyanate reactions (the amine used in the ester aminolysis reactions was iso-propylamine).

2.4.5 The isothiocyanate – thiocyanate equilibrium and the effects of temperature: comments on the early findings of Doran, Dixon and Hawthorne^{3k-m,o}

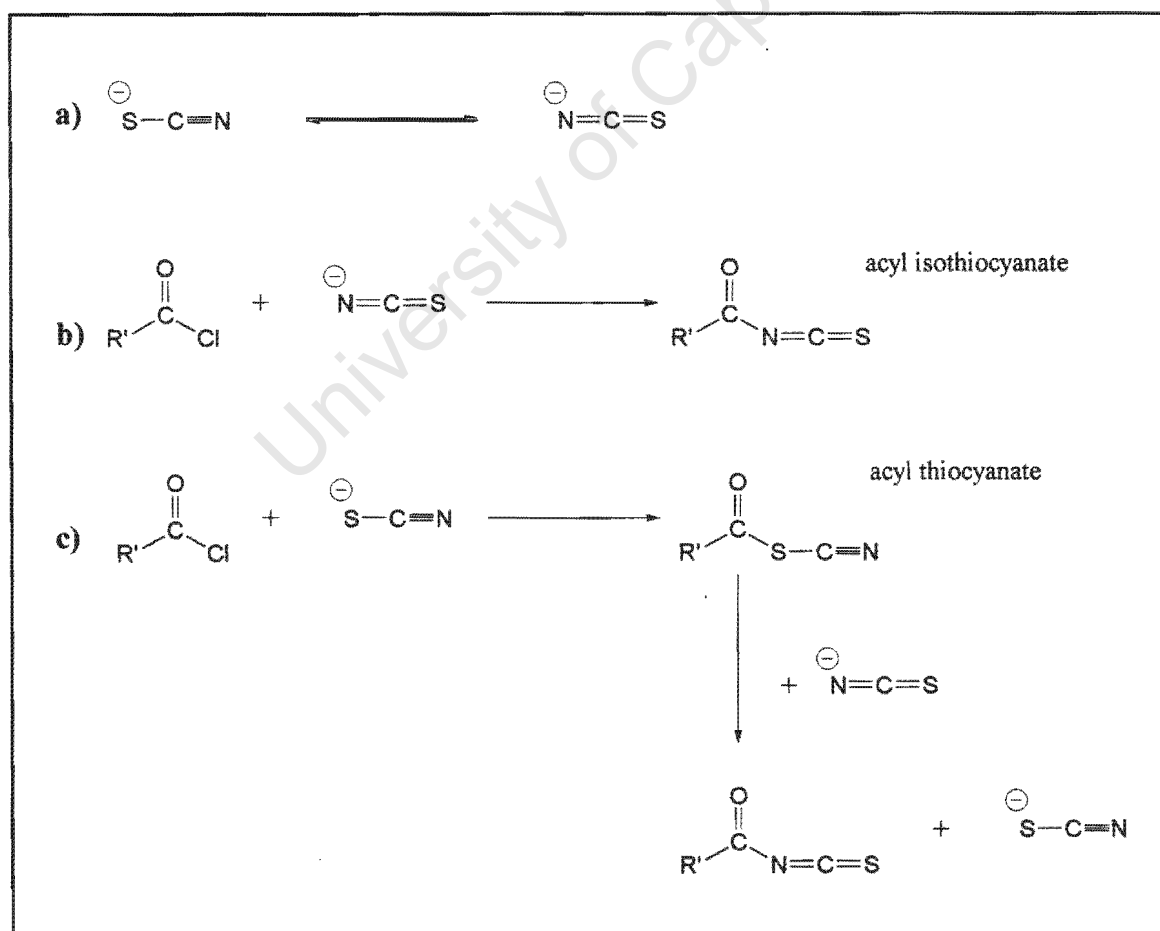
In acetone, thiocyanate ions (SCN^-) exist in equilibrium with isothiocyanate ions (NCS^-)². Since the sulphur and the nitrogen nucleophiles can react with a carbonyl carbon, it is not unreasonable to expect that both acyl thiocyanate and acyl isothiocyanate are formed when acyl halides are added to these solutions².

Doran, Dixon and Hawthorne^{3k,l} suggested that acyl thiocyanate and acyl isothiocyanate also co-existed in equilibrium, and that *N'*-acylthioureas were produced when amines reacted with the isothiocyanate form. According to them, substituted amides only arose when the amines reacted with the acyl thiocyanate. As evidence for the latter they cited the fact that thiocyanic acid (HSCN) was a by-product that only accompanied the process of amide formation. The substituents of the amine and the acyl thio- or isothiocyanate were important, they argued, because they influenced the position of the acyl thiocyanate – acyl isothiocyanate equilibrium. In their view it was this equilibrium that ultimately determined the relative proportions of *N'*-acylthiourea and amide produced from these reactions. Until fairly recently it is a view that has also been supported by others³⁴.

However, Doran, Dixon and Hawthorne's^{3k,l} proposals proved inadequate in many respects. They could not explain why the position of this equilibrium depended on the particular combination of amine and acyl isothiocyanate. Furthermore, attempts to isolate acyl thiocyanates proved unsuccessful. So-called equilibrium mixtures of acyl thiocyanate and acyl isothiocyanate were found to contain only the isothiocyanate. Dixon and Taylor^{3o} also came to realise that thiocyanic acid was not necessarily derived only from acyl thiocyanate. NCS ions, eliminated from acyl isothiocyanate by amine substitution, could readily isomerise to the ⁻SCN form.

Today, it is accepted that reactions of acyl halides with equilibrium mixtures of ⁻SCN and NCS ions produce only acyl isothiocyanates as end products^{2,5}. Although acyl thiocyanates are also formed initially, these are subsequently converted to acyl isothiocyanates as well. ⁻SCN is a better leaving group than NCS^{2,25}, and acyl thiocyanate will undergo further substitution with free NCS ions (see reaction c, figure 2.8). The NCS - ⁻SCN equilibrium ensures that the conversion of acyl thiocyanate to acyl isothiocyanate is allowed to proceed to completion

Figure 2.8 The thiocyanate – isothiocyanate equilibrium and its role in the synthesis of acyl isothiocyanates from acyl chlorides



In 1905 Doran and Dixon^{3k} reported on a chance observation from the reaction between aniline and acetyl isothiocyanate. At low temperatures (0°C) they found that the reaction produced 10% of the desired acylthiourea, with the dominant product being the amide. When the reaction was repeated at 50 – 60°C, this value increased to 50%. They found that even higher yields of acylthiourea (80 – 90%) could be obtained if the reaction was carried out in refluxing benzene (80°C). Hawthorne followed up these results with a more extensive study^{3m} that included reactions between propionyl isothiocyanate and aniline and acetyl isothiocyanate and *o*-toluidine. In both cases a similar trend was found: with increasing temperature the yield of acylthiourea was improved significantly. An exception was, however, also pointed out. In reactions with piperidine, temperature seemed to have no influence, as in these instances the amide remained the dominant product.

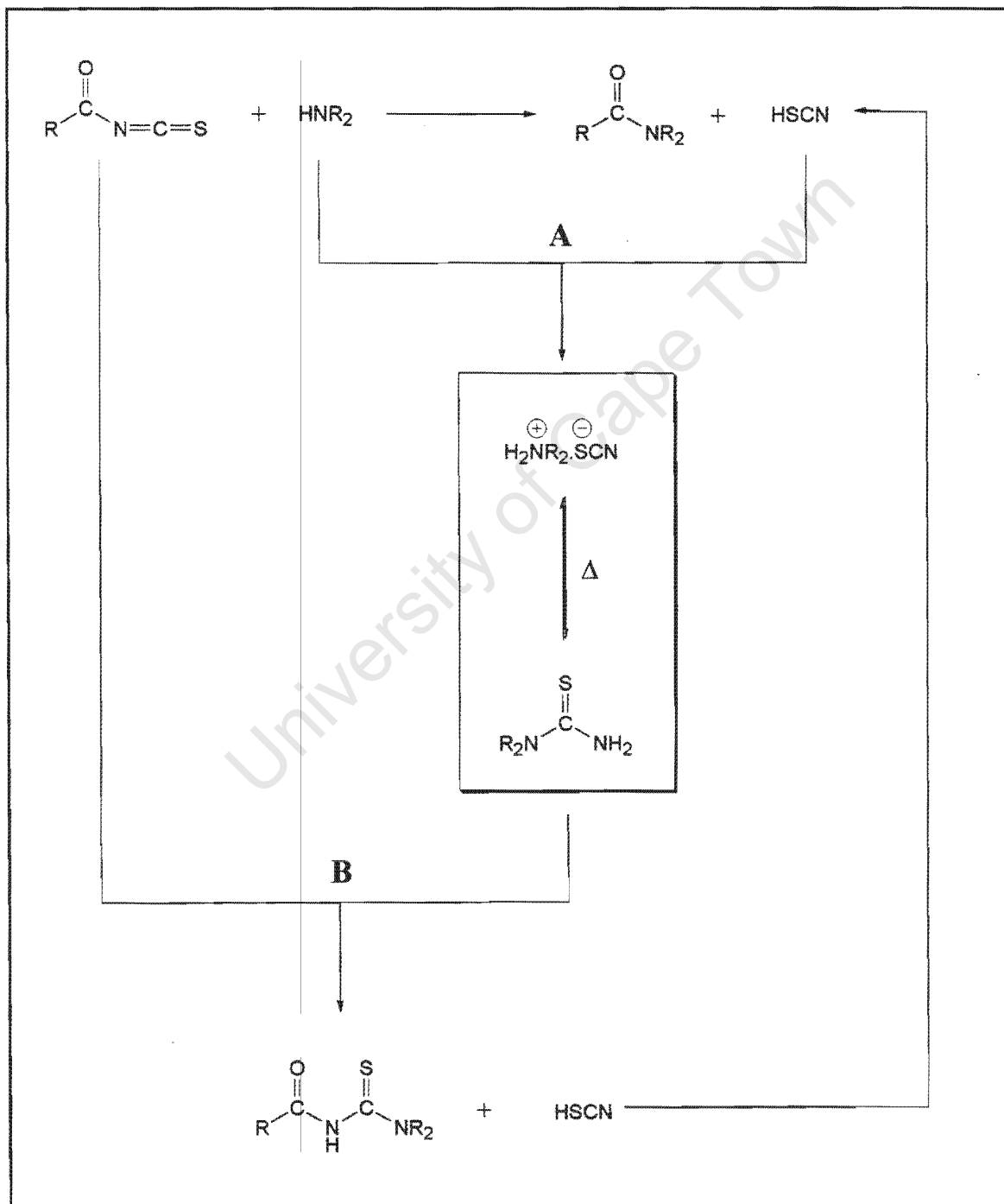
A detailed investigation into the effect of temperature was not carried out in the course of this work. This was due to the limited time available to complete this project, and also because the study was to be restricted to reactions in acetone (boiling point of 56°C), according to the more popular Douglass and Dains version of the synthesis. Since the range of amines used in this study included mainly smaller aliphatic examples, working at significantly elevated temperatures also proved impractical. However, the decision not to proceed with a detailed study was also based on some preliminary tests. Pyrrolidine and piperidine were added to butanoyl isothiocyanate in acetone, at 0°C and under refluxing conditions. In both sets of reactions, however, the amide : acylthiourea product ratios remained constant.

Although no other experiments were carried out to study this phenomenon, it is tempting to speculate on the reasons for Doran and Dixon's observations. There appear to be no obvious links between the effects of F strain described in section 2.4 and the influence of temperature, and it is difficult to understand why the regioselective behaviour of the amine should change significantly with temperature. However, when an amide is formed from the addition of an acyl isothiocyanate and an amine, there is a minor side reaction that is strongly dependent on temperature.

During the process of amide formation, the -NCS moiety of the acyl isothiocyanate is eliminated in the form of thiocyanic acid. This acid can trap any free amine as an amine thiocyanate salt. Doran and Dixon^{3k} isolated this side product when amide formation was prevalent. Although this salt is readily soluble in acetone, it is only marginally soluble in benzene and toluene. Even at raised temperatures, it will exist as an insoluble melt in these solvents (see chapter 4). Temperature is important, however, because amine thiocyanate salts can isomerise to simple *N*-substituted thioureas³⁵ in an equilibrium process that is strongly temperature-dependent. Apart from being more soluble in benzene and toluene, these thioureas are strong nucleophiles⁷. When added directly to acyl chlorides they will also form *N*-substituted *N'*-acylthioureas³⁶⁻³⁸. It seems plausible that these simple thioureas might also react with acyl isothiocyanates in a similar manner. If thiourea addition takes place at the carbonyl carbon, an *N*-substituted *N'*-acylthiourea is formed and the NCS moiety is eliminated. In Doran and Dixon's experiments, the yields of acylthiourea may thus have improved because the inert amine thiocyanate salt was increasingly converted to an active thiourea nucleophile at higher temperatures. It is also possible to explain why they failed to observe any changes for

the reactions of piperidine, since not all thiocyanate salts are easily converted. Unlike aniline thiocyanate, which is readily converted to phenyl thiourea^{3k,39}, the thermal conversion of piperidine thiocyanate is notoriously difficult [see chapter 4]. For this amine the thiocyanate salt – thiourea equilibrium position remains firmly on the side of the salt, even at higher temperatures.

Figure 2.9 Schematic representation of the proposed effect of temperature on the reactions of acyl isothiocyanates and amines in benzene and toluene

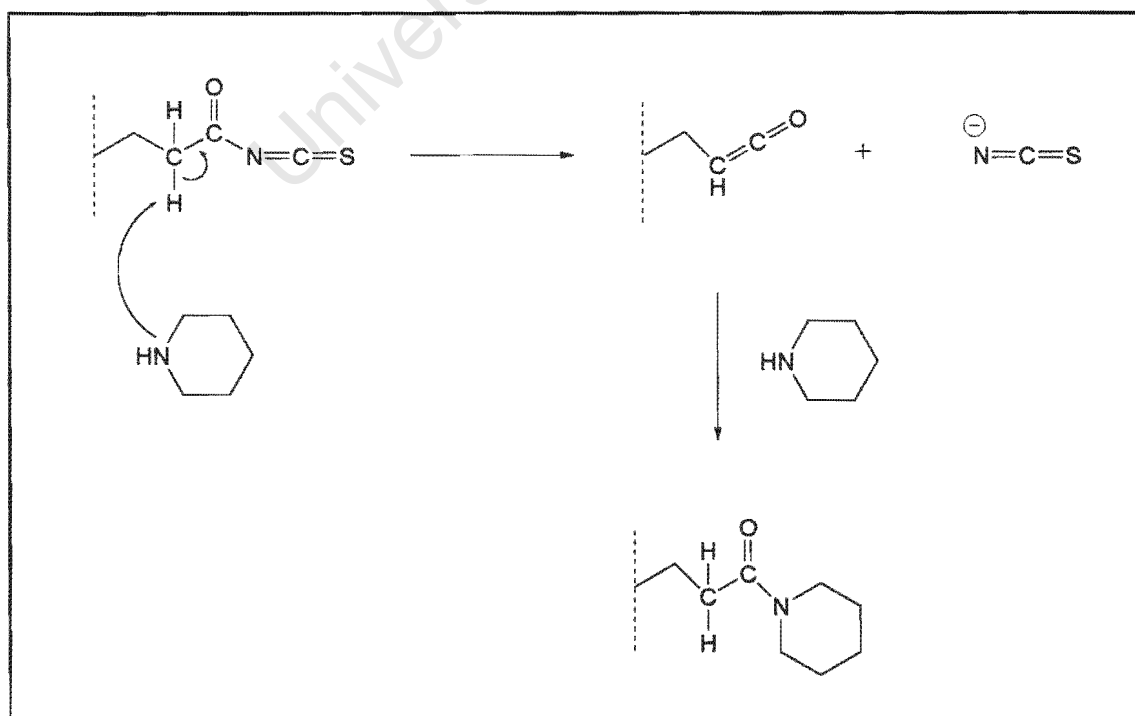


2.4.6 Amide formation via ketene intermediates

It is significant that substantial quantities of *N*-substituted amides were isolated from the reactions of butanoyl and 1-methylpropanoyl isothiocyanate (table 2.1) while in most reactions of 2,2-dimethylpropanoyl isothiocyanate, amides were virtually absent (table 2.2). As a feasible explanation it was considered that the amides could have been derived via a mechanism that requires formation of a ketene intermediate. Only butanoyl and 1-methylpropanoyl isothiocyanate have protons on the α carbons of their aliphatic side chains. Since these protons are rendered acidic by the proximity of the electron withdrawing carbonyl group^{10,41}, they might be susceptible to base attack from the amines. The loss of such a proton would give rise to a carbanion, which could, with elimination of the isothiocyanate group, stabilise to form a ketene. The carbonyl carbon of a ketene is an active electrophilic centre, quite susceptible to nucleophilic attack. Further addition of amine would thus give rise to the *N*-substituted amide, a process well documented in the literature⁴².

In terms of this proposal the reactions of 2,2-dimethylpropanoyl isothiocyanate would also not be considered anomalous. Amides would not be expected to form because the aliphatic substituent, in this case, is a tertiary butyl group. Since this has no protons on the α carbon, the prospect for ketene formation is eliminated. Nearly quantitative yields of 2,2-dimethylpropanoylthiourea are achieved because the amine is restricted to simple addition at the original acyl isothiocyanate. (The same argument could be used to explain why *N*-substituted *N'*-benzoylthioureas are so abundantly described in the literature. Ketene, and subsequent amide formation would be prevented by the absence of acidic protons on the α carbon of the benzene ring.)

Figure 2.10 Mechanism for amide formation via ketene intermediate



In part, the ketene-based proposal also appeared to clarify why piperidine and pyrrolidine produced amides when added to butanoyl isothiocyanate, while reactions with diethyl- and dibutylamine always gave *N*-substituted butanoylthioureas (table 2.1). Cyclic secondary amines are generally slightly more basic than their acyclic analogues⁸. Though small in aqueous solution, this difference appears more pronounced in aprotic organic solvents^{43,44} (In benzene, Log K_B values of piperidine and pyrrolidine are typically 0.5 to 1.0 above the corresponding values for the two dialkyl amines – see table 3.5, chapter 3). It seemed reasonable to suggest that as weaker bases, diethyl- and dibutylamine did not readily abstract protons from the acyl isothiocyanate, and that as a result, the process of amide formation did not compete significantly with the synthesis of the butanoylthiourea.

In spite of the results which appear to support this proposal, there is a significant body of evidence contained in tables 2.1, 2.2, and 2.3 to indicate that amide formation, in these reactions, does not necessarily proceed via ketene intermediates. This first emerged when the series of amines was extended to include morpholine (f), one of the weakest secondary amine bases⁴³. When added to butanoyl isothiocyanate it reacted to give morpholine substituted butyramide as the dominant product (table 2.1). In terms of the proposed ketene mechanism this result was unexpected. Morpholine, like diethyl- and dibutylamine, was considered too weakly basic to convert an acyl isothiocyanate to a ketene. Such unexpected results were also recorded for the reactions of propyl- and butylamine (table 2.3). Although these primary amines are listed as weaker bases than diethyl- and dibutylamine⁴³, they also reacted with butanoyl isothiocyanate to give *N*-substituted amides as dominant products. If these bases are indeed too weak to convert acyl isothiocyanates to ketenes, the process of amide formation must have occurred by another mechanism. Amides were also the major reaction products when propyl- and butylamine were added to 2,2-dimethylpropyl isothiocyanate (table 2.3). Since this isothiocyanate cannot be converted to a ketene by the action of an amine base, the outcome is a clear indication that a ketene is not a necessary intermediate when acyl isothiocyanates and amines combine to form amides.

2.5 Concluding Remarks

To end this chapter it is appropriate to summarise the most important conclusions from the results outlined above:

Reactions between acyl isothiocyanates and aliphatic amines give rise to *N*-substituted amides and *N*-substituted *N'*-acylthioureas because acyl isothiocyanates possess two active electrophilic centres: a carbonyl carbon and a thiocarbonyl carbon. Nucleophilic attack by the amine at the former will lead to substitution of the isothiocyanate moiety and formation of the amide. Addition of the amine at the latter site produces the *N*-substituted acylthiourea.

Of the two centres, the carbonyl carbon is the favoured site for nucleophilic attack of primary and secondary aliphatic amines. Although this may appear to be a severe drawback as far as the synthesis of *N*-substituted-

N'-acylthiourea ligands is concerned, it is fortunate that reactions at this site are extremely sensitive to steric effects. It is therefore possible to significantly alter the regioselectivity of the reaction. More specifically, by selecting either acyl isothiocyanates with bulky acyl substituents, or moderately bulky amines, it is possible to reduce the rate of nucleophilic attack at the carbonyl carbon to such a degree, that addition at the thiocarbonyl carbon becomes the dominant process.

2.6 Experimental Procedures and Characterisation

2.6.1 Synthesis and separation of *N*-substituted *N'*-acylthioureas and *N*-substituted amides

Only newly purchased commercially available reagents were used for this work. All acyl chlorides were at least of 98% purity and were used without additional purification. Amines, also of at least 98% purity, were first stirred over calcium hydride for 24 hours and distilled under nitrogen before use. Analytical grade potassium thiocyanate was thoroughly dried in a heated vacuum pistol. The acetone solvent was also of analytical grade purity. It was heated to reflux over potassium carbonate and type 4Å Linde molecular sieves and was only distilled immediately prior to use. Particular care was taken to avoid unnecessary exposure of any of the reagents to air and the title compounds were all synthesized under nitrogen.

Acyl chloride (0.03 mol) was dissolved in anhydrous acetone (75 ml) and added dropwise to a solution of potassium thiocyanate (0.03 mol) in anhydrous acetone (75 ml). This reaction mixture was heated to reflux for 45 minutes to ensure complete formation of the acyl isothiocyanate. It was then allowed to cool to room temperature (20 – 25°C). The amine (0.03 mol), also dissolved in anhydrous acetone (75 ml), was added at a drop-wise rate over a period of ten minutes. After addition, the reaction mixture was left to stir at room temperature for a further ten minutes. Following this, it was heated to reflux again for an hour to complete the reaction.* After cooling, the reaction mixture was poured into 75 ml of distilled water and left to stand to allow evaporation of the acetone.

Reactions that gave single product crystalline materials in excess of 90% of the theoretical *N*-substituted *N'*-acylthiourea yield were treated as follows: The crystals were filtered, dried and recrystallised from acetone – water or ethanol – water mixtures. In these instances, no attempt was made to isolate and characterise amide side-product from the aqueous filtrate.

Reactions that did not give single product crystalline materials, or where the product amount did not exceed 90% of the expected acylthiourea yield were treated as follows: Reaction precipitates were filtered and dried under high vacuum, and then re-dissolved in chloroform. Dissolved products still present in the aqueous filtrate were extracted with chloroform and then added to the re-dissolved precipitate. The combined reaction products were then separated by column chromatography, using Silica Gel 60 as stationary phase (50g / g of product). As eluent a chloroform or methylene chloride solution with 0 – 10% acetone (by volume) was used.

* This process was modified for dimethylamine which is a gas at room temperature. A two-fold excess (0.06 mol) was slowly bubbled into the acyl isothiocyanate solution over a period of 60 minutes. The mixture was then left to stir at room temperature for a further two hours under a positive pressure of nitrogen.

2.6.2 Characterisation of *N*-substituted *N'*-acylthioureas and *N*-substituted amides

All melting points were determined on a Reichert-Jung thermovar attached to a DP-4 digital thermometer and are uncorrected. Elemental analysis for % C, H, N and S were performed on a Fisons Elemental Analyser EA 1108. ^1H and ^{13}C NMR spectra were recorded at 25°C in CDCl_3 using 5 mm tubes and a Varian VXR-200 Fourier transform spectrometer operating at 200 and 50.32 MHz. ^1H and ^{13}C chemical shifts are referred to the central line of the solvent resonance relative to tetramethylsilane and are estimated to be accurate to ± 0.05 ppm. Mass spectra were recorded for certain compounds on a VG Micromass 16F mass spectrometer.

N,N-diethyl-*N'*-butanoylthiourea (IIAa – table 2.1): 85.7% yield, oil, Calculated for $\text{C}_9\text{H}_{18}\text{N}_2\text{OS}$: C, 53.41; H, 8.98; N, 13.85; S, 15.85, Found: C, 53.07; H, 8.91; N, 13.85; S, 15.93, NMR $\delta(^1\text{H})$: 0.94 (t, 3H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 1.26 (t, 6H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.66 (m, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 2.31 (t, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 3.45 + 3.90 (br q + br q, 2H + 2H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 8.43 (br s, 1H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 11.63, 13.03, 18.55, 38.71, 47.66, 170.05, 179.14.

N,N-diethylbutyramide (IIIAa – table 2.1): 7.9% yield, oil, Calculated for $\text{C}_8\text{H}_{17}\text{NO}$: C, 67.07; H, 11.98; N, 9.78, Found: C, 67.32; H, 11.62; N, 10.05, NMR $\delta(^1\text{H})$: 0.93 (t, 3H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 1.07 + 1.14 (t + t, 3H + 3H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.63 (m, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 2.24 (t, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 3.27 + 3.33 (q + q, 2H + 2H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), $\delta(^{13}\text{C})$: 12.41, 13.89, 18.80, 34.97, 39.95, 41.89, 172.14.

N,N-dibutyl-*N'*-butanoylthiourea (IIAb – table 2.1): 86.4% yield, mp 24°C, Calculated for $\text{C}_{13}\text{H}_{26}\text{N}_2\text{OS}$: C, 60.40; H, 10.16; N, 10.84; S, 12.41, Found: C, 60.61; H, 10.49; N, 10.86; S, 12.16, NMR $\delta(^1\text{H})$: 0.93 (unres m, 9H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.31 (m, 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.66 (unres m, 6H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 2.30 (t, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 3.43 + 3.89 (br t + br t, 2H + 2H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 8.18 (s, 1H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 13.66, 18.55, 19.99, 28.44, 29.97, 38.74, 53.04, 169.77, 179.54.

N,N-dibutylbutyramide (IIIAb – table 2.1): 9.3% yield, oil, Calculated for $\text{C}_{12}\text{H}_{25}\text{NO}$: C, 72.28; H, 12.66; N, 7.03, Found: C, 71.13; H, 13.28; N, 7.52, NMR $\delta(^1\text{H})$: 0.91 (unres m, 9H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.28 (m, 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.49 (m, 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.64 (m, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 2.24 (t, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 3.18 + 3.28 (t + t, 2H + 2H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), $\delta(^{13}\text{C})$: 13.83, 18.85, 20.07, 20.23, 29.92, 31.25, 35.02, 45.55, 47.68, 172.45.

N-(*cis*-2,6-dimethylpiperidyl)-*N'*-butanoylthiourea (IIAc – table 2.1): 89.2% yield, mp 65 – 67°C, Calculated for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{OS}$: C, 59.45; H, 9.17; N, 11.56; S, 13.23, Found: C, 59.58; H, 8.90; N, 11.77; S, 13.19, NMR $\delta(^1\text{H})$: 0.96 (t, 3H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 1.20 – 1.90 (br unres m, 12H, $-\text{N}(\text{CH}(\text{CH}_3)\text{CH}_2)_2$), 1.64 (m, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 2.30 (t, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 4.38 + 5.10

(br m + br m, 1H + 1H, -N<(CH(CH₃)CH₂)₂>CH₂), 8.15 (br s, 1H, >N'H), $\delta(^{13}\text{C})$: 13.44, 13.58, 18.54, 18.79, 20.81, 29.41, 30.07, 38.78, 54.41, 169.83, 179.23.

***N*-piperidyl-*N'*-butanoylthiourea (IIAd – table 2.1):** 8.5% yield, mp 97°C, Calculated for C₁₀H₁₈N₂OS: C, 56.02; H, 8.48; N, 13.07; S, 14.96, Found: C, 56.05; H, 8.64; N, 13.05; S, 14.64, NMR $\delta(^1\text{H})$: 0.95 (t, 3H, CH₃CH₂CH₂C(O)-), 1.68 (unres m, 8H, CH₃CH₂CH₂C(O)-, -N<(CH₂CH₂)₂>CH₂), 2.29 (t, 2H, CH₃CH₂CH₂C(O)-) 3.50 + 4.05 (br t + br t, 2H + 2H, -N<(CH₂CH₂)₂>CH₂), 8.46 (s, 1H, >N'H), $\delta(^{13}\text{C})$: 13.64, 18.50, 23.85, 25.53, 38.76, 52.87, 169.12, 177.91.

***N*-piperidylbutyramide (IIIAd – table 2.1):** 64.4% yield, oil, Calculated for C₉H₁₇NO: C, 69.61; H, 11.06; N, 9.02, Found: C, 69.03; H, 11.15; N, 8.76, NMR $\delta(^1\text{H})$: 0.93 (t, 3H, CH₃CH₂CH₂C(O)-), 1.57 (unres m, 8H, CH₃CH₂CH₂C(O)-, -N<(CH₂CH₂)₂>CH₂), 2.26 (t, 2H, CH₃CH₂CH₂C(O)-) 3.36 + 3.51 (t + t, 2H + 2H, -N<(CH₂CH₂)₂>CH₂), $\delta(^{13}\text{C})$: 13.99, 18.83, 24.54, 25.56, 26.53, 35.34, 42.54, 46.67, 171.32.

***N*-pyrrolidyl-*N'*-butanoylthiourea (IIAe – table 2.1):** 3.6% yield, mp 55 – 58°C, Calculated for C₉H₁₆N₂OS: C, 53.95; H, 8.07; N, 13.99; S, 16.01, Found: C, 53.70; H, 8.07; N, 14.45; S, 16.55, NMR $\delta(^1\text{H})$: 0.95 (t, 3H, CH₃CH₂CH₂C(O)-), 1.67 (m, 2H, CH₃CH₂CH₂C(O)-), 1.97 (m, 4H, -N<(CH₂CH₂)₂), 2.32 (t, 2H, CH₃CH₂CH₂C(O)-) 3.60 + 3.80 (t + t, 2H + 2H, -N<(CH₂CH₂)₂), 8.60 (s, 1H, >N'H), $\delta(^{13}\text{C})$: 13.60, 18.65, 24.57, 26.15, 38.68, 52.81, 54.31, 169.54, 176.24.

***N*-pyrrolidylbutyramide (IIIAe – table 2.1):** 68.9% yield, oil, Calculated for C₈H₁₅NO·H₂O: C, 60.32; H, 10.78; N, 8.80, Found: C, 61.31; H, 10.99; N, 9.52, NMR $\delta(^1\text{H})$: 0.94 (t, 3H, CH₃CH₂CH₂C(O)-), 1.65 (m, 2H, CH₃CH₂CH₂C(O)-), 1.87 (m, 4H, -N<(CH₂CH₂)₂), 2.22 (t, 2H, CH₃CH₂CH₂C(O)-), 3.39 + 3.43 (t + t, 2H + 2H, -N<(CH₂CH₂)₂), $\delta(^{13}\text{C})$: 13.92, 18.25, 24.30, 26.02, 36.64, 45.45, 46.52, 171.65, *m/z*: 141 (calc for C₈H₁₅NO: 141.24).

***N*-morpholino-*N'*-butanoylthiourea (IIAf – table 2.1):** 17.8% yield, mp 105 – 107°C, Calculated for C₉H₁₆N₂O₂S: C, 49.96; H, 7.47; N, 12.95; S, 14.82, Found: C, 50.05; H, 7.63; N, 12.98; S, 14.56, NMR $\delta(^1\text{H})$: 0.95 (t, 3H, CH₃CH₂CH₂C(O)-), 1.67 (m, 2H, CH₃CH₂CH₂C(O)-), 2.30 (t, 2H, CH₃CH₂CH₂C(O)-) 3.60 + 4.05 (br unres t + br unres t, 2H + 2H, -N<(CH₂CH₂)₂>O), 3.77 (unres t, 4H, -N<(CH₂CH₂)₂>O), 8.47 (s, 1H, >N'H), $\delta(^{13}\text{C})$: 13.62, 18.45, 38.78, 52.09, 66.19, 169.16, 178.91.

***N*-morpholinobutyramide (IIIAf – table 2.1):** 76.1% yield, oil, Calculated for C₈H₁₅NO₂: C, 61.10; H, 9.63; N, 8.91, Found: C, 61.42; H, 9.68; N, 8.92, NMR $\delta(^1\text{H})$: 0.94 (t, 3H, CH₃CH₂CH₂C(O)-), 1.64 (m, 2H, CH₃CH₂CH₂C(O)-), 2.27 (t, 2H, CH₃CH₂CH₂C(O)-) 3.43 (t, 2H, -N<(CH₂CH₂)₂>O), 3.62 (unres m, 6H, -N<(CH₂CH₂)₂>O), $\delta(^{13}\text{C})$: 13.89, 18.60, 34.95, 41.80, 45.99, 66.63, 66.89, 171.70.

***N,N*-dimethyl-*N'*-butanoylthiourea (IIAg – table 2.1):** 10.7% yield, oil, Calculated for C₇H₁₄N₂OS: C, 48.23; H, 8.11; N, 16.08; S, 18.40, Found: C, 47.96; H, 8.34; N, 16.05; S, 18.28, NMR $\delta(^1\text{H})$: 0.95 (t, 3H,

$\text{CH}_3\text{CH}_2\text{CH}_2\text{C(O)-}$), 1.68 (m, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C(O)-}$), 2.29 (t, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C(O)-}$), 3.14 + 3.40 (s + s, 6H, $-\text{N}(\text{CH}_3)_2$), 8.55 (s, 1H, $>\text{N'H}$), $\delta(^{13}\text{C})$: 13.62, 18.60, 43.16, 44.03, 169.59, 180.05.

***N,N*-dimethylbutyramide (III Ag – table 2.1):** 76.1% yield, oil, calculated for $\text{C}_6\text{H}_{13}\text{NO}\cdot\text{H}_2\text{O}$: C, 54.09; H, 11.37; N, 10.52, Found: C, 54.11; H, 11.61; N, 10.62, NMR $\delta(^1\text{H})$: 0.91 (t, 3H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C(O)-}$), 1.60 (m, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C(O)-}$), 2.23 (t, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C(O)-}$), 2.89 + 2.95 (s + s, 6H, $-\text{N}(\text{CH}_3)_2$), $\delta(^{13}\text{C})$: 13.88, 18.49, 35.23, 37.17, 173.05, m/z : 115 (calc for $\text{C}_6\text{H}_{13}\text{NO}$: 115.20).

***N,N*-dibutyl-*N'*-(2-methylpropanoyl)thiourea (IIBb – table 2.1):** 97.0% yield, mp 48 – 49°C, Calculated for $\text{C}_{13}\text{H}_{26}\text{N}_2\text{OS}$: C, 60.40; H, 10.16; N, 10.84; S, 12.41, Found: C, 60.31; H, 10.54; N, 10.99; S, 12.22, NMR $\delta(^1\text{H})$: 0.92 (unres t, 6H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.18 (d, 6H, $\text{CH}_3\text{CH}(\text{CH}_3)\text{C(O)-}$), 1.32 (m, 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.64 (m, 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 2.53 (m, 1H, $\text{CH}_3\text{CH}(\text{CH}_3)\text{C(O)-}$), 3.41 + 3.90 (t + t, 2H + 2H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 8.10 (s, 1H, $>\text{N'H}$), $\delta(^{13}\text{C})$: 13.72, 18.93, 20.00, 28.46, 29.97, 35.91, 52.98, 53.13, 173.28, 179.71.

***N*-piperidyl-*N'*-(2-methylpropanoyl)thiourea (IIBc – table 2.1):** 26.1% yield, (mp 83 – 85°C), Calculated for $\text{C}_{10}\text{H}_{18}\text{N}_2\text{OS}$: C, 56.02; H, 8.48; N, 13.07; S, 14.96, Found: C, 56.09; H, 8.65; N, 13.13; S, 14.81, NMR $\delta(^1\text{H})$: 1.19 (d, 6H, $\text{CH}_3\text{CH}(\text{CH}_3)\text{C(O)-}$), 1.69 (br unres m, 6H, $-\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 2.49 (m, 1H, $\text{CH}_3\text{CH}(\text{CH}_3)\text{C(O)-}$), 3.48 + 4.08 (unres t + unres t, 2H + 2H, $-\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 8.00 (s, 1H, $>\text{N'H}$), $\delta(^{13}\text{C})$: 18.96, 23.85, 25.30, 25.95, 36.12, 52.92, 172.67, 178.10.

***N*-piperidyl-2-methylpropanamide (IIIBc – table 2.1):** 73.1% yield, oil, Calculated for $\text{C}_9\text{H}_{17}\text{NO}$: C, 69.61; H, 11.40; N, 9.02, Found: C, 69.81; H, 11.21; N, 9.01, NMR $\delta(^1\text{H})$: 1.09 (d, 6H, $\text{CH}_3\text{CH}(\text{CH}_3)\text{C(O)-}$), 1.57 (unres m, 6H, $-\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 2.78 (m, 1H, $\text{CH}_3\text{CH}(\text{CH}_3)\text{C(O)-}$), 3.42 + 3.53 (t + t, 2H + 2H, $-\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), $\delta(^{13}\text{C})$: 19.45, 24.67, 25.62, 26.75, 29.99, 42.75, 46.41.

***N,N*-diethyl-*N'*-(2,2-dimethylpropanoyl)thiourea (IICa – table 2.2):** 98.0% yield, mp 90 – 91°C, Calculated for $\text{C}_{10}\text{H}_{20}\text{N}_2\text{OS}$: C, 55.50; H, 9.33; N, 12.95; S, 14.82, Found: C, 55.58; H, 9.09; N, 13.17; S, 15.06, NMR $\delta(^1\text{H})$: 1.23 (unres s + t, 15H, $(\text{CH}_3)_3\text{CC(O)-}$, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.44 + 3.93 (unres q + unres q, 2H + 2H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 7.65 (s, 1H, $>\text{N'H}$), $\delta(^{13}\text{C})$: 11.49, 13.14, 27.03, 47.56, 47.89, 174.72, 179.65.

***N,N*-dibutyl-*N'*-(2,2-dimethylpropanoyl)thiourea (IICb – table 2.2):** 97.6% yield, mp 84°C, Calculated for $\text{C}_{14}\text{H}_{28}\text{N}_2\text{O}$: C, 61.70; H, 10.38; N, 10.28; S, 11.77, Found: C, 61.56; H, 10.63; N, 10.31; S, 11.25, NMR $\delta(^1\text{H})$: 0.90 + 0.93 (t + t, 3H + 3H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.24 (s, 9H, $(\text{CH}_3)_3\text{CC(O)-}$), 1.33 (m, 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.64 (m, 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 3.39 + 3.90 (t + t, 2H + 2H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 7.64 (s, 1H, $>\text{N'H}$), $\delta(^{13}\text{C})$: 13.68, 13.79, 27.05, 28.47, 30.00, 39.61, 52.88, 53.30, 174.52, 180.02.

***N*-piperidyl-*N'*-(2,2-dimethylpropanoyl)thiourea (IICd – table 2.2):** 96.1% yield, mp 90 – 92°C, Calculated for $\text{C}_{11}\text{H}_{20}\text{N}_2\text{OS}$: C, 57.84; H, 8.84; N, 12.27; S, 14.04, Found: C, 58.15; H, 9.09; N, 12.34; S,

13.88, NMR $\delta(^1\text{H})$: 1.24 (s, 9H, $(\text{CH}_3)_3\text{CC}(\text{O})-$), 1.68 (unres m, 6H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2 > \text{CH}_2$), 3.44 + 4.06 (unres t + unres t, 2H + 2H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2 > \text{CH}_2$), 7.81 (s, 1H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 23.83, 25.19, 26.01, 27.06, 52.87, 174.08, 178.49.

***N*-piperidyl-2,2-dimethylpropanamide (IIICd – table 2.2):** 1.1% yield, oil, Calculated for $\text{C}_{10}\text{H}_{19}\text{NO}$: C, 70.94; H, 11.33; N, 8.28, Found: C, 70.05; H, 11.82; N, 8.66, NMR $\delta(^1\text{H})$: 1.22 (s, 9H, $(\text{CH}_3)_3\text{CC}(\text{O})-$), 1.53 (m, 6H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2 > \text{CH}_2$), 3.51 (t, 4H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2 > \text{CH}_2$), $\delta(^{13}\text{C})$: 24.68, 26.12, 28.41, 38.62, 46.18, 176.05.

***N*-pyrrolidyl-*N'*-(2,2-dimethylpropanoyl)thiourea (IIICe – table 2.2):** 90.1% yield, mp 136°C, Calculated for $\text{C}_{10}\text{H}_{18}\text{N}_2\text{OS}$: C, 56.02; H, 8.48; N, 13.07; S, 14.96, Found: C, 56.02; H, 8.77; N, 13.25; S, 14.79, NMR $\delta(^1\text{H})$: 1.23 (s, 9H, $(\text{CH}_3)_3\text{CC}(\text{O})-$), 1.96 (m, 4H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2$), 3.54 + 3.80 (t + t, 2H + 2H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2$), 7.85 (br s, 1H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 24.59, 26.15, 39.62, 52.52, 54.43, 174.38, 176.66.

***N*-morpholino-*N'*-(2,2-dimethylpropanoyl)thiourea (IIICf – table 2.2):** 97.2% yield, mp 134 – 135°C (lit⁵: 136 – 137°C), Calculated for $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: C, 52.13; H, 7.89; N, 12.16; S, 13.92, Found: C, 52.04; H, 8.25; N, 12.25; S, 13.83, NMR $\delta(^1\text{H})$: 1.23 (s, 9H, $(\text{CH}_3)_3\text{CC}(\text{O})-$), 3.48 + 4.12 (unres t + unres t, 2H + 2H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2 > \text{O}$), 3.77 (t, 4H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2 > \text{O}$), 7.90 (s, 1H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 27.01, 39.70, 51.76, 52.26, 66.17, 174.19, 179.49.

***N,N*-dimethyl-*N'*-(2,2-dimethylpropanoyl)thiourea (IIICg – table 2.2):** 99.0% yield, mp 81 – 82°C (lit⁵: 78 – 79°C), Calculated for $\text{C}_8\text{H}_{16}\text{N}_2\text{OS}$: C, 51.02; H, 8.58; N, 14.88; S, 17.03, Found: C, 51.33; H, 8.94; N, 15.13; S, 17.01, NMR $\delta(^1\text{H})$: 1.24 (s, 9H, $(\text{CH}_3)_3\text{CC}(\text{O})-$), 3.11 + 3.41 (s + s, 3H + 3H, $-\text{N}(\text{CH}_3)_2$), 7.85 (br s, 1H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 27.04, 39.61, 42.90, 44.15, 174.36, 180.32.

***N*-propyl-*N'*-butanoylthiourea (IIAa – table 2.3):** 14.3% yield, mp 68°C, Calculated for $\text{C}_8\text{H}_{16}\text{N}_2\text{OS}$: C, 51.02; H, 8.58; N, 14.88; S, 17.03, Found: C, 51.68; H, 9.31; N, 15.00; S, 17.35, NMR $\delta(^1\text{H})$: 0.96 (m, 6H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, $-\text{NHCH}_2\text{CH}_2\text{CH}_3$), 1.67 (m, 4H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, $-\text{NHCH}_2\text{CH}_2\text{CH}_3$), 2.31 (t, 2H, $-\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 3.58 (m, 2H, $-\text{NHCH}_2\text{CH}_2\text{CH}_3$), 9.31 (s, 1H, $>\text{N}'\text{H}$), 10.60 (br s, 1H, $-\text{NHCH}_2\text{CH}_2\text{CH}_3$), $\delta(^{13}\text{C})$: 11.34, 13.45, 18.19, 21.45, 38.81, 47.19, 174.22, 179.65.

***N*-propylbutyramide (IIAa – table 2.3):** 74.9% yield, oil, Calculated for $\text{C}_7\text{H}_{15}\text{NO}$: C, 65.05; H, 11.72; N, 10.84, Found: C, 64.64; H, 12.14; N, 10.80, NMR $\delta(^1\text{H})$: 0.88 (m, 6H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, $-\text{NHCH}_2\text{CH}_2\text{CH}_3$), 1.47 (m, 2H, $-\text{NHCH}_2\text{CH}_2\text{CH}_3$), 1.61 (m, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 2.10 (t, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 3.15 (m, 2H, $-\text{NHCH}_2\text{CH}_2\text{CH}_3$), 5.85 (br s, 1H, $-\text{NHCH}_2\text{CH}_2\text{CH}_3$), $\delta(^{13}\text{C})$: 11.23, 13.63, 19.15, 22.78, 38.63, 41.06, 173.04.

***N*-butyl-*N'*-butanoylthiourea (IIAi – table 2.3):** 10.4% yield, mp 53 – 55°C, Calculated for $\text{C}_9\text{H}_{18}\text{N}_2\text{OS}$: C, 53.41; H, 8.98; N, 13.85; S, 15.85, Found: C, 53.27; H, 9.12; N, 13.74; S, 15.72, NMR $\delta(^1\text{H})$: 0.94 (m,

6H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C(O)-}$, $\text{-NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.39 (m, 2H, $\text{-NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.65 (m, 4H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C(O)-}$, $\text{-NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.30 (t, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C(O)-}$), 3.62 (m, 2H, $\text{-NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 9.20 (s, 1H, $>\text{N'H}$), 10.58 (br s, 1H, $\text{-NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), $\delta(^{13}\text{C})$: 13.47, 13.63, 18.20, 20.06, 30.18, 38.86, 45.30, 174.14, 179.58.

***N*-butylbutyramide (IIIAi – table 2.3):** 64.0% yield, oil, Calculated for $\text{C}_8\text{H}_{17}\text{NO}$: C, 67.07; H, 11.99; N, 9.78, Found: C, 66.21; H, 12.50; N, 9.77, NMR $\delta(^1\text{H})$: 0.89 (m, 6H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C(O)-}$, $\text{-NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.32 (m, 2H, $\text{-NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.43 (m, 2H, $\text{-NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.62 (m, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C(O)-}$), 2.11 (t, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C(O)-}$), 3.21 (m, 2H, $\text{-NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 5.70 (br s, 1H, $\text{-NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), $\delta(^{13}\text{C})$: 13.66, 19.17, 20.00, 31.68, 38.69, 39.12, 172.99.

***N*-propyl-*N'*-decanoylthiourea (IIDh – table 2.3):** 8.8% yield, mp 60°C, Calculated for $\text{C}_{14}\text{H}_{28}\text{N}_2\text{OS}$: C, 61.70; H, 10.38; N, 10.28, S, 11.77, Found: C, 61.79; H, 10.36; N, 10.39; S, 11.85, NMR $\delta(^1\text{H})$: 0.89 (t, 3H, $\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{CH}_2\text{C(O)-}$), 0.98 (t, 3H), 1.25 (unres m, 12H, $\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{CH}_2\text{C(O)-}$), 1.66 (unres m, 4H, $\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{CH}_2\text{C(O)-}$, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), 2.32 (t, 2H, $\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{CH}_2\text{C(O)-}$), 3.59 (m, 2H, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), 9.17 (s, 1H, $>\text{N'H}$), 10.60 (br s, 1H, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), $\delta(^{13}\text{C})$: 11.41, 14.07, 21.52, 22.63, 24.75, 28.99 – 29.33 (m), 31.81, 37.15, 47.28, 174.33, 179.71.

***N*-propyldecanamide (IIIDh – table 2.3):** 56.5% yield, mp 44°C, Calculated for $\text{C}_{13}\text{H}_{27}\text{NO}$: C, 73.16; H, 12.78; N, 6.56, Found: C, 72.00; H, 13.26; N, 7.13, NMR $\delta(^1\text{H})$: 0.87 (m, 6H, $\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{CH}_2\text{C(O)-}$, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), 1.24 (unres m, 12H, $\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{CH}_2\text{C(O)-}$), 1.51 (unres m, 4H, $\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{CH}_2\text{C(O)-}$, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), 2.14 (t, 2H, $\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{CH}_2\text{C(O)-}$), 3.19 (m, 2H, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), 5.62 (br s, 1H, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), $\delta(^{13}\text{C})$: 11.33, 14.05, 22.63, 22.90, 25.85, 29.24 – 29.43 (m), 31.83, 36.90, 41.14, 173.14.

***N*-propyl-*N'*-(2,2-dimethylpropanoyl)thiourea (IICh – table 2.3):** 30.2% yield, mp 41 – 43°C, Calculated for $\text{C}_9\text{H}_{18}\text{N}_2\text{OS}$: C, 53.41; H, 8.98; N, 13.85; S, 15.85, Found: C, 53.83; H, 9.04; N, 14.17; S, 16.08, NMR $\delta(^1\text{H})$: 0.98 (t, 3H, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), 1.24 (s, 9H, $(\text{CH}_3)_3\text{CC(O)-}$), 1.68 (m, 2H, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), 3.58 (m, 2H, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), 8.40 (s, 1H, $>\text{N'H}$), 10.61 (br s, 1H, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), $\delta(^{13}\text{C})$: 11.43, 21.47, 26.93, 39.81, 47.51, 179.16, 179.89.

***N*-propyl-2,2-dimethylpropanamide (IIICb – table 2.3):** 39.0% yield, mp 35 – 38°C, Calculated for $\text{C}_8\text{H}_{17}\text{NO}$: C, 67.07; H, 11.99; N, 9.78, Found: C, 67.11; H, 12.42; N, 9.95, NMR $\delta(^1\text{H})$: 0.89 (t, 3H, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), 1.17 (s, 9H, $(\text{CH}_3)_3\text{CC(O)-}$), 1.50 (m, 2H, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), 3.19 (m, 2H, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), 5.65 (br s, 1H, $\text{-NHCH}_2\text{CH}_2\text{CH}_3$), $\delta(^{13}\text{C})$: 11.25, 22.82, 27.59, 38.60, 41.16, 178.32.

***N*-butyl-*N'*-(2,2-dimethylpropanoyl)thiourea (IICi – table 2.3):** 25.3% yield, oil, Calculated for $\text{C}_{10}\text{H}_{20}\text{N}_2\text{OS}$: C, 55.50; H, 9.33; N, 12.95; S, 14.82, Found: C, 55.89; H, 9.66; N, 12.79; S, 14.65, NMR $\delta(^1\text{H})$: 0.93 (t, 3H, $\text{-NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.24 (s, 9H, $(\text{CH}_3)_3\text{CC(O)-}$), 1.39 (m, 2H, $\text{-NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$),

1.63 (m, 2H, -NHCH₂CH₂CH₂CH₃), 3.61 (m, 2H, -NHCH₂CH₂CH₂CH₃), 8.40 (s, 1H, >N'H), 10.58 (br s, 1H, -NHCH₂CH₂CH₂CH₃), $\delta(^{13}\text{C})$: 13.62, 20.08, 26.89, 30.14, 39.75, 45.53, 179.13, 179.78.

N-butyl-2,2-dimethylpropanamide (IIIc - table 2.3): 40.5% yield, oil, Calculated for C₉H₁₉NO: C, 68.72; H, 12.20; N, 8.91, Found: C, 68.02; H, 12.40; N, 9.05, NMR $\delta(^1\text{H})$: 0.89 (t, 3H, -NHCH₂CH₂CH₂CH₃), 1.16 (s, 9H, (CH₃)₃CC(O)-), 1.32 (m, 2H, -NHCH₂CH₂CH₂CH₃), 1.44 (m, 2H, -NHCH₂CH₂CH₂CH₃), 3.20 (m, 2H, -NHCH₂CH₂CH₂CH₃), 5.62 (br s, 1H, -NHCH₂CH₂CH₂CH₃), $\delta(^{13}\text{C})$: 13.70, 20.00, 27.55, 31.68, 38.55, 39.21, 178.27.

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CHAPTER 3

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Synthesis of *N*-substituted *N'*-aroylthioureas: Factors affecting the reaction between aroyl isothiocyanates and aliphatic amines

3.1 Introduction

In contrast to the synthesis of *N'*-acylthioureas, the Dixon¹, or Douglass and Dains procedure has been applied with considerable success to the synthesis of *N*-substituted *N'*-aroylthioureas. The combination of aroyl isothiocyanates and amines usually provides satisfactory yields of the target molecules. Although quantitative yields are rarely attained, it is not surprising that the amide side-reaction is seldom referred to in the literature. In part, however, the lack of concern with this potential interference might also be attributed to an early publication by Elmore and Ogle², and to a more recent kinetic study by Imrich *et al.*³. Elmore and Ogle² reported that amidic products were only formed when the amine nucleophile was dissociated. This required reaction solvents with an aqueous component and a suitably high pH. According to them, the reaction of benzoyl isothiocyanate and cyclohexylamine would only produce the substituted benzoylthiourea if it was carried out in anhydrous benzene. The absence of amidic products from reactions of cyclohexylamine, butylamine and glycine ethyl ester was also reported by Imrich *et al.*³. They added these nucleophiles to several *para*-substituted benzoyl isothiocyanates and concluded from spectrophotometric measurements of the crude reaction solutions that only benzoylthioureas were formed. The accuracy of this finding has to be questioned. Only on one occasion, namely from the combination of glycine ethyl ester and *p*-chlorobenzoyl isothiocyanate, were the products quantitatively isolated to verify the spectroscopic measurement. It is quite possible that small fractions of amidic side-products from the other reactions were overlooked by relying on the spectroscopic analysis.

From the work carried out in the course of this project there is little doubt that the reactions with benzoyl and *para*-substituted benzoyl isothiocyanates frequently produce minor amounts of *N*-substituted benzamides. Depending on the *para* substituent and on the amine used, there are occasions when this side-product may even dominate. This was first observed when piperidine was added to benzoyl isothiocyanate. The resultant product mixture contained a 45% yield of the piperidyl substituted benzamide while the desired *N*-piperidyl-*N'*-benzoylthiourea was the secondary component with a yield of 42%. The outcome was quite unexpected and the reaction was repeated on two further occasions, each time with a completely new set of reagents. However, in no instance did the yields of either component vary by more than 3% from the original values. An almost identical outcome was subsequently also communicated to the author from an independent source⁴. More careful scrutiny of some lesser known literature confirmed that amides have indeed been isolated from reactions with aroyl isothiocyanates in the past⁵⁻⁸. This was particularly the case when reagents like piperidine⁷, methyl- and dimethylamine⁸, and *p*-nitrobenzoyl isothiocyanate⁸ were used.

For the work described in this chapter, the qualitative study from chapter 2 was extended to reactions of aroyl isothiocyanates. That is, selected benzoyl isothiocyanates were added to a series of primary and secondary aliphatic amines and the products from these combinations quantitatively isolated and characterised. In addition, however, a brief computational investigation into the electrophilic properties of acyl and benzoyl isothiocyanates was also undertaken. This was done in collaboration with Dr. Achim Lienke ⁹ using the quantum chemical software Gaussian 94 ¹⁰. The data generated from this study is presented and compared to the experimental results at the end of the chapter.

3.2 Experimental Approach

The main aroyl isothiocyanates selected for these investigations were benzoyl isothiocyanate (**IE**) and a variety of *para*-substituted analogues. The latter were chosen to determine the influence of electronic (rather than steric) factors on the reactivity of the isothiocyanates. Included in this group were *p*-methoxybenzoyl (**IF**), *p*-chlorobenzoyl (**IG**), and *p*-nitrobenzoyl (**IH**) isothiocyanates, thus representing a progression from electron releasing substituents to electron withdrawing groups. On occasion *p*-heptoxybenzoyl (**IK**), *p*-tert-butylbenzoyl (**IL**), and the *meta* substituted nitrobenzoyl (**IJ**) isothiocyanates were used as well. The set of amines used in this study, was the same as the series used for the reactions with the acyl isothiocyanates (chapter 2). Again, this was done to ensure that at least two examples of secondary cyclic, secondary dialkyl, and primary alkyl amines were included in the group.

The experimental procedure was also based on the 'one pot' method of Douglass and Dains and details of the synthesis and product recovery are as described in sections 2.2 and 2.6. As before, every effort was made to use only fresh reagents. Reactions were carried out under nitrogen, and once again, particular care was taken to ensure that solvent and reagents were thoroughly dried immediately prior to use.

3.3 Results

As expected, benzoylthioureas were usually the major derivatives isolated from the benzoyl and *para* substituted benzoyl isothiocyanates. Although this trend was expected, yields were often found to be less than quantitative. In such cases, significant amounts of substituted benzamides were also recovered and could largely account for the balance of the starting materials used. Where nitrobenzoyl isothiocyanates (**IH**) or the cyclic amines, piperidine and pyrrolidine (**d**, **e**), were used as reagents, this trend was often reversed. In these instances, the benzamide products dominated while the benzoylthioureas fulfilled the role of side-products.

Results from all the reactions of the benzoyl and *para* substituted benzoyl isothiocyanate (**IE**) are summarised in tables 3.1a to 3.3 (for reactions that were repeated, average product yields are listed).

Table 3.1a Product yields from the reactions of benzoyl isothiocyanate with secondary and primary aliphatic amines

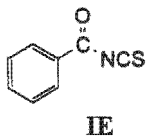
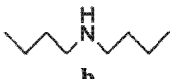
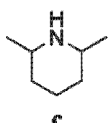
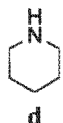
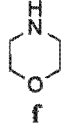
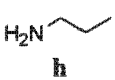
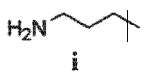
Aroyl isothiocyanate	Amine	Yield aroylthiourea (%)	Yield amide (%)	Product ratio P_r
$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NCS}$	$\text{HNR}_2 \text{ or } \text{HN}(\text{CH}_2)_n \text{ or } \text{H}_2\text{NR}$	$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}-\overset{\text{S}}{\parallel}{\text{C}}-\text{NR}_2$	$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NR}_2$	$\frac{\text{Yield III}}{\text{Yield II}}$
I		II	III	
 IE	 a	93.2	-	<0.10
	 b	95.8	-	<0.10
	 c	96.5	-	< 0.11
	 d	41.8	44.8	1.07
	 e	29.0	52.1	1.80
	 f	66.7	26.7	0.40
	 g	52.7	46.2	0.88
	 h	60.9	29.5	0.48
	 i	64.3	28.6	0.44

Table 3.1b Product yields from the reactions of *p*-nitrobenzoyl isothiocyanate with piperidine and *cis*-2,6-dimethylpiperidine

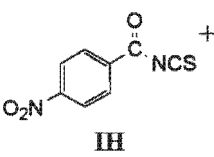
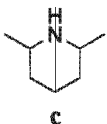
Aroyl isothiocyanate	Secondary amine	Yield aroylthiourea (%)	Yield amide (%)	Product ratio P_r
$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NCS}$	$\text{HNR}_2 \text{ or } \text{HN}(\text{CH}_2)_n$	$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}-\overset{\text{S}}{\parallel}{\text{C}}-\text{NR}_2$	$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NR}_2$	$\frac{\text{Yield III}}{\text{Yield II}}$
I		II	III	
 IH	 c	89	?	<0.12
	 d	17.9	73.3	4.09

Table 3.2 Product yields from the reactions of piperidine with benzoyl isothiocyanate, *para* substituted benzoyl isothiocyanates and *m*-nitrobenzoyl isothiocyanate

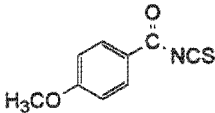
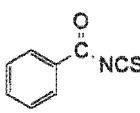
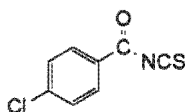
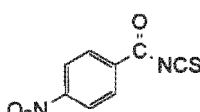
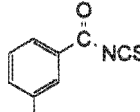
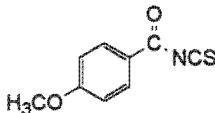
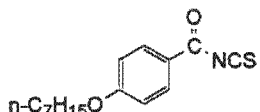
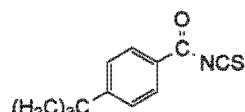
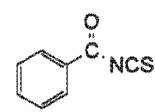
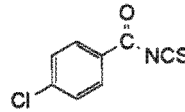
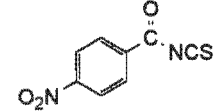
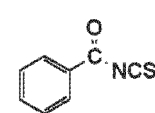
Aroyl isothiocyanate	Secondary amine	Yield aroylthiourea (%)	Yield amide (%)	Product ratio P_r
$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NCS}$	HNR_2 or $\text{HN}(\text{CH}_2)_n$	$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}-\overset{\text{S}}{\parallel}{\text{C}}-\text{NR}_2$	$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NR}_2$	$\frac{\text{Yield III}}{\text{Yield II}}$
I		II	III	
 IF		67.8	24.1	0.36
 IE		41.8	44.8	1.07
 IG	+ 	44.2	48.8	1.10
 IH		17.9	73.3	4.09
 IJ		21.0	71.6	3.41

Table 3.3 Product yields from the reactions of propylamine with benzoyl isothiocyanate and *para* substituted benzoyl isothiocyanates, and butylamine with benzoyl isothiocyanate

Aroyl isothiocyanate	Primary amine	Yield aroylthiourea (%)	Yield amide (%)	Product ratio P_r
$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NCS}$ I	H_2NR	$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}-\overset{\text{S}}{\parallel}{\text{C}}-\text{NHR}$ II	$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NHR}$ III	$\frac{\text{Yield III}}{\text{Yield II}}$
 IF		90.0	8.7	0.10
 IK		95.2	-	<0.05
 IL	+ $\text{H}_2\text{N}-\text{CH}_2\text{CH}_2\text{CH}_3$ h	72.8	19.0	0.26
 IE		60.9	29.5	0.48
 IG		66.9	23.4	0.35
 IH		27.4	51.4	1.88
 IE	+ $\text{H}_2\text{N}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ i	64.3	23.6	0.37

Results from all the reactions of benzoyl isothiocyanate (**IE**) appear in table 3.1a. In reaction with this reagent, the secondary amines other than pyrrolidine and piperidine, favoured the thiocarbonyl carbon as a reaction site, and predominantly reacted to form *N*-substituted *N'*-benzoylthioureas. Benzamide side-products were, however, also isolated in most cases. Similar results were recorded with the primary amines, propyl- and butylamine (**h**, **i**), as well. Pyrrolidine and piperidine (**d**, **e**), on the other hand, preferred to attack the carbonyl carbon of this isothiocyanate and produced greater yields of substituted benzamide and lower proportions of benzoylthiourea.

Yields from two reactions of *p*-nitrobenzoyl isothiocyanate (**IH**) are listed in table 3.1b. Products from the addition of *cis*-2,6-dimethylpiperidine (**c**) were unstable and decomposed on a silica gel column. However, elemental microanalysis, ^1H and ^{13}C NMR indicated that the crude reaction precipitate was the substituted *p*-nitrobenzoylthiourea (see section 3.6) and that it contained very little impurity. The yield of this compound was high and accounted for at least 85% of the reagents used. *p*-Nitrobenzamide from this reaction, was not isolated. With piperidine (**d**), *p*-nitrobenzoyl isothiocyanate gave a very low yield (<20%) of the substituted benzoylthiourea.

The effect of *para*-substituents on reactions of benzoyl isothiocyanates can be seen in tables 3.2 and 3.3. In reactions with piperidine and propylamine (**d**, **h**) it is clear that electron withdrawing substituents on the benzene ring tend to increase the extent of substituted benzamide formation. However, although this trend is evident with both amines, it is also noticeable that the proportion of benzamide side-product is consistently lower in the reactions of propylamine, the primary amine.

3.4 Discussion

In many respects the above results illustrate how similar aroyl isothiocyanates are to their acyl isothiocyanate counterparts. The carbonyl and thiocarbonyl carbons of aroyl isothiocyanates also actively compete with each other for an amine nucleophile. From the experimental data, there is no evidence to suggest that changing the aliphatic acyl substituent to an aromatic one in any way alters the mechanism or product of reaction at either electrophilic site. For aminolysis reactions, this is not unusual¹¹. Hence, amine attack at the carbonyl carbon of benzoyl isothiocyanates also leads to substitution of the isothiocyanate moiety and formation of the amidic product, while aroylthioureas are formed when amine addition takes place at the thiocarbonyl carbon.

Introducing an aromatic R' group does, however, have a marked effect on the reactivity of the carbonyl carbon. In acyl isothiocyanates with aliphatic R' groups, the carbonyl carbon was considerably more reactive towards amines than the thiocarbonyl carbon, and acylthiourea formation only dominated when steric factors hindered nucleophilic attack at the former site. With benzoyl isothiocyanates the competing reactions take place at more comparable rates. This is an advantage, because minor influences that would have been masked by large reactivity differences, have a more noticeable effect on the outcome of the

reaction. Although the results in tables 3.1a and 3.1b are also linked to the effects of F strain, there is ample evidence that other, more subtle influences can dictate benzamide – benzoylthiourea product ratios (P_r) as well. Apart from the obvious effects of the *para*-ring substituents, there are indications that P_r values are quite sensitive to small variations in the basicity of the amine nucleophile. This was found despite using a series of amines with a very narrow range of pK_a values^{12,13}. Another trend that does not reflect steric hindrance of any kind, is the consistent inclination of the primary amines to react at the thiocarbonyl carbon of benzoyl isothiocyanates. The significance of this is underlined by the fact that piperidine, a secondary and more bulky amine, never shows quite the same preference and reacts with more uniform distribution between the two electrophilic centres.

3.4.1 The role of steric effects on reactions of benzoyl isothiocyanates and aliphatic amines

There is little doubt, that the alkyl substituents of the secondary amines also play an important steric role in the reactions with benzoyl isothiocyanates. This is evident from the data listed in table 3.1a where it is again possible to divide the secondary amines into two groups, based on their F-strain properties and regioselective behaviour. Although the cyclic amines and dimethylamine produced substantially improved quantities of benzoylthioureas, benzamide fractions from these reactions ranged between 25 and 55%. This again distinguished them as a group from the dialkyl amines, which repeatedly produced close to quantitative yields of benzoylthiourea. Here too, the results of reactions with *cis*-2,6-dimethylpiperidine and dimethylamine serve to confirm the important steric influence of β methyl and methylene groups on the regioselectivity. The former, representing a rigid linear analogue of diethylamine, was restricted to addition at the thiocarbonyl carbon of benzoyl isothiocyanate, while the dimethylamine, without β groups, reacted with almost even distribution between the carbonyl and thiocarbonyl carbon.

The same F strain effects were also observed in reactions carried out with *p*-nitrobenzoyl isothiocyanate (table 3.1b). As if to confirm reports of its tendency to form amidic products⁸, this reagent and piperidine combined to produce the piperidyl-substituted *p*-nitrobenzamide in 73% yield. However, with the steric protection afforded by β methyl groups, the nitrogen nucleophile of 2,6-substituted piperidine was confined, as expected, to addition at the thiocarbonyl carbon of this aroyl isothiocyanate.

By comparison with the F strain effects of the amine substituents, the steric role of the phenyl ring of benzoyl isothiocyanates is a minor one. Unlike the tertiary butyl group of 2,2-dimethylpropanoyl isothiocyanate, this aroyl R' group does not provide an effective steric hindrance to nucleophilic attack at the carbonyl carbon. Evidence for this was also provided by the reactions of *meta*- and *para*-nitrobenzoyl isothiocyanates with piperidine (table 3.2), where in each case the benzamide yields exceeded 70%. Although the steric bulk of a benzene ring lies between that of an iso-propyl group and a tertiary butyl group¹⁴, these amide yields are as high as the amide yields isolated from the reactions of butanoyl isothiocyanate with unhindered secondary amines (see table 2.1, chapter 2). In aroyl-type compounds, the aromatic ring and the carbonyl group adopt a coplanar conformation to maximise the degree of conjugation

between them^{14,15}. With the aroyl isothiocyanates, this orientation ensures that steric hindrance from the ring is considerably reduced, since an amine nucleophile approaches perpendicularly to this plane in order to react at the carbonyl carbon^{14,16}.

3.4.2 Electronic influences on the reactivity of benzoyl isothiocyanates

Far more important, than any steric changes, are the electronic changes that are introduced by replacing an aliphatic R' group with a phenyl ring. In a targeted synthesis of *N*-substituted *N'*-aroylthioureas these influences contribute significantly to the success of the Douglass and Dains procedure. To understand this it is necessary to compare how the change to an aromatic R' substituent affects the competing carbonyl and thiocarbonyl centres.

As an unconjugated substituent, a phenyl ring is considered mildly electron withdrawing^{14,17,18}. However, because of the expected conjugation with the carbonyl moiety, such a direct comparison with alkyl groups is not appropriate. As an aroyl substituent, the phenyl ring has a deactivating rather than activating effect on the electrophilicity of the carbonyl carbon, even though conjugation ensures that steric hindrances are minimised. In this regard two aspects are important. Electron delocalisation from the phenyl ring will diminish the effect of the partial positive charge on the carbonyl carbon, and decrease its ability to attract the nitrogen nucleophile¹⁴. Conjugation between the carbonyl group and the phenyl ring also represents a stabilisation of the ground state aroyl isothiocyanate. This increases the activation energy required for nucleophilic addition, since conjugation is lost on formation of the tetrahedral intermediate^{15,18}. Experimentally, these deactivating influences are believed to account for the observation that benzoyl isothiocyanates are significantly less susceptible to hydrolysis than acyl isothiocyanates with aliphatic R' groups^{2,19,20}.

Detailed IR, UV and ¹³C NMR studies of isocyanates and isothiocyanates with aroyl or acyl substituents have shown that there is very little conjugative interaction between the carbonyl group and the iso(thio)cyanate moiety²⁰⁻²⁵. The C-N bond between these two groups has very little double bond character and the influence of the carbonyl group on the adjacent iso(thio)cyanate is thus primarily *inductively* electron withdrawing.

The lack of conjugation between the carbonyl and iso(thio)cyanate moieties is important, because it dictates that any electronic interaction between the iso(thio)cyanate and an R' group is also primarily of an inductive nature. However, because these groups are two bond lengths apart from each other, the interactions are considerably attenuated (inductive effects transmitted through σ bonds are known to decrease rapidly with distance^{17,26,27}). The diminished influence of R' on the iso(thio)cyanate moiety, compared to its effect on the carbonyl group, is quite evident from the spectroscopic studies. Benzoyl, and particularly acyl isocyanates, have been studied in considerable detail. R' group variations that caused ¹³C NMR shifts of 30 ppm or more for the carbonyl carbon resonance (140 – 180 ppm), did little to affect the

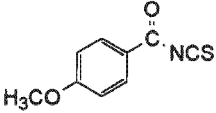
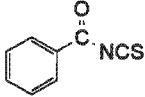
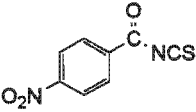
carbon signal of the isocyanate group, which remained confined to a very narrow range between 129 ppm and 131 ppm²³. Based on this spectroscopic evidence, it would also seem reasonable to assume that the change from an aliphatic R' group to an aromatic one, only has a marginal effect on the reactivity of the thiocarbonyl carbon. By far the more important contribution from an aromatic R' group, is its deactivating effect on the carbonyl carbon.

3.4.3 The effect of *para*-ring substituents on the reactivity of benzoyl isothiocyanates

Any uncertainties concerning the importance of electronic factors were dispelled when benzoyl isothiocyanates with *para*-substituents were added to piperidine and propylamine. From these reactions it became evident that competition between the carbonyl and thiocarbonyl carbon for the amine nucleophile also depended on the substituents of the phenyl ring. The results in table 3.2 and 3.3 show that proportions of benzamide products steadily increased as electron releasing substituents were systematically replaced by groups that were more electron withdrawing. Since *para*- and *meta*-substituents do not present any steric hindrance, and since both amine nucleophiles could be sterically accommodated at either electrophilic site, the observed trends reflect only electronic influences.

Unfortunately, the spectroscopic studies referred to in section 3.4.2²³⁻²⁵ did not include an investigation of *para*-substituent effects. However, a brief ¹³C NMR comparison of benzoyl, *p*-methoxybenzoyl, and *p*-nitrobenzoyl isothiocyanate appeared to confirm the expectation that *para*-substituent effects are far more pronounced at the carbonyl carbon (δ range = 161.1 to 151.6 ppm) than at the carbon of the isothiocyanate (δ range = 146.7 to 149.0 ppm).

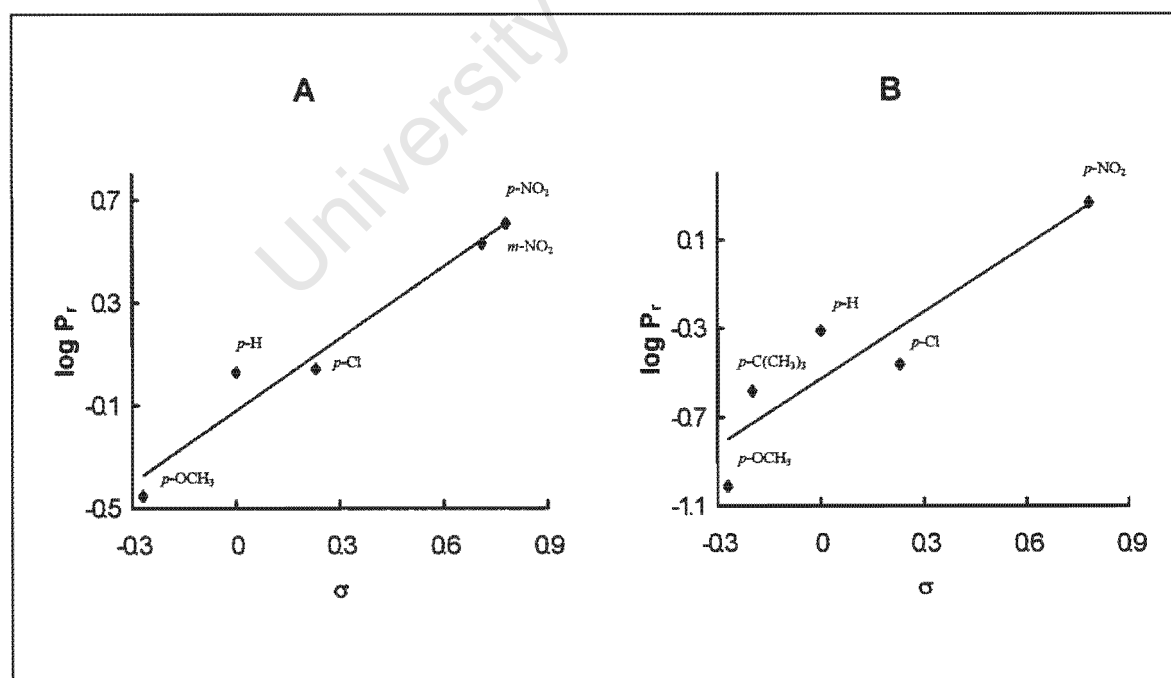
Table 3.4 Comparing ¹³C NMR resonances of the carbonyl and thiocarbonyl carbons of *para* substituted benzoyl isothiocyanates

Benzoyl isothiocyanate	$\delta^{13}\text{C}$ (ppm) C=O	$\delta^{13}\text{C}$ (ppm) -N=C=S
	159.9	146.7
	161.1	147.5
	151.6	149.0

As such, the findings conform to previous observations that the degree of conjugation between the carbonyl and isothiocyanate groups is limited, and that influences from an *R'* group affect the isothiocyanate far less than they affect the carbonyl group. Thus, as far as the electrophilic reactivities are concerned, it seems reasonable to assume that a *para*-substituent effect also manifests itself primarily at the carbonyl carbon. In practical terms this means that increased benzamide yields are derived from *p*-nitrobenzoyl isothiocyanates because the electron withdrawing nitro group activates the carbonyl carbon. With electron releasing substituents, nucleophilic attack at the thiocarbonyl carbon becomes more prevalent, but only because the electrophilicity and reactivity of the carbonyl carbon is reduced.

From the assumptions that amine addition at the thiocarbonyl carbon is negligibly affected by a *para*-substituent, and therefore, that the product ratios (P_r) depend only on the rate of nucleophilic attack at the carbonyl carbon, it would be expected that $\log P_r$ and Hammett substituent constants, σ_p , be linearly related to each other^{17,28}. For the series of reactions with piperidine, this is clearly the case (see graph A in figure 3.1a). The Hammett relationship, in this instance, has a linear correlation coefficient, R^2 , of 0.960 and a reaction constant, ρ , of 0.93. The latter compares reasonably well to the value of 1.18 which was reported for nucleophilic substitution of *para* substituted benzoyl chlorides with aniline, a reaction series closely related by the nature of the electrophilic centre and the nucleophile²⁹.

Figure 3.1a Hammett plots of $\log P_r$ versus σ values²⁸ for the reactions of *para* substituted* benzoyl isothiocyanates with piperidine (graph A, $\rho = 0.93$, $R^2 = 0.958$) and propylamine (graph B, $\rho = 1.00$, $R^2 = 0.837$)

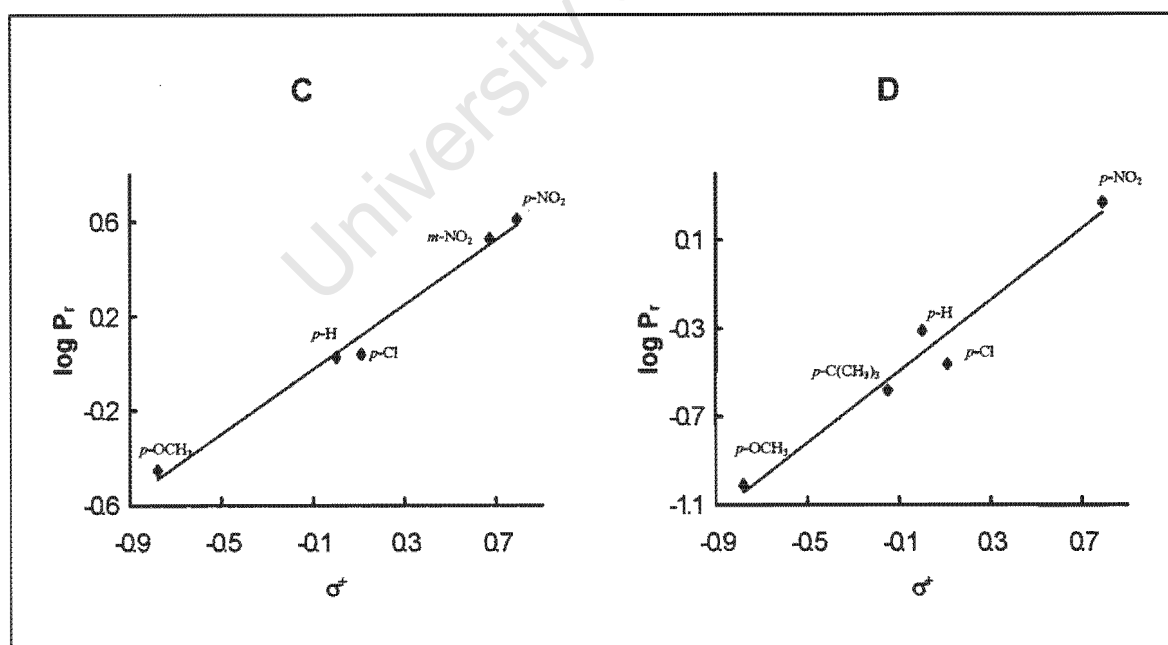


* In graph A, the $\log P_r$ value from the reaction of *m*-nitrobenzoyl isothiocyanate and piperidine is included as well.

For the reactions of the benzoyl isothiocyanates and propylamine, the ρ value of 1.00 is also comparable (graph B in figure 3.1a), but in this case, the Hammett plot shows considerably more scatter and the linear correlation is poor ($R^2 = 0.837$). However, in this regard, it is important to recall that a *para*-substituent influences not only the partial positive charge on the carbonyl carbon, but also the degree of conjugation between the phenyl ring and the carbonyl group (section 3.4.2). Under these circumstances, the substituents which exert an electron donating resonance can impart a greater stabilisation to the carbonyl carbon (and increase the activation energy required to form the unconjugated tetrahedral intermediate) than would be expected from their Hammett σ values¹⁷.

For reactions, where the influence of resonance donation is enhanced, Brown and Okamoto³⁰ determined a set of modified substituent constants, σ^+ . When these are used in the Hammett plot for the propylamine reactions, the linear correlation improves dramatically ($R^2 = 0.960$, see graph D in figure 3.1b). As expected, the data points for the $-\text{OCH}_3$ and $-\text{Cl}$ substituents are affected most, since these are both resonance donating groups. The ρ^+ reaction constant determined from the slope of the line is 0.81. For the series of reactions with piperidine, the $\log P_r$ values also show a significantly improved linear correlation with σ^+ constants (graph C, figure 3.1b). In this instance, the R^2 value increases to 0.988 and the ρ^+ value is 0.68.

Figure 3.1b Hammett plots of $\log P_r$ versus σ^+ values³⁰ for the reactions of *para* substituted* benzoyl isothiocyanates with piperidine (graph C, $\rho^+ = 0.68$, $R^2 = 0.988$) and propylamine (graph D, $\rho^+ = 0.81$, $R^2 = 0.960$)



* In graph C, the $\log P_r$ value from the reaction of *m*-nitrobenzoyl isothiocyanate and piperidine is included as well.

The improved correlation with σ^+ values also conforms to the proposal that benzamide – benzoylthiourea ratios reflect reactivity changes of the carbonyl and not the thiocarbonyl carbon. Since these correlations reflect the important influence of resonance interactions and since spectroscopic evidence indicates that such interaction between an *R'* group and the iso(thio)cyanate moiety is negligible, the primary response to these influences must occur at the carbonyl group.

To many, the above discussion may seem protracted since the fact that the *para*-substituent affects the carbonyl carbon more than it affects the thiocarbonyl carbon seems intuitively obvious. Yet Imrich *et al.*³ have argued with conviction, that these substituents only influence nucleophilic reaction at the latter site. According to them, the introduction of an electron withdrawing nitro group enhanced the rate of *N'*-benzoylthiourea formation. Clearly, such an effect cannot be observed if its primary influence is to enhance the electrophilicity and the nucleophilic substitution reaction at the competing carbonyl carbon. However, as was pointed out earlier (section 3.1), Imrich *et al.*³ made a fundamental error in assuming that reactions of benzoyl isothiocyanates and amines only produced *N'*-benzoylthioureas when carried out in anhydrous organic solvents. In their kinetic studies, this was exacerbated by the decision to monitor, during the course of a reaction, only the concentration of the benzoyl isothiocyanate reagent. Since this can be consumed by reaction at either electrophilic centre, the rate constants reported probably reflect on the nucleophilic substitution at the carbonyl carbon. The σ values listed by them, compare well to the values determined in the course of this project. For the reactions with butylamine in acetonitrile, Imrich *et al.*³ found a ρ value of 1.19, while with cyclohexylamine as the nucleophile, a ρ value of 0.83 was determined. As such, these are quite similar to the figures of 1.00 and 0.93 determined in the course of this work for the reactions with piperidine and propylamine in anhydrous acetone. Imrich's rate constants, also show improved linear correlation with σ^+ values. R^2 values improve from 0.925 to 0.953 for their butylamine reactions, and from 0.937 to 0.946 for the reactions with cyclohexylamine, when σ values are replaced by σ^+ . Again, this suggests an enhanced resonance contribution, an influence more likely to manifest itself at the carbonyl carbon.

Because of the competing reaction at the carbonyl carbon, the effects of *para*-ring substituents on the reactivity of the thiocarbonyl carbon of benzoyl isothiocyanates, could only be established by using hindered secondary amine nucleophiles that are sterically precluded from reacting at the carbonyl carbon.

3.4.4 Non-steric nucleophilic properties of the amine

Electronic influences on the Douglass and Dains synthesis do not only stem from variations of the aroyl isothiocyanate, but also depend, in part, on electronic properties associated with the amine reagent. There is clear indication from data in tables 3.1a, 3.2 and 3.3, that the nucleophilic behaviour of the amine is not entirely dependent on the steric constraints imposed by the geometry of its alkyl substituents. In the series of reactions between benzoyl isothiocyanate and the unhindered secondary amines (reactions with amines **d** – **g** in table 3.1a), for example, the benzamide : benzoylthiourea *P_r* ratios varied according to the basicity of

the amine used (see pK_a values in table 3.5). The highest P_r value (1.80) was recorded from the reaction with pyrrolidine, the most basic amine ($pK_a = 11.27$). The product ratio decreased to 1.07 for the reaction with piperidine ($pK_a = 11.12$), to 0.88 with dimethylamine ($pK_a = 10.78$), and to 0.40 with morpholine ($pK_a = 8.36$)*. The P_r values for morpholine and piperidine probably reflect electronic differences most accurately. Of the four amines, these two are geometrically the most similar, so the chances of misinterpreting minor steric effects as electronic influences are reduced. (Furthermore, the yields and P_r ratios listed in table 3.1a for both amines, represent averaged values from at least duplicate sets of reactions).

Table 3.5 Amine pK_a values^{12,13} in water and $\log K_B$ values³¹ of amine – 2,4-dinitrophenol ion-pair formation constants (K_B) in benzene

	Amine	pK_a	Log K_B
a	diethylamine	11.02	3.18
b	dibutylamine	11.25	2.94
c	<i>cis</i> -2,6-dimethylpiperidine	-	-
d	piperidine	11.12	3.65
e	pyrrolidine	11.27	3.88
f	morpholine	8.36	1.85
g	dimethylamine	10.78	-
h	propylamine	10.60	2.00
i	butylamine	10.67	2.04

The rate of nucleophilic attack at a carbonyl carbon is known to decrease with decreasing pK_a of the nucleophile, and therefore, in the presence of a competing side-reaction, it would not be completely unexpected to find diminished yields of benzamide from reactions with weaker amine bases³². Aminolysis reactions at carbonyl carbons have been investigated extensively and the observation that nucleophilic reactivity corresponds to the basicity order, has been confirmed on many occasions³³⁻⁴². The trend is typical of hard nucleophile – hard electrophile interactions and also applies when the reactions are carried out in non-aqueous, aprotic solvents^{14,32}.

* A very similar relationship between P_r values and amine pK_a is also evident from the analogous set of reactions with butanoyl isothiocyanate – see table 2.1, chapter 2. Although this may be significant, the trend should be viewed with some caution. The butanoylthiourea yields, especially in the reactions with pyrrolidine and piperidine, are very low. A yield variation of 3% (determined from duplicate reactions) is thus relatively large, and will have a marked effect on the value of P_r .

For benzoyl isothiocyanates, where the competing reaction is the nucleophilic addition at the thiocarbonyl carbon, this leaves three possible explanations to account for the decreasing P_r values i.e. the increased fraction of benzoylthiourea product:

- i) either the rate of addition at the thiocarbonyl carbon is not affected by the pK_a of the amine and remains constant, or
- ii) the rate of addition is enhanced by using weaker amine bases, or
- iii) the rate of addition also decreases with weaker amine bases, but to a lesser degree than the substitution process at the carbonyl carbon.

Of these, the latter is the most likely reason since kinetic investigations with alkyl, phenyl and acridine isothiocyanates have also all shown the rate of amine addition to decrease with decreasing basicity^{3,43-47}. Here too, the trend applies, regardless of whether the reactions are carried out in aqueous solvents or aprotic organic solvents. The improved yields of benzoylthiourea must therefore be attributed to the fact that substitution at the carbonyl carbon is more sensitive to the nucleophilic order and is retarded to a greater extent by using weaker amine bases. Unfortunately, it is difficult to obtain confirmation from the literature in this regard. To facilitate comparison, nucleophilic susceptibilities (β_{nuc}) are determined from the slopes of Brønsted-type plots of $\log k$ versus pK_a . These values, for aminolysis reactions of acyl halides, anhydrides and esters, typically range between 0.2 and 1.0, but with aliphatic amines as nucleophiles, they are usually confined between 0.2 and 0.51³³⁻⁴². A remarkably similar picture emerges for reactions of alkyl and phenyl isothiocyanates. Overall, β_{nuc} values vary from 0.2 to 1.3, but with aliphatic amine nucleophiles, the range of values also decreases to between 0.2 and 0.5^{3,43-47}. It is possible that a greater susceptibility difference in benzoyl isothiocyanates could be attributed to the fact that the isothiocyanate moiety is adjacent to an electron withdrawing carbonyl group. With the enhanced electrophilicity, the thiocarbonyl carbon might be less sensitive than usual to nucleophilic variation, an effect that would be in accordance with the reactivity – selectivity principle^{14,48}.

Another clear indication, that the nucleophilic behaviour of the amine did not only depend on steric constraints, was provided by the reactions with propylamine and butylamine (table 3.1a and 3.3). Compared to piperidine, these primary amines consistently favoured the pathway of addition to the thiocarbonyl carbon of benzoyl and *para* substituted benzoyl isothiocyanates. Under steric control, the opposite trend would have been expected. Again, the nucleophilic order appears linked to the basicity order as pK_a values for these primary amines ($pK_a = 10.60$ and 10.67 , see table 3.5) are roughly 0.5 units lower than the pK_a of piperidine. However, for this relatively small drop in pK_a the observed P_r differences are unexpectedly large. With unsubstituted benzoyl isothiocyanate the two primary amines gave benzamide : benzoylthiourea ratios that closely matched the low P_r values obtained using morpholine (see table 3.1a). The latter is typically considered to be a much weaker base, with a pK_a value more than 2.5 units below that of piperidine. Although this aspect is not fully understood, it may be linked to the fact that the reactions were carried out in anhydrous acetone. For amines, it is well known that solvents have a marked effect on the order of basicity⁴⁹, and a particularly relevant example of this has been provided by Frenna *et al.*³¹. As a

measure of basicities in benzene, they determined the ion-pair formation constants, K_B , for a variety of aliphatic amines with 2,4-dinitrophenol. Under these conditions, the basicities of propylamine, butylamine and morpholine are much closer together. Log K_B values (table 3.5) are 2.00, 2.04 and 1.85 respectively, and all are significantly below the values of 3.88 and 3.65 reported for pyrrolidine and piperidine.

Apart from the basicity differences, another explanation to be considered, is that hydrogen bonding may influence these reactions. Differences between secondary and primary amine reactivity may be more pronounced because the latter have two hydrogen atoms on the nitrogen nucleophile. Although such effects are usually observed in reactions with weakly basic nucleophiles, where proton transfer and breakdown of the intermediate are rate determining, there is recent experimental evidence to indicate that hydrogen bonding can also influence reactions with strongly basic amines, where nucleophilic attack is rate determining¹¹. In particular, a four centre type transition state involving a hydrogen bonded bridged structure has been proposed for aminolysis reactions of phenyl dithioacetates in acetonitrile.

3.5 Modelling the Electrophilic Reactivity of Acyl and Aroyl Isothiocyanates

According to frontier orbital theory^{17,50}, at least three electronic (i.e. non-steric) forces can contribute to the activation energy during the stages of transition state formation between an electrophile and a nucleophile. This can be represented by the following expression:

$$\Delta E = E(\text{core}) + E(\text{electrostatic}) + E(\text{overlap}) \quad 3.1$$

In this equation, the $E(\text{core})$ term is a positive term that represents the electron – electron repulsion energy that arises when the electrons in the closed shells of the two reactants repel each other. The $E(\text{electrostatic})$ term represents an attractive electrostatic force due to interaction of the positive and negative charges of the electrophile and the nucleophile, while the $E(\text{overlap})$ term represents the interaction of filled orbitals on the one reagent with the unfilled orbitals of the other. Since the latter two terms represent attractive forces, they are both negative. The full equation with the three terms of the interaction was derived by Klopman⁵¹ and Salem⁵², and is as follows:

$$\Delta E = - \sum_{ab} (q_a + q_b) \beta_{ab} S_{ab} + \sum_{k < l} \frac{q_k q_l}{\epsilon r_{kl}} + \sum_r^{\text{occ}} \sum_s^{\text{unocc}} - \sum_s^{\text{occ}} \sum_r^{\text{unocc}} \frac{2(\sum_{ab} c_{ra} c_{sb})^2}{E_r - E_s} \quad 3.2$$

where q_a and q_b are the electron populations in the atomic orbitals a and b
 β and S are resonance and overlap integrals respectively
 q_k and q_l are the total charges on atoms k and l
 ϵ is the local dielectric constant, and r_{kl} the distance between atoms k and l
 c_{ra} is the coefficient of atomic orbital a in molecular r of one reactant, similarly c_{sb} applies to the other reactant
 E_r is the energy of molecular orbital r of one reactant, similarly E_s applies to the other reactant

Fortunately, under certain conditions, this expression can be simplified considerably^{17,50}. For example, for the situation where a molecule can be attacked at two possible sites by a reagent, the $E(\text{core})$ term essentially remains constant for attack at either site^{17,50}. Since this condition does indeed apply when an amine nucleophile attacks either the carbonyl or thiocarbonyl carbon of an acyl or aroyl isothiocyanate, only the last two terms need be considered as having the potential to influence the reaction pathway. The $E(\text{overlap})$ term of the equation can, however, also be simplified considerably, as the most important orbital interactions between two reacting species are those between the HOMO and LUMO frontier orbitals. (In basic arithmetical terms, they are the orbitals with the smallest value of $E_r - E_s$ and hence make the largest contribution to the third term^{17,50}). Thus, with these simplifications, Klopman⁵¹ and Salem's⁵² equation can be reduced to the form:

$$\Delta E = \frac{-q_n q_e}{\epsilon r} + \frac{2(c_n c_e \beta)^2}{E_{\text{HOMO}} - E_{\text{LUMO}}} \quad 3.3$$

where q_n and q_e are charges on the nucleophile and electrophile respectively
 c_n and c_e are the coefficients of the HOMO and LUMO at the interacting centres of each reagent

In this form, the equation is of interest since it presents the underlying principle on which the division between hard – hard and soft – soft acid – base interactions is based¹⁷. The first term is particularly important in hard – hard reactions since interactions of this type are primarily attributed to electrostatic attraction between opposite charges. On the other hand, contributions from the orbital term are more important in soft – soft interactions, since these are characterised by reaction partners that possess symmetry-compatible HOMOs and LUMOs that are close in energy.

During the course of this project, geometry-optimised structures of various acyl and benzoyl isothiocyanates* were calculated^{9,10}. These were first used to estimate and compare the atomic charges associated with the carbonyl and thiocarbonyl carbons, and then, to compare the contributions of each centre to the relevant frontier orbital. Although reactions between amines and carbonyl carbons are commonly regarded as hard base – hard acid reactions, it was pointed out in chapter 2, that the reaction between the thiocarbonyl carbon and an amine is not as easily classified. The charge and frontier orbital calculations were therefore intended to establish whether the trends amongst the experimentally determined P_r product ratios correlated with charge differences between the two electrophilic centres (i.e. suggesting that the reaction outcome was indeed dictated by the electrostatic term), or alternatively, whether they were linked to the relative frontier orbital contribution of each centre (hence indicating that the reaction pathway was significantly influenced by the orbital term).

* Considering the number of heavy atoms involved and due to computational limitations it was not feasible to calculate actual amine – acyl (aroyl) isothiocyanate transition states. By focusing only on the isothiocyanate reagent it was also possible to compare the influences of a greater variety of acyl and aroyl substituents on the reactivity.

Although the calculations were originally only intended to provide further insight into the relative importance of the electrostatic and frontier orbital terms to the amine – isothiocyanate reactions, the benzoyl and substituted benzoyl isothiocyanates models were also used to estimate the stabilisation energies associated with the benzene ring – carbonyl group conjugation. This was done to help verify the experimental finding (see section 3.4.3) that resonance and conjugation effects have a particularly important influence on the relative reactivity of the two electrophilic centres in benzoyl isothiocyanates.

3.5.1 Optimising the geometry of acyl and benzoyl isothiocyanates

Geometry-optimised models were calculated for acetyl, 2,2-dimethylpropanoyl, benzoyl, *p*-chlorobenzoyl, *p*-methoxybenzoyl, and *p*-nitrobenzoyl isothiocyanate by applying C_s symmetry. The calculations were carried out using density functional theory. Exchange-correlation effects were estimated by Becke's Three Parameter Hybrid method⁵³ and for the correlation energy, the functions of Lee, Yang and Parr (B3LYP) were used⁵⁴. Calculations for the carbonyl and isothiocyanate moieties were performed at the 6-31G(d) *ab initio* level. The acyl and benzoyl R' substituents, however, were calculated using the 3-21G basis set. (Compared to a full application of the 6-31G(d) basis set, this approach saved considerable computational time and did not affect the calculated geometry).

Since no acyl and benzoyl isothiocyanates have been analysed by x-ray crystallography, it was difficult to verify the calculated results. However, as a test of the optimisation procedure, the calculations were also carried out for *p*-bromophenylisothiocyanate. These results were found to be in excellent agreement with published x-ray data for this phenylisothiocyanate^{55,56}. (For interest, the calculated bond lengths and the relevant x-ray data are listed in appendix 1.)

The important acyl and benzoyl isothiocyanate bond lengths and angles determined from the optimisations are listed in table 3.6. These indicate that the geometry of the carbonyl and isothiocyanate moieties remains virtually constant, regardless of the alkyl or phenyl R' substituent on the carbonyl carbon. The only bond that is influenced by the R' substituents, is that between the carbonyl carbon and the substituent itself i.e. $R'-C(O)$. For the benzoyl isothiocyanates this bond is, as anticipated from conjugation, somewhat shorter than for the two acyl isothiocyanates. The expected *para*-substituent influences also seem to be reflected in this particular bond, as it increases from 1.466 Å to 1.481 Å when the resonance donating *p*-methoxy group is replaced by the electron withdrawing nitro group. However, changes from alkyl to phenyl R' groups and the introduction of *para*-substituents on the latter appear to have negligible influence on the bond between the carbonyl carbon and the nitrogen of the isothiocyanate i.e. $C(O)-NCS$. This corresponds with results of the published spectroscopic studies which indicated that there is little or no conjugation between these two moieties²⁰⁻²⁵, and further confirms that *para*-substituents in benzoyl isothiocyanates should influence the carbonyl carbon far more than the thiocarbonyl carbon (see discussion in sections 3.4.2 and 3.4.3).

Table 3.6 Calculated bond lengths and bond angles for the carbonyl and isothiocyanate moieties of various acyl and benzoyl isothiocyanates

Acyl/Aroyl isothiocyanate $\text{R}'-\overset{\text{O}}{\underset{\text{ }}{\text{C}}}-\text{N}=\text{C}=\text{S}$	Calculated bond lengths (Å)					Bond Angle $\overset{\text{O}}{\underset{\text{ }}{\text{C}}}-\widehat{\text{N}}-\text{C}=\text{S}$
	$\text{R}'-\text{C}(\text{O})$	$\text{C}=\text{O}$	$\text{C}(\text{O})-\text{N}$	$\text{N}=\text{C}(\text{S})$	$\text{C}=\text{S}$	
$\text{H}_3\text{C}-\overset{\text{O}}{\underset{\text{ }}{\text{C}}}-\text{NCS}$	1.506	1.207	1.423	1.212	1.573	138.9
$\text{C}(\text{CH}_3)_3-\overset{\text{O}}{\underset{\text{ }}{\text{C}}}-\text{NCS}$	1.530	1.209	1.424	1.211	1.574	138.8
$\text{H}_3\text{CO}-\text{C}_6\text{H}_4-\overset{\text{O}}{\underset{\text{ }}{\text{C}}}-\text{NCS}$	1.466	1.214	1.430	1.210	1.575	137.7
$\text{C}_6\text{H}_5-\overset{\text{O}}{\underset{\text{ }}{\text{C}}}-\text{NCS}$	1.475	1.212	1.425	1.211	1.573	137.5
$\text{Cl}-\text{C}_6\text{H}_4-\overset{\text{O}}{\underset{\text{ }}{\text{C}}}-\text{NCS}$	1.476	1.213	1.422	1.213	1.570	136.8
$\text{O}_2\text{N}-\text{C}_6\text{H}_4-\overset{\text{O}}{\underset{\text{ }}{\text{C}}}-\text{NCS}$	1.481	1.212	1.417	1.215	1.568	136.4

3.5.2 Determining molecular charge distributions in acyl and benzoyl isothiocyanates

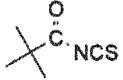
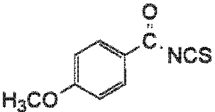
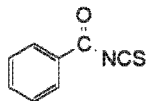
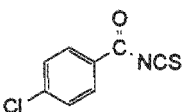
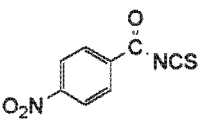
Unfortunately, it is not possible to directly measure the charges associated with individual atoms in a molecule. However, a number of quantum chemical methods have been used to derive 'atomic charges'. For simulating such electrostatic properties, a suitable method is to derive the electrostatic potential from electron densities at a large number of points around the molecule of interest⁵⁷. (The electrostatic potential is defined as the energy of interaction of a point positive charge with the nuclei and electrons of a molecule and its value depends on the location of the point positive charge.) A least-squares procedure is then employed to derive individual atomic charges that fit the electrostatic potential calculated for the molecule.

Amongst the procedures based on this approach, the main difference lies in the selection of points where the electron density and electrostatic potential is calculated. With the geometry-optimised acyl and benzoyl isothiocyanates, the points for calculation were selected according to the Merz-Kollman scheme^{58,59}. Of the commonly used methods, this scheme was recently shown to give the best description of a molecule's electrostatic properties⁵⁷. The electron densities at the selected points were found by single point B3LYP / 6-311++G(2d, 2p) calculations. The fitted atomic charges calculated for the atoms of the carbonyl and isothiocyanate moieties are listed in table 3.7 on the following page (the values are given in units of electrons, *e*).

The most striking aspect of the calculated charges is that in *all* the acyl and benzoyl isothiocyanate models, the carbonyl carbon appears to be significantly more positive than the thiocarbonyl carbon. Certainly, this is in excellent agreement with the experimental data for the *acyl* isothiocyanate – amine reactions, which showed that substitution at the reactive carbonyl carbon predominated (in the absence of steric hindrances). However, the calculated charges do not reflect the fact that with benzoyl isothiocyanates, most amine nucleophiles favoured the thiocarbonyl carbon. Even though R' group substitutions do primarily affect the charge of the carbonyl carbon, it is clear that the charge on this centre is not reduced significantly enough in benzoyl isothiocyanates to account for the experimentally observed change in regioselectivity.

Amongst the carbonyl carbons, it was surprising to find that one of the lowest positive values was calculated for 2,2-dimethylpropanoyl isothiocyanate (0.64 *e*). This suggests that aliphatic R' groups like the tertiary butyl group may indeed have some electronic influence on the reactivity of this centre. However, that this influence is relatively small, and that the deactivating effect of the tertiary butyl group is primarily of steric origin, is borne out by the fact that the primary amines (i.e. the sterically most exposed nucleophiles) were not prevented from reacting predominantly at the carbonyl carbon of this isothiocyanate (see table 2.3, chapter 2). The relatively minor role of the charge variations is also illustrated by the fact that the carbonyl carbon charges for *p*-chlorobenzoyl and 2,2-dimethylpropanoyl isothiocyanate are very similar (0.63 *e* and 0.64 *e* respectively). With the former, however, the regioselectivity of propylamine was reversed (i.e. despite the similar charges and despite a less hindered carbonyl carbon, propylamine and *p*-chlorobenzoyl isothiocyanate combined to produce mainly the benzoylthiourea - see table 3.3).

Table 3.7 Calculated Merz-Kollman^{58,59} charges for the atoms of the carbonyl and isothiocyanate moieties of various acyl and benzoyl isothiocyanates

Acyl/Aroyl isothiocyanate $\text{R}'-\overset{\text{O}}{\underset{\text{ }}{\text{C}}}-\text{N}=\text{C}=\text{S}$	Atomic charges (<i>e</i>)				
	C(=O)	O	N	C(=S)	S
$\text{H}_3\text{C}-\overset{\text{O}}{\underset{\text{ }}{\text{C}}}-\text{NCS}$	0.84	-0.51	-0.27	0.07	-0.01
	0.64	-0.44	-0.14	0.03	-0.05
	0.68	-0.48	-0.17	0.03	-0.03
	0.73	-0.49	-0.21	0.03	-0.01
	0.63	-0.46	-0.20	0.05	-0.01
	0.77	-0.49	-0.19	0.01	0.03

For the benzoyl isothiocyanates the Merz-Kollman^{58,59} charges also show that the carbonyl carbon is the centre that is most influenced by *para*-substituents on the phenyl ring. In accordance with known inductive and resonance effects¹⁷, this centre was found to be the most positive for *p*-nitrobenzoyl isothiocyanate (0.77 *e*), followed successively by the carbons of benzoyl and *p*-methoxybenzoyl isothiocyanate (0.73 *e* and 0.68 *e* respectively). However, that this charge variation was responsible for the corresponding decrease in amide : thiourea ratios observed for these isothiocyanates (see P_r values from reactions with piperidine and propylamine, tables 3.2 and 3.3), is questionable. The three charges fall almost midway between the values calculated for acetyl and 2,2-dimethylpropanoyl isothiocyanate (0.84 *e* and 0.64 *e*), and both of these reagents were found to give mainly amidic products when added to primary amines. Furthermore, the charge determined for the carbonyl carbon of *p*-chlorobenzoyl isothiocyanate is unexpectedly low (0.63 *e*). From the resonance and inductive properties of the chloro group¹⁷, and from the experimental P_r ratios (table 3.2 and 3.3), a value closer to the charge calculated for the carbonyl carbon of benzoyl isothiocyanate would have been anticipated. The reasons for this apparent anomaly are not clear.

3.5.3 Comparing frontier orbital contributions in acyl and aroyl isothiocyanates

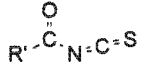
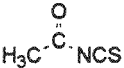
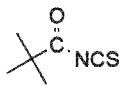
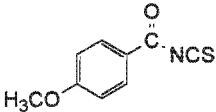
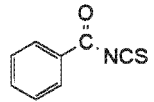
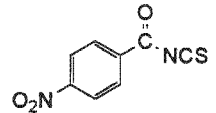
It was pointed out earlier, that although carbonyl carbon – amine reactions are traditionally^{17,32} regarded as examples of hard – hard interactions, it was not certain that the thiocarbonyl carbon of acyl or aroyl isothiocyanates could also be classified as a hard electrophile (see also discussion in section 2.4.1, chapter 2). On the premise that it is the softer centre, however, it seemed reasonable to propose that its electrophilic reactivity might be more significantly influenced by HOMO – LUMO interactions. In practical terms this meant that the observed reactivity of the benzoyl isothiocyanates might be explained if it was found that the thiocarbonyl carbon contributed more significantly to the LUMO in benzoyl isothiocyanates than in acyl isothiocyanates (i.e. that, in benzoyl isothiocyanates, the value c_e (equation 3.3) was significantly larger for the thiocarbonyl carbon than it was for the carbonyl carbon).

From the geometry-optimised models, the LUMOs were derived by single point energy calculation at the Hartree-Fock / 6-311++G(2d,2p) level. To compare the contributions from the carbonyl and thiocarbonyl carbons to the LUMO (i.e. to compare the magnitude of the LUMO at each centre), a net atomic population analysis was carried out. The LUMO energies for the various isothiocyanates and the net populations for their two centres are listed in table 3.8.

For the benzoyl and substituted benzoyl isothiocyanates, the population analysis indicates that the carbonyl carbon provides a marginally greater contribution to the LUMO than the thiocarbonyl carbon. However, in the two acyl isothiocyanates a greater portion of the LUMO is actually located on the thiocarbonyl carbon. Thus, under the control of the HOMO – LUMO term, a high acylthiourea and low amide yield would have been expected from the acyl isothiocyanate – amine reaction, while a slightly higher benzamide than benzoylthiourea yield would have been anticipated from the reactions of the benzoyl isothiocyanates. That

the experimental results gave virtually the opposite trends, strongly suggests that the orbital term does not play a significant role in these reactions.

Table 3.8 LUMO energies and population analysis for various acyl and benzoyl isothiocyanates

Acyl/benzoyl isothiocyanate 	LUMO energy (eV)	Net population C(=O)	Net population C(=S)
	-1.93	0.23	0.32
	-1.85	0.23	0.32
	-2.03	0.19	0.17
	-2.29	0.18	0.16
	-3.40	0.06	0.04

3.5.4 The effect of phenyl ring – carbonyl group conjugation in benzoyl isothiocyanates

In section 3.4.3, the Hammett plots provided an indication that the reactivity of the carbonyl carbon in benzoyl isothiocyanates was particularly sensitive to the degree of conjugation that existed between the phenyl ring and the carbonyl group. It was pointed out that this conjugation stabilisation was lost when nucleophilic attack at the carbonyl carbon led to the formation of a tetrahedral intermediate. In effect the stabilisation can be regarded as an additional activation energy that only affects the reactivity of the carbonyl carbon in benzoyl isothiocyanates. The reactivity of the thiocarbonyl carbon is not influenced,

although nucleophilic addition at this centre does become more pronounced as the reactivity of the carbonyl carbon decreases.

For obvious reasons, the original geometry-optimised benzoyl isothiocyanates were calculated in conjugation-stabilised form, i.e. with the phenyl ring and carbonyl-isothiocyanate moieties in co-planar configuration. To remove this conjugation and to provide an estimate of the conjugation energy, however, the phenyl and carbonyl-isothiocyanate groups of these models were subsequently set at 90° (C_s symmetry was maintained). With the rings now orientated perpendicularly to the plane of the carbonyl-isothiocyanate moiety, and without further geometry optimisation, the energies of the models were recalculated, and then compared to the original values. The differences, which are listed as the E_c values in table 3.9, provide at least some measure of the conjugation stabilisation that must be overcome during nucleophilic substitution at the carbonyl carbon. Since the product ratio of competing reactions under kinetic control will change by a factor of ten for every 5.7 kJ/mol difference in activation energy¹⁴, these values are substantial.

Table 3.9 Calculated conjugation energies (E_c) and experimentally derived $\Delta\Delta G^*_{XY}$ values (all in kJ.mol⁻¹). The latter have been calculated using the P_r values from the series of reactions with piperidine, and also the series of reactions with propylamine

Benzoyl isothiocyanate	Conjugation energy	Energy differences	$\Delta\Delta G^*_{(X)(NO_2)}$ (T = 293K)	
	E_c	$E_c(X) - E_c(NO_2)$	(piperidine)	(propylamine)
	42.54	12.71	5.95	7.19
	34.91	5.08	3.28	3.34
	35.51	5.68	3.22	4.12
	29.83	0.00	0.00	0.00

Of particular interest is that the estimated energies vary, as expected, according to the *para*-substituent found on the phenyl ring. These variations, which are also given as differences relative to the conjugation energy for *p*-nitrobenzoyl isothiocyanate ($E_c(X) - E_c(\text{NO}_2)$), correlate remarkably well to the experimental amide : thiourea P_r ratios recorded from reactions with piperidine and propylamine. Thus, *p*-nitrobenzoyl isothiocyanate, the least conjugated reagent, gave the highest P_r ratios, while *p*-methoxybenzoyl isothiocyanate, the reagent with the most conjugation stabilised carbonyl centre, gave the lowest P_r ratios. Even more conspicuous are the conjugation energies calculated for benzoyl and *p*-chlorobenzoyl isothiocyanate. Unlike the charges calculated for their carbonyl carbons (see table 3.7), their E_c values are very similar to each other, and as such, they reflect that these isothiocyanates also gave similar P_r ratios when reacted with the above amines.

The correlation between the experimental P_r ratios and the calculated conjugation energies is not coincidental, and may be traced to a more fundamental relationship. Since the addition and substitution reactions in an acyl or benzoyl isothiocyanate are both under kinetic control (see section 2.4.1, chapter 2), the difference in activation energy ($\Delta\Delta G^\ddagger$) for the two pathways can be calculated from the P_r value by rearranging the equation¹⁴

$$P_r = \frac{[e^{-\Delta G^\ddagger/RT}]_{C=O}}{[e^{-\Delta G^\ddagger/RT}]_{C=S}} = e^{-\Delta\Delta G^\ddagger/RT} \quad 3.4$$

where T = temperature in K and $R = 8.33 \times 10^{-3} \text{ kJ.mol}^{-1}.\text{K}^{-1}$

However, under the assumption that nucleophilic addition at the thiocarbonyl carbon is not affected by the *para*-substituents, the term $[e^{-\Delta G^\ddagger/RT}]_{C=S}$ can be regarded as a constant (C), common to all benzoyl isothiocyanates in reaction with the same amine. With $\Delta G^\ddagger$ for substitution at the carbonyl carbon as the only variable, it becomes possible to calculate an activation energy difference, $\Delta\Delta G_{XY}^\ddagger$, for substitution in two different benzoyl isothiocyanates by comparing their P_r values. Thus, for two benzoyl isothiocyanates with the *para*-substituents X and Y ,

$$\frac{[P_r]_X}{[P_r]_Y} = \frac{[e^{-\Delta G^\ddagger/RT}]_{C=O} / C]_X}{[e^{-\Delta G^\ddagger/RT}]_{C=O} / C]_Y} = e^{-\Delta\Delta G_{XY}^\ddagger/RT} \quad 3.5$$

The magnitude of $\Delta\Delta G_{XY}^\ddagger$ should depend only on the two *para*-substituents, or more specifically, on the inductive and resonance influences that they exert on the carbonyl carbons. Resonance effects on the conjugative stabilisation of the carbonyl carbons will also contribute to this term. From the *para* position any steric differences between the substituents should have a negligible influence.

$\Delta\Delta G_{XY}^*$ values, determined from the P_r ratios of the benzoyl isothiocyanate – piperidine reactions (using P_r values from table 3.2) and from the benzoyl isothiocyanate – propylamine reactions (P_r values from table 3.3) verify that indeed the degree of conjugation is particularly important (table 3.9). With the P_r values for *p*-nitrobenzoyl isothiocyanate as denominators, two remarkably similar sets of $\Delta\Delta G_{XY}^*$ values emerge from these two series of reactions. (This in itself is reassuring because it confirms that these experimentally derived values reflect only the influences of the *para*-substituents and that they are independent of the amine nucleophile that was used for the set of reactions). More significant, however, is that both sets also correlate closely to the computationally determined conjugation energy differences. They reflect very similar decreasing trends in going from *p*-methoxy- to *p*-nitrobenzoyl isothiocyanate, and although the $\Delta\Delta G_{XY}^*$ values are somewhat lower, they are certainly of comparable magnitude. As such, it appears unlikely that charge or other variations between the carbonyl carbons contribute nearly as significantly. (The computationally determined conjugation energies may be somewhat high since they were calculated with the phenyl rings and carbonyl – isothiocyanate moieties at right angles to each other. This does not necessarily reflect the configuration of the transition state, and it is not inconceivable that some degree of electron delocalisation may persist throughout the reaction.)

3.6 Concluding Remarks

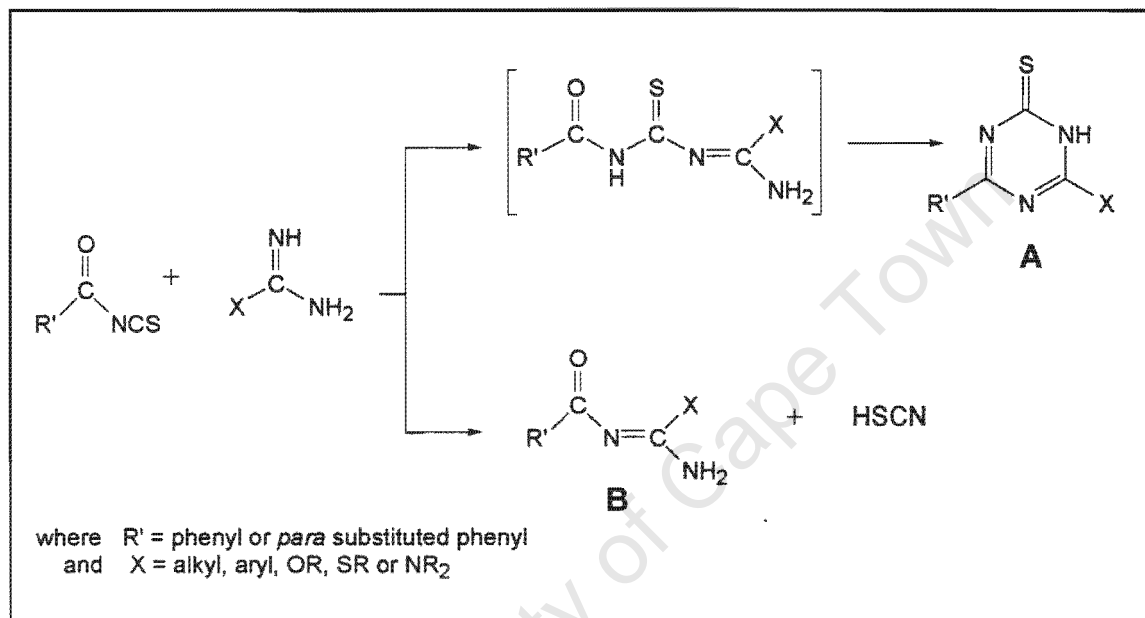
From the work described in this chapter there is no doubt that amide side-product formation is also possible when amines are reacted with aroyl isothiocyanates. Although conjugation significantly reduces the electrophilic reactivity of the carbonyl carbon in benzoyl isothiocyanates, this centre continues to compete with the thiocarbonyl carbon for reaction of the amine nucleophile. Although this competition is sensitive to the degree of conjugative stabilisation, the outcome of these reactions also depends on the basicity and geometry of the amine nucleophile.

In choosing to separate and identify the products from the *p*-chlorobenzoyl isothiocyanate – glycine ethyl ester reaction, Imrich *et al.*³ had inadvertently selected a reaction in which conditions definitely favoured thiourea, rather than amide formation. The nucleophile was a primary amine that was also significantly less basic than either propylamine or butylamine. For optimising benzoylthiourea yields in the Douglass and Dains procedure, only a sterically bulky amine, with adequate F-strain protection from its alkyl substituents, might have proved more effective. The choice of *p*-chlorobenzoyl isothiocyanate as the electrophile was also important. Resonance donation from the chloro group contributes significantly to conjugation stabilisation of the carbonyl carbon in this reagent. In this respect, only the methoxy group might have proved more effective.

During the collation of the results for this chapter it was of interest to discover that another group of compounds that are derived from the combination of an aroyl isothiocyanate and a nitrogen nucleophile, are the *s*-triazinethiones⁶⁰. Rather remarkably, the synthesis of these compounds appears to be similarly complicated by competing reactions at the carbonyl and thiocarbonyl centres of the isothiocyanate reagent.

As in the Douglass and Dains procedure, the first step of the synthesis requires addition of the nucleophile to the thiocarbonyl carbon, and again, this process is opposed by nucleophilic attack and substitution of the isothiocyanate moiety at the carbonyl centre (see figure 3.2). The addition reaction is followed by a spontaneous cyclisation step to give the desired product, while the substitution gives rise to unwanted aroyl amidines. Undoubtedly of most interest, are the variables that are reported to influence these competing processes.

Figure 3.2 Competitive triazinethione (A) and aroyl amidine (B) formation from the reaction of benzoyl and *para* substituted benzoyl isothiocyanates with amidines⁶⁰



From an extensive experimental investigation⁶⁰, it was determined that addition and triazine formation is encouraged by using the lesser basic nucleophiles. Thus, isothioureia and isourea proved more suitable than benzamidines, which in turn gave better results than acetamidine. Significantly higher triazine yields were also noted when benzoyl isothiocyanates with electron releasing *para*-substituents were used. Here too, the substituents function was to decrease the reactivity of the carbonyl carbon. Steric shielding of the carbonyl carbon was also reported to be very effective. This was achieved by using *ortho* substituted benzoyl isothiocyanates like 2,4,6-trimethylbenzoyl isothiocyanate and virtually eliminated the problem of aroyl amidine formation. It is quite possible that this approach may also be successfully applied in *N'*-benzoylthiourea synthesis.

Thus far, the similarities between the Douglass and Dains synthesis and the synthesis of the *s*-triazinethiones seem to have been overlooked by others working with *N'*-acyl- and *N'*-aroylthioureas. This may be because the *s*-triazinethiones are nitrogen heterocycles that bear no structural resemblance to either *N'*-acyl- and *N'*-benzoylthioureas, and because the nucleophiles that are used, namely isothioureas, isoureas, and amidines, appear to be substantially different from simple primary and secondary amines.

However, the factors affecting the two synthetic procedures appear to be so similar, that it was of little surprise to learn that acetyl isothiocyanate proved exceptionally unsuitable as a reagent for triazinethione synthesis, and only gave target yields of 2%⁶⁰. As was observed for the *N'*-acylthiourea synthesis in this project, steric shielding may be the only means of limiting amidine substitution at the reactive carbonyl carbon of acyl isothiocyanates.

3.7 Experimental Procedures and Characterisation

3.7.1 Synthesis and separation of *N*-substituted *N'*-benzoylthioureas and *N*-substituted benzamides

Reactions between benzoyl isothiocyanates and amines were carried out according to the procedures described for acyl isothiocyanate – amine reactions in section 2.6.1. Thus, solvents and reagents were purified and used in the proportions as specified. Separation and purification of product mixtures was also achieved using column chromatography, with Silica Gel 60 as stationary phase and chloroform or methylene chloride solutions with 0 – 10% acetone as eluent.

3.7.2 Preparation of benzoyl and *para* substituted benzoyl isothiocyanates for ^{13}C NMR spectroscopy

Under nitrogen, benzoyl or *para* substituted benzoyl chloride (0.01 mol) was dissolved in anhydrous acetone (30 ml) and added dropwise to a solution of potassium thiocyanate (0.01 mol) in anhydrous acetone (30 ml). This reaction mixture was heated to reflux for 45 minutes. It was then cooled to room temperature, and filtered under nitrogen to remove the KCl precipitate. 2 ml aliquots of the filtrate were placed under a stream of nitrogen gas to evaporate the acetone. The oil remaining was placed in a vacuum dessicator for 15 minutes and then dissolved in deuterated acetone (1 ml) for NMR spectroscopy.

3.7.3 Characterisation of *N*-substituted *N'*-benzoylthioureas and *N*-substituted benzamides

N,N-diethyl-*N'*-benzoylthiourea (II Ea – table 3.1a): 93.2% yield, mp 98 – 100°C (lit⁶¹: 98°C), Calculated for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{OS}$: C, 60.97; H, 6.84; N, 11.85; S, 13.57, Found: C, 61.20; H, 7.23; N, 12.21; S, 13.74, NMR $\delta(^1\text{H})$: 1.32 (unres t, 6H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.61 + 4.00 (unres q + unres q, 2H + 2H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 7.45 (dd, 2H, $\text{O}(3,5)$), 7.56 (t, 1H, $\text{O}(4)$), 7.81 (d, 2H, $\text{O}(2,6)$), 8.40 (br s, 1H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 11.51, 13.23, 47.83, 127.83, 128.81, 132.66, 132.85, 163.81, 179.37.

N,N-dibutyl-*N'*-benzoylthiourea (II Eb – table 3.1a): 95.8% yield, mp 88 – 89°C (lit⁶¹: 93°C), Calculated for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{OS}$: C, 65.70; H, 8.29; N, 9.58; S, 10.96, Found: C, 65.58; H, 8.59; N, 9.76; S, 10.89, NMR $\delta(^1\text{H})$: 0.90 + 0.98 (t + t, 6H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.29 + 1.44 (m + m, 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.65 + 1.79 (m + m, 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 3.52 + 3.97 (t + t, 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 7.46 (dd, 2H, $\text{O}(3,5)$), 7.57 (t, 1H, $\text{O}(4)$), 7.83 (d, 2H, $\text{O}(2,6)$), 8.33 (br s, 1H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 13.69, 13.84, 20.04, 28.47, 30.13, 53.03, 53.21, 127.76, 128.84, 132.84, 163.30, 179.74.

N-(*cis*-2,6-dimethylpiperidyl)-*N'*-benzoylthiourea (II Ec – table 3.1a): 96.5% yield, mp: 131 – 133°C, Calculated for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{OS}$: C, 65.17; H, 7.31; N, 10.14; S, 11.60 Found: C, 65.22; H, 7.36; N, 10.23; S, 11.41, NMR $\delta(^1\text{H})$: 1.20–2.00 (br unres m, 12H, $-\text{N}(\text{CH}(\text{CH}_3)\text{CH}_2)_2$), 4.51 + 5.21 (br m + br m, 2H,

-N<(CH(CH₃)CH₂)₂>CH₂), 7.45 (dd, 2H, Ø(3,5)), 7.55 (t, 1H, Ø(4)), 7.84 (d, 2H, Ø(2,6)), 8.42 (v br s, 1H, >N'H), $\delta(^{13}\text{C})$: 13.49, 18.78, 20.92, 29.41, 30.12, 54.26, 54.57, 127.75, 128.74, 132.73, 132.78, 163.94, 179.65.

***N*-piperidyl-*N'*-benzoylthiourea (IIEd – table 3.1a):** 41.8% yield, mp 124 - 126°C (lit⁶²: 126 - 128°C), Calculated for C₁₃H₁₆N₂OS: C, 62.86; H, 6.51; N, 11.28; S, 12.91, Found: C, 62.86; H, 6.67; N, 11.39; S, 12.72, NMR $\delta(^1\text{H})$: 1.72 (unres m, 6H, -N<(CH₂CH₂)₂>CH₂), 3.59 + 4.15 (unres t + unres t, 2H + 2H, -N<(CH₂CH₂)₂>CH₂), 7.46 (dd, 2H, Ø(3,5)), 7.56 (t, 1H, Ø(4)), 7.83 (d, 2H, Ø(2,6)), 8.39 (br s, 1H, >N'H), $\delta(^{13}\text{C})$: 23.89, 25.30, 26.07, 52.80, 53.10, 127.81, 128.89, 132.58, 132.96, 163.18, 178.18.

***N*-piperidylbenzamide (IIEd – table 3.1a):** 44.8% yield, oil, Calculated for C₁₂H₁₅NO: C, 76.14; H, 8.00; N, 7.40, Found: C, 75.70; H, 8.10; N, 7.39, NMR $\delta(^1\text{H})$: 1.45-1.74 (br unres m, 6H, -N<(CH₂CH₂)₂>CH₂), 3.33 + 3.68 (unres t + unres t, 2H + 2H, -N<(CH₂CH₂)₂>CH₂), 7.37 (unres m, 5H, Ø(2,3,4,5,6)), $\delta(^{13}\text{C})$: 24.59, 25.79, 26.40, 43.11, 48.70, 126.76, 128.35, 129.29, 136.55, 170.28.

***N*-pyrrolidyl-*N'*-benzoylthiourea (IIIE – table 3.1a):** 29.0% yield, mp 131 - 133°C (lit⁶²: 133 - 134°C), Calculated for C₁₂H₁₄N₂OS: C, 61.51; H, 6.03; N, 11.96; S, 13.68, Found: C, 61.65; H, 6.44; N, 12.05; S, 13.58, NMR $\delta(^1\text{H})$: 1.98 + 2.03 (m + m, 2H + 2H, -N<(CH₂CH₂)₂), 3.69 + 3.87 (t + t, 2H + 2H, -N<(CH₂CH₂)₂), 7.46 (dd, 2H, Ø(3,5)), 7.56 (t, 1H, Ø(4)), 7.83 (d, 2H, Ø(2,6)), 8.58 (br s, 1H, >N'H), $\delta(^{13}\text{C})$: 24.59, 26.19, 52.84, 54.48, 127.87, 128.79, 132.56, 132.87, 163.27, 176.39.

***N*-pyrrolidylbenzamide (IIIE – table 3.1a):** 52.1% yield, oil, Calculated for C₁₁H₁₃NO·½H₂O: C, 71.70; H, 7.67; N, 7.60, Found: C, 72.52; H, 7.66; N, 7.43, NMR $\delta(^1\text{H})$: 1.84 + 1.93 (m + m, 2H + 2H, -N<(CH₂CH₂)₂), 3.39 + 3.62 (t + t, 2H + 2H, -N<(CH₂CH₂)₂), 7.37 (unres m, 3H, Ø(3,4,5)), 7.48 (d, 2H, Ø(2,6)), $\delta(^{13}\text{C})$: 24.38, 26.30, 46.08, 49.51, 126.98, 128.14, 129.67, 137.18, 169.64, *m/z*: 175 (calc for C₁₁H₁₃NO: 175.24).

***N*-morpholino-*N'*-benzoylthiourea (IIIf – table 3.1a):** 66.7% yield, mp 142 - 143°, Calculated for C₁₂H₁₄N₂O₂S: C, 57.57; H, 5.65; N, 11.19; S, 12.81, Found: C, 57.89; H, 5.89; N, 11.49; S, 12.95, NMR $\delta(^1\text{H})$: 3.82 (br unres m, 4H, -N<(CH₂CH₂)₂>O), 3.67 + 4.22 (br unres t + br unres t, 2H + 2H, -N<(CH₂CH₂)₂>O), 7.49 (dd, 2H, Ø(3,5)), 7.57 (t, 1H, Ø(4)), 7.83 (d, 2H, Ø(2,6)), 8.53 (br s, 1H, >N'H), $\delta(^{13}\text{C})$: 51.73, 52.46, 66.21, 127.80, 128.95, 132.28, 133.15, 163.25, 179.23.

***N*-morpholinebenzamide (IIIf – table 3.1a):** 26.7% yield, mp 72 - 73°C (lit⁶³: 74°C), Calculated for C₁₁H₁₃NO₂: C, 69.08; H, 6.87; N, 7.32, Found: C, 68.75; H, 7.19; N, 7.48, NMR $\delta(^1\text{H})$: 3.40-3.80 (br unres m, 8H, -N<(CH₂CH₂)₂>O), 7.38 (unres m, 5H, Ø(2,3,4,5,6)), $\delta(^{13}\text{C})$: 42.50, 48.00, 66.85, 127.04, 128.53, 129.85, 135.27, 170.42.

***N,N*-dimethyl-*N'*-benzoylthiourea (IIeG – table 3.1a):** 52.7% yield, mp 129°C (lit⁶¹: 128°C), Calculated for C₁₀H₁₂N₂OS: C, 57.65; H, 5.82; N, 13.45; S, 15.40, Found: C, 57.44; H, 5.86; N, 13.55; S, 15.77, NMR δ(¹H): 3.24 + 3.40 (s + s, 3H + 3H, -N(CH₃)₂), 7.45 (dd, 2H, Ø(3,5)), 7.57 (t, 1H, Ø(4)), 7.82 (d, 2H, Ø(2,6)), 8.28 (br s, 1H, >N'H), δ(¹³C): 43.17, 44.30, 127.75, 128.78, 132.32, 132.90, 163.23, 179.94.

***N,N*-dimethylbenzamide (IIIeG – table 3.1a):** 46.2% yield, oil, Calculated for C₉H₁₁NO·2H₂O: C, 58.35; H, 8.19; N, 7.56, Found: C, 60.59; H, 8.54; N, 7.77, NMR δ(¹H): 2.92 + 3.04 (s + s, 3H + 3H, -N(CH₃)₂), 7.34 (unres m, 5H, Ø(2,3,4,5,6)), δ(¹³C): 35.34, 39.59, 126.91, 128.24, 129.41, 136.22, 171.50, *m/z*: 149 (calc for C₉H₁₁NO: 149.21).

***N*-propyl-*N'*-benzoylthiourea (IIeH – table 3.1a):** 60.9% yield, mp 131 - 132°C (lit⁶⁴: 133 - 134°C), Calculated for C₁₁H₁₄N₂OS: C, 59.42; H, 6.36; N, 12.60; S, 14.42, Found: C, 59.31; H, 6.49; N, 11.57; S, 13.95, NMR δ(¹H): 1.02 (t, 3H, -NHCH₂CH₂CH₃), 1.74 (m, 2H, -NHCH₂CH₂CH₃), 3.69 (m, 2H, -NHCH₂CH₂CH₃), 7.51 (dd, 2H, Ø(3,5)), 7.62 (t, 1H, Ø(4)), 7.83 (d, 2H, Ø(2,6)), 9.02 (br s, 1H, >N'H), 10.74 (br s, 1H, -NHCH₂CH₂CH₃), δ(¹³C): 11.40, 21.50, 47.54, 127.34, 129.05, 131.79, 133.43, 166.80, 179.71.

***N*-propylbenzamide (IIIeH – table 3.1a):** 29.5% yield, mp 81 - 83°C (lit⁶⁵: 79 - 80°C), Calculated for C₁₀H₁₃NO: C, 73.57; H, 8.04; N, 8.58, Found: C, 73.14; H, 8.36; N, 8.71, NMR δ(¹H): 0.96 (t, 3H, -NHCH₂CH₂CH₃), 1.62 (m, 2H, -NHCH₂CH₂CH₃), 3.40 (m, 2H, -NHCH₂CH₂CH₃), 6.39 (br s, 1H, -NHCH₂CH₂CH₃), 7.39 (dd, 2H, Ø(3,5)), 7.44 (t, 1H, Ø(4)), 7.75 (d, 2H, Ø(2,6)), δ(¹³C): 11.35, 22.84, 41.70, 126.79, 128.42, 131.18, 134.83, 167.54.

***N*-butyl-*N'*-benzoylthiourea (IIeI – table 3.1a):** 64.3% yield, mp 49°C, Calculated for C₁₂H₁₆N₂OS: C, 60.97; H, 6.84; N, 11.85; S, 13.57, Found: C, 61.21; H, 6.91; N, 12.08; S, 13.07, NMR δ(¹H): 0.96 (t, 3H, -NHCH₂CH₂CH₂CH₃), 1.43 (m, 2H, -NHCH₂CH₂CH₂CH₃), 1.69 (m, 2H, -NHCH₂CH₂CH₂CH₃), 3.69 (m, 2H, -NHCH₂CH₂CH₂CH₃), 7.48 (dd, 2H, Ø(3,5)), 7.60 (t, 1H, Ø(4)), 7.81 (d, 2H, Ø(2,6)), 9.00 (br s, 1H, >N'H), 10.69 (br s, 1H, -NHCH₂CH₂CH₂CH₃), δ(¹³C): 13.77, 20.20, 30.25, 45.64, 127.28, 128.98, 131.71, 133.37, 166.71, 179.47.

***N*-butylbenzamide (IIIeI – table 3.1a):** 28.6% yield, oil, Calculated for C₁₁H₁₅NO: C, 74.52; H, 8.55; N, 7.90, Found: C, 74.06; H, 9.06; N, 7.91, NMR δ(¹H): 0.92 (t, 3H, -NHCH₂CH₂CH₂CH₃), 1.37 (m, 2H, -NHCH₂CH₂CH₂CH₃), 1.55 (m, 2H, -NHCH₂CH₂CH₂CH₃), 3.41 (m, 2H, -NHCH₂CH₂CH₂CH₃), 6.38 (br s, 1H, -NHCH₂CH₂CH₂CH₃), 7.40 (m, 3H, Ø(3,4,5) phenyl), 7.75 (d, 2H, Ø(2,6)), δ(¹³C): 13.79, 20.18, 31.71, 39.80, 126.73, 128.33, 131.11, 134.72, 167.42.

***N*-(*cis*-2,6-dimethylpiperidyl)-*N'*-(*p*-nitrobenzoyl)thiourea (IIIc – table 3.1b):** 86% yield (crude), mp 109 - 112°C, Calculated for C₁₅H₁₉N₃O₃S: C, 56.04; H, 5.97; N, 13.08; S, 9.98, Found: C, 55.75; H, 5.86; N, 12.73; S, 9.40, NMR δ(¹H): 1.38 (d, 6H, -N<(CH(CH₃)CH₂)₂>CH₂) 1.50 - 2.00 (br unres m, 6H,

-N<(CH(CH₃)CH₂)₂>CH₂), 4.55 + 5.20 (br m + br m, 1H + 1H, -N<(CH(CH₃)CH₂)₂>CH₂), 8.03 (d, 2H, Ø(2,6)), 8.28 (d, 2H, Ø(3,5)), $\delta(^{13}\text{C})$: 13.48, 18.80, 21.01, 54.20, 123.85, 129.13, 138.41, 150.20, 162.69, 179.32.

***N*-piperidyl-*N'*-(*p*-nitrobenzoyl)thiourea (IIHd – table 3.1b):** 17.9% yield, mp 160 – 162°C, Calculated for C₁₃H₁₅N₃O₃S: C, 53.23; H, 5.16; N, 14.33; S, 10.93, Found: C, 53.28; H, 5.26; N, 14.48; S, 11.03, NMR $\delta(^1\text{H})$: 1.73 (br unres m, 6H, -N<(CH₂CH₂)₂>CH₂), 3.58 + 4.15 (unres t + unres t, 2H + 2H, -N<(CH₂CH₂)₂>CH₂), 8.01 (d, 2H, Ø(2,6)), 8.31 (d, 2H, Ø(3,5)), 8.76 (br s, 1H, >N'H), $\delta(^{13}\text{C})$: 23.75, 25.24, 26.02, 52.87, 123.96, 129.10, 137.97, 150.32, 161.39, 177.33.

***N*-piperidyl-*p*-nitrobenzamide (IIIHd – table 3.1b):** 73.3% yield, mp 115 – 116°C (lit⁶⁶: 120 – 121°C), Calculated for C₁₂H₁₄N₂O₃: C, 61.52; H, 6.04; N, 11.96, Found: C, 61.82; H, 6.46; N, 11.91, NMR $\delta(^1\text{H})$: 1.52 (unres m, 2H, -N<(CH₂CH₂)₂>CH₂), 1.68 (unres m, 4H, -N<(CH₂CH₂)₂>CH₂), 3.27 + 3.71 (unres t + unres t, 2H + 2H, -N<(CH₂CH₂)₂>CH₂), 7.54 (d, 2H, Ø(2,6)), 8.25 (d, 2H, Ø(3,5)), $\delta(^{13}\text{C})$: 24.36, 25.46, 6.45, 43.15, 48.59, 123.79, 127.74, 142.67, 148.15, 167.83.

***N*-piperidyl-*N'*-(*p*-methoxybenzoyl)thiourea (IIIfd – table 3.2):** 67.8% yield, mp 139°C, Calculated for C₁₄H₁₈N₂O₂S: C, 60.39; H, 6.53; N, 10.06; S, 11.52, Found: C, 60.38; H, 6.94; N, 10.12; S, 11.38, NMR $\delta(^1\text{H})$: 1.70 (br unres m, 6H, -N<(CH₂CH₂)₂>CH₂), 3.55 + 4.15 (unres t + unres t, 2H + 2H, -N<(CH₂CH₂)₂>CH₂), 3.85 (s, 3H, Ø-OCH₃), 6.93 (d, 2H, Ø(3,5)), 7.79 (d, 2H, Ø(2,6)), 8.37 (br s, 1H, >N'H), $\delta(^{13}\text{C})$: 23.84, 25.26, 25.97, 52.83, 55.49, 114.06, 124.70, 129.86, 162.68, 163.32, 178.45.

***N*-piperidyl-*p*-methoxybenzamide (IIIfd – table 3.2):** 24.1% yield, oil, Calculated for C₁₃H₁₇NO₂: C, 71.19; H, 7.83; N, 6.39, Found: C, 70.24; H, 7.99; N, 6.41, NMR $\delta(^1\text{H})$: 1.58 (br m, 6H, -N<(CH₂CH₂)₂>CH₂), 3.48 (br unres t, 4H, -N<(CH₂CH₂)₂>CH₂), 3.81 (s, 3H, Ø-OCH₃), 6.88 (d, 2H, Ø(2,6)), 7.35 (d, 2H, Ø(3,5)), $\delta(^{13}\text{C})$: 24.60, 26.06, 43.40, 48.20, 55.26, 113.58, 128.55, 128.78, 160.46, 170.26.

***N*-piperidyl-*N'*-(*p*-chlorobenzoyl)thiourea (IIId – table 3.2):** 44.2% yield, mp 133 – 134°C, Calculated for C₁₃H₁₅ClN₂OS: C, 55.20; H, 5.36; N, 9.91; S, 11.34, Found: C, 55.42; H, 5.53; N, 10.07; S, 11.53, NMR $\delta(^1\text{H})$: 1.72 (br m, 6H, -N<(CH₂CH₂)₂>CH₂), 3.55 + 4.14 (unres t + unres t, 2H + 2H, -N<(CH₂CH₂)₂>CH₂), 7.44 (d, 2H, Ø(3,5)), 7.77 (d, 2H, Ø(2,6)), 8.46 (br s, 1H, >N'H), $\delta(^{13}\text{C})$: 23.83, 25.26, 26.02, 52.87, 129.16, 129.28, 130.95, 139.38, 162.26, 177.96.

***N*-piperidyl-*p*-chlorobenzamide (IIId – table 3.2):** 48.8% yield, mp 79 – 81°C (lit⁶⁷: 69 – 72°C), Calculated for C₁₂H₁₄ClNO: C, 64.42; H, 6.32; N, 6.26, Found: C, 64.49; H, 6.53; N, 6.39, NMR $\delta(^1\text{H})$: 1.45-1.70 (br unres m, 6H, -N<(CH₂CH₂)₂>CH₂), 3.30 + 3.65 (unres t + unres t, 2H + 2H, -N<(CH₂CH₂)₂>CH₂), 7.34 (m, 4H, Ø(2,3,5,6)), $\delta(^{13}\text{C})$: 24.52, 26.06, 26.35, 43.18, 48.74, 128.36, 128.66, 134.85, 135.39, 169.21.

***N*-piperidyl-*N'*-(*m*-nitrobenzoyl)thiourea (IIJd – table 3.2):** 21.0% yield, mp 139 – 142°C, Calculated for $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.16; N, 14.33; S, 10.93, Found: C, 53.51; H, 5.17; N, 14.37; S, 10.91, NMR $\delta(^1H)$: 1.72 (br unres m, 6H, $-N<(\underline{CH_2CH_2})_2>\underline{CH_2}$), 3.58 + 4.15 (unres t + unres t, 2H + 2H, $-N<(\underline{CH_2CH_2})_2>\underline{CH_2}$), 7.68 (dd, 1H, $\emptyset(5)$), 8.17 (d, 1H, $\emptyset(6)$), 8.40 (d, 1H, $\emptyset(4)$), 8.66 (s, 1H, $\emptyset(2)$), 8.86 (br s, 1H, $>\underline{N'H}$), $\delta(^{13}C)$: 23.83, 25.62, 26.07, 52.85, 122.92, 127.21, 130.04, 133.55, 134.09, 148.20, 161.00, 177.24.

***N*-piperidyl-*m*-nitrobenzamide (IIJd – table 3.2):** 71.6% yield, mp 80 – 82°C, Calculated for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.04; N, 11.96, Found: C, 61.85; H, 6.12; N, 12.06, NMR $\delta(^1H)$: 1.55 (unres m, 2H, $-N<(\underline{CH_2CH_2})_2>\underline{CH_2}$), 1.68 (unres m, 4H, $-N<(\underline{CH_2CH_2})_2>\underline{CH_2}$), 3.25 + 3.70 (unres t + unres t, 2H + 2H, $-N<(\underline{CH_2CH_2})_2>\underline{CH_2}$), 7.58 (dd, 1H, $\emptyset(5)$), 7.71 (d, 1H, $\emptyset(6)$), 8.24 (unres m, 2H, $\emptyset(2,4)$), $\delta(^{13}C)$: 24.44, 25.57, 26.51, 43.40, 48.82, 121.97, 124.10, 129.61, 132.77, 137.95, 147.95, 167.42.

***N*-propyl-*N'*-(*p*-methoxybenzoyl)thiourea (IIFh – table 3.3):** 90.0% yield, mp 74 – 75°C, Calculated for $C_{12}H_{16}N_2O_2S$: C, 57.11; H, 6.40; N, 11.10; S, 12.71, Found: C, 56.93; H, 6.80; N, 11.23; S, 12.38, NMR $\delta(^1H)$: 1.01 (t, 3H, $-NHCH_2CH_2\underline{CH_3}$), 1.73 (m, 2H, $-NHCH_2\underline{CH_2}CH_3$), 3.65 (m, 2H, $-NH\underline{CH_2}CH_2CH_3$), 3.86 (s, 3H, $\emptyset-O\underline{CH_3}$), 6.96 (d, 2H, $\emptyset(3,5)$), 7.80 (d, 2H, $\emptyset(2,6)$), 9.00 (br s, 1H, $>\underline{N'H}$), 10.79 (br s, 1H, $-NHCH_2CH_2CH_3$), $\delta(^{13}C)$: 11.45, 21.57, 47.53, 55.57, 114.35, 123.75, 129.58, 163.83, 166.29, 179.94.

***N*-propyl-*p*-methoxybenzamide (IIFh – table 3.3):** 8.7% yield, mp 60 – 62°C (lit⁶⁸: 60 – 64°C), Calculated for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.84; N, 7.25, Found: C, 68.39; H, 8.44; N, 7.47, NMR $\delta(^1H)$: 0.96 (t, 3H, $-NHCH_2CH_2\underline{CH_3}$), 1.61 (m, 2H, $-NHCH_2\underline{CH_2}CH_3$), 3.38 (m, 2H, $-NH\underline{CH_2}CH_2CH_3$), 3.82 (s, 3H, $\emptyset-O\underline{CH_3}$), 6.22 (br s, 1H, $-NHCH_2CH_2CH_3$), 6.89 (d, 2H, $\emptyset(3,5)$), 7.73 (d, 2H, $\emptyset(2,6)$), $\delta(^{13}C)$: 11.41, 22.96, 41.69, 55.35, 113.66, 127.16, 128.60, 161.99, 167.06.

***N*-propyl-*N'*-(*p*-heptoxybenzoyl)thiourea (IIKh – table 3.3):** 95.2% yield, mp 86°C, Calculated for $C_{18}H_{28}N_2O_2S$: C, 64.23; H, 8.40; N, 8.32; S, 9.53, Found: C, 64.55; H, 8.69; N, 8.51; S, 9.47, NMR $\delta(^1H)$: 0.88 (t, 3H, $\emptyset-OCH_2CH_2CH_2CH_2CH_2CH_2\underline{CH_3}$), 1.01 (t, 3H, $-NHCH_2CH_2\underline{CH_3}$), 1.36 (unres m, 8H, $\emptyset-OCH_2CH_2CH_2CH_2CH_2CH_2CH_2\underline{CH_3}$), 1.73 (unres m, 4H, $-NHCH_2\underline{CH_2}CH_3$ and $\emptyset-OCH_2\underline{CH_2}CH_2CH_2CH_2CH_2CH_2\underline{CH_3}$), 3.66 (m, 2H, $-NH\underline{CH_2}CH_2CH_3$), 4.01 (t, 2H, $\emptyset-O\underline{CH_2}CH_2CH_2CH_2CH_2CH_2CH_2\underline{CH_3}$), 6.95 (d, 2H, $\emptyset(3,5)$), 7.78 (d, 2H, $\emptyset(2,6)$), 8.92 (s, 1H, $>\underline{N'H}$), 10.77 (br s, 1H, $-NHCH_2CH_2CH_3$), $\delta(^{13}C)$: 11.46, 14.04, 21.59, 22.56, 25.89, 28.98, 31.71, 47.54, 68.46, 114.81, 123.41, 129.51, 163.50, 166.27, 179.94.

***N*-propyl-*N'*-(*p*-*t*-butylbenzoyl)thiourea (IIKh – table 3.3):** 72.8% yield, mp 86 – 87°C, Calculated for $C_{15}H_{22}N_2OS$: C, 64.69; H, 7.98; N, 10.06; S, 11.52, Found: C, 64.33; H, 8.27; N, 10.16; S, 11.36, NMR $\delta(^1H)$: 1.02 (t, 3H, $-NHCH_2CH_2\underline{CH_3}$), 1.33 (s, 9H, $\emptyset-C(\underline{CH_3})_3$), 1.74 (m, 2H, $-NHCH_2\underline{CH_2}CH_3$), 3.66 (m, 2H, $-NH\underline{CH_2}CH_2CH_3$), 7.50 (d, 2H, $\emptyset(3,5)$), 7.76 (d, 2H, $\emptyset(2,6)$), 8.97 (br s, 1H, $>\underline{N'H}$), 10.78 (br s, 1H, $-NHCH_2CH_2CH_3$), $\delta(^{13}C)$: 11.46, 14.04, 21.59, 22.56, 25.89, 28.98, 31.71, 47.54, 68.46, 114.81, 123.41, 129.51, 163.50, 166.27, 179.94.

-NHCH₂CH₂CH₃), $\delta(^{13}\text{C})$: 11.45, 21.56, 31.01, 35.18, 47.57, 126.08, 127.31, 128.84, 157.49, 166.73, 179.85.

***N*-propyl-*p*-*t*-butylbenzamide (IIILh – table 3.3):** 19.0% yield, oil, Calculated for C₁₄H₂₁NO: C, 76.65; H, 9.67; N, 6.39, Found: C, 75.63; H, 10.09; N, 6.62, NMR $\delta(^1\text{H})$: 0.95 (t, 3H, -NHCH₂CH₂CH₃), 1.31 (s, 9H, $\text{O}-\text{C}(\text{CH}_3)_3$), 1.61 (m, 2H, -NHCH₂CH₂CH₃), 3.39 (m, 2H, -NHCH₂CH₂CH₃), 6.33 (br s, 1H, -NHCH₂CH₂CH₃), 7.41 (d, 2H, $\text{O}(3,5)$), 7.70 (d, 2H, $\text{O}(2,6)$), $\delta(^{13}\text{C})$: 11.41, 22.96, 31.16, 34.87, 41.68, 125.41, 126.69, 132.00, 154.71, 167.52.

***N*-propyl-*N'*-(*p*-chlorobenzoyl)thiourea (IIGh – table 3.3):** 66.9% yield, mp: 87 - 88°C, Calculated for C₁₁H₁₃ClN₂OS: C, 51.45; H, 5.11; N, 10.91; S, 12.49, Found: C, 51.76; H, 5.07; N, 10.84; S, 12.26, NMR $\delta(^1\text{H})$: 1.01 (t, 3H, -NHCH₂CH₂CH₃), 1.73 (m, 2H, -NHCH₂CH₂CH₃), 3.65 (m, 2H, -NHCH₂CH₂CH₃), 7.48 (d, 2H, $\text{O}(3,5)$), 7.76 (d, 2H, $\text{O}(2,6)$), 9.02 (br s, 1H, >N'H), 10.66 (br s, 1H, -NHCH₂CH₂CH₃), $\delta(^{13}\text{C})$: 11.38, 21.47, 47.56, 128.81, 129.38, 130.15, 140.02, 165.76, 179.52.

***N*-propyl-*p*-chlorobenzamide (IIIGh – table 3.3):** 23.4% yield, mp 96 - 97°C (lit⁶⁸: 95 - 100°C), Calculated for C₁₀H₁₂ClNO: C, 60.75; H, 6.13; N, 7.09, Found: C, 60.63; H, 6.31; N, 7.15, NMR $\delta(^1\text{H})$: 0.95 (t, 3H, -NHCH₂CH₂CH₃), 1.61 (m, 2H, -NHCH₂CH₂CH₃), 3.37 (m, 2H, -NHCH₂CH₂CH₃), 6.38 (br s, 1H, -NHCH₂CH₂CH₃), 7.35 (d, 2H, $\text{O}(3,5)$), 7.69 (d, 2H, $\text{O}(2,6)$), $\delta(^{13}\text{C})$: 11.39, 22.84, 41.84, 128.30, 128.71, 133.21, 137.46, 166.53.

***N*-propyl-*N'*-(*p*-nitrobenzoyl)thiourea (IIHh – table 3.3):** 27.4% yield, mp 109 - 110°C, Calculated for C₁₁H₁₃N₃O₃S: C, 49.42; H, 4.94; N, 15.72; S, 12.00, Found: C, 49.34; H, 5.12; N, 10.75; S, 11.93, NMR $\delta(^1\text{H})$: 1.02 (t, 3H, -NHCH₂CH₂CH₃), 1.74 (m, 2H, -NHCH₂CH₂CH₃), 3.65 (m, 2H, -NHCH₂CH₂CH₃), 8.03 (d, 2H, $\text{O}(2,6)$), 8.35 (d, 2H, $\text{O}(3,5)$), 9.33 (br s, 1H, >N'H), 10.57 (br s, 1H, -NHCH₂CH₂CH₃), $\delta(^{13}\text{C})$: 11.41, 21.47, 47.68, 124.18, 128.86, 137.37, 150.58, 165.08, 179.25.

***N*-propyl-*p*-nitrobenzamide (IIIHh – table 3.3):** 51.4% yield, mp 102 - 103°C (lit⁶⁸: 100 - 104°C), Calculated for C₁₀H₁₂N₂O₃: C, 57.67; H, 5.82; N, 13.46, Found: C, 57.68; H, 5.94; N, 10.74, NMR $\delta(^1\text{H})$: 0.96 (t, 3H, -NHCH₂CH₂CH₃), 1.64 (m, 2H, -NHCH₂CH₂CH₃), 3.41 (m, 2H, -NHCH₂CH₂CH₃), 6.55 (br s, 1H, -NHCH₂CH₂CH₃), 7.91 (d, 2H, $\text{O}(2,6)$), 8.23 (d, 2H, $\text{O}(3,5)$), $\delta(^{13}\text{C})$: 11.38, 22.74, 42.08, 123.70, 128.08, 140.44, 149.44, 165.58.

***p*-methoxybenzoyl isothiocyanate:** NMR $\delta(^{13}\text{C})$: 55.38, 114.52, 122.80, 132.75, 146.70, 159.86, 165.60.

benzoyl isothiocyanate: NMR $\delta(^{13}\text{C})$: 129.16, 130.24, 130.64, 135.28, 147.48, 161.06.

***p*-nitrobenzoyl isothiocyanate:** NMR $\delta(^{13}\text{C})$: 124.01, 131.51, 135.75, 149.03, 151.63, 160.35.

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CHAPTER 4

University of Cape Town

Alternative approaches to the synthesis of *N*-substituted *N'*-acyl- and *N'*-aroylthioureas

4.1 Introduction

In the previous chapters it was shown that the Douglass and Dains reaction is effective for the synthesis of *N*-substituted *N'*-aroylthioureas, because electronic properties usually favour the addition of the aroyl isothiocyanate and amine reagents. However, with acyl isothiocyanates, and a few aroyl isothiocyanates, the electronic conditions are not favourable, and the addition only prevails under stringent steric control i.e. at least one of the reagents must have substituents with sufficient steric bulk to hinder the competing process of amide formation. With primary amines, for which the nitrogen nucleophile is particularly exposed, even large acyl substituents on the isothiocyanate do not adequately prevent this substitution reaction. It is conceivable that a variety of new *N'*-acylthioureas could be synthesized if this limitation were overcome or avoided.

During the course of this project, attempts were made to synthesize *N'*-acylthioureas by means other than the conventional Douglass and Dains procedure. This was done, as much out of curiosity, as with the aim of achieving at least 50% yields for those *N'*-acylthioureas for which the amine – acyl isothiocyanate combination had proved unsuitable. The investigation was not intended to cover an exhaustive search for alternative reactions, but merely to test a few approaches that appeared practical and simple enough to complement the convenience of Douglass and Dains' method.

Of the three possibilities studied, the first reaction involved the substitution of an *N*-substituted thiocarbamoyl chloride by an amide. The intended process was to be a nucleophilic attack from the amidic nitrogen, with the perceived advantage that it was directed at an electrophilic reagent with only one active site. However, the possibility that the oxygen of the amide, rather than its nitrogen, would attack the thiocarbonyl carbon had to be considered as a potential interference. Avoiding the two competing electrophilic centres of the acyl isothiocyanate was also the rationale behind the second procedure. This involved a reaction in which an acyl chloride was added to a thiourea with one unsubstituted nitrogen atom. Although Dixon, Hawthorne and Taylor¹⁻⁴ actively investigated such reactions between the years of 1900 and 1912, their work, which produced encouraging results, appears to have attracted very little subsequent attention.

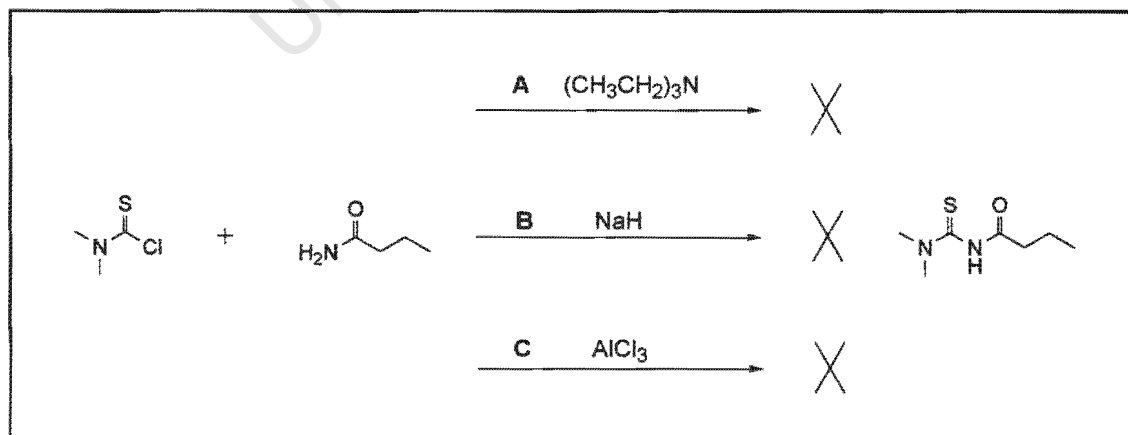
The third and final approach, was based on a modification in the Douglass and Dains reaction. Before being added to the acyl isothiocyanate, unhindered amines like dimethylamine, piperidine and propylamine were protected with a trimethylsilyl group. This bulky but labile group was intended as a steric hindrance, preventing the amine from approaching and reacting at the carbonyl carbon.

4.2 Reactions of *N,N*-dimethylthiocarbamoyl chloride and butyramide

As pointed out above, the addition of these two reagents was intended to lead to a reaction between the unsubstituted nitrogen of the butyramide and the electrophilic thiocarbonyl carbon of the thiocarbamoyl chloride. As such, the reaction appeared to present another one-pot alternative to the Douglass and Dains process. The dimethyl substituted thiocarbamoyl chloride is a stable, low melting point solid that is readily available commercially. Since the unhindered dimethylamine moiety is already attached at the thiocarbonyl carbon in this reagent, the synthesis is potentially reduced to a single step procedure. Avoiding the practical inconvenience of having to introduce dimethylamine gas to the reaction mixture (see section 2.6.1), was regarded as an additional convenience. However, despite several attempts, the combination did not produce the desired *N,N*-dimethyl-*N'*-butanoylthiourea.

At first, equimolar quantities of amide and thiocarbamoyl chloride were simply added in anhydrous THF, along with 1.5 equivalents of triethylamine (A, figure 4.1). The latter was intended to trap hydrogen chloride that was expected as a by-product from the reaction. The mixtures were left to reflux under a nitrogen atmosphere for up to 24 hours, but did not yield any *N'*-butanoylthiourea. In renewed attempts, sodium hydride was added to the reaction mixture (B, figure 4.1). This strong base is typically used to remove a hydrogen atom from the nitrogen of an amide ⁵. Here, it was hoped that the enhanced nucleophilicity of the resulting amidate ion would help to ensure that the desired reaction took place. When this approach also failed, attempts were made to activate the thiocarbamoyl chloride instead. This was done by adding aluminium chloride, a Friedel-Crafts catalyst that enhances the carbocationic character of the thiocarbonyl carbon (C, figure 4.1) ⁶. Although thiocarbamoyl chlorides will react with aromatic hydrocarbons to give thioamides in this way ^{7,8}, the desired reaction with the butyramide did not occur.

Figure 4.1 Schematic representation of the unsuccessful attempts to synthesize *N,N*-dimethyl-*N'*-butanoylthiourea from *N,N*-dimethylthiocarbamoyl chloride and butyramide



In all attempts, the reaction mixtures were left to reflux under nitrogen for several hours. Progress, however, was monitored at regular intervals, using thin layer chromatography and authentic *N,N*-dimethyl-*N'*-

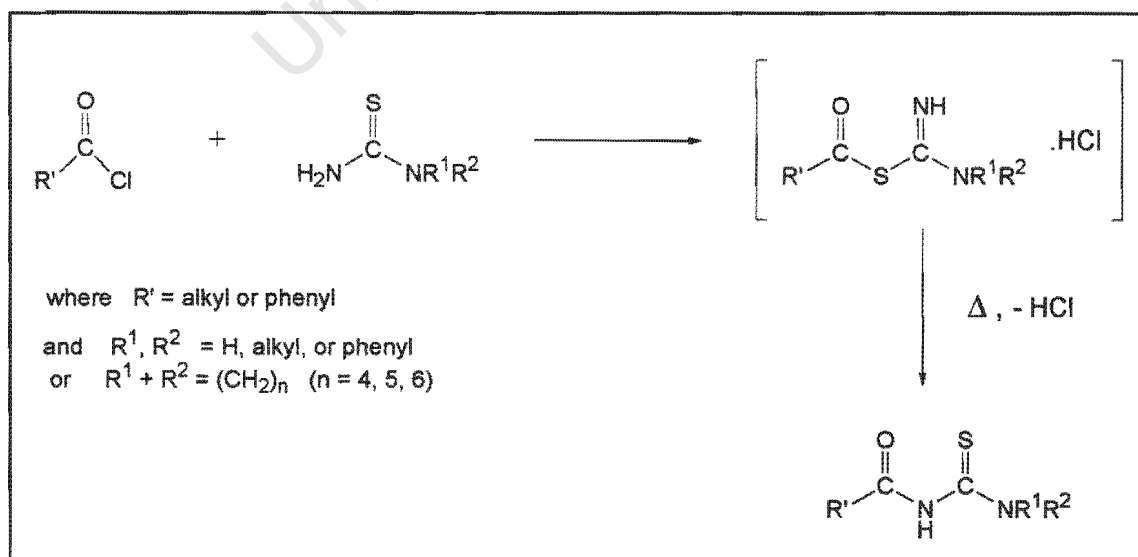
butanoylthiourea as a standard. To further confirm the negative results indicated on the chromatographic plates, the crude product mixtures were recovered and further submitted for characterisation by ^1H and ^{13}C NMR spectroscopy. Since none of the resulting spectra contained any resonances that corresponded to the characteristic peaks of the authentic compound, no attempt was made to separate and identify individual products.

Apart from these negative results, further investigation into these reactions was also discouraged by the fact that relatively few other *N*-substituted thiocarbamoyl chlorides are available commercially. (In South Africa, *N,N*-diethyl thiocarbamoyl chloride was the only other variant that could be purchased). Although various procedures for the synthesis of these compounds are described in the literature⁷, they usually involve the use of very toxic reagents (i.e. thiophosgene) or reagents that are also not commonly available (eg. *N*-substituted thiuram disulfides)⁹⁻¹¹.

4.3 Reactions of acyl chlorides with *N*-mono- and *N,N*-disubstituted thioureas

In 1907, Dixon and Hawthorne¹ described several *N*-substituted *N'*-acetylthioureas that had been synthesized in anhydrous acetone, by reacting acetyl chloride with simple thiourea and a variety of *N*-phenylthioureas (figure 4.2). They showed that the reactions initially proceeded via acylation at the sulphur and that a hydrogen chloride salt of *S*-substituted pseudothiourea was formed. Although they were primarily concerned with the constitution of this intermediate, they found that the hydrogen chloride was easily removed and the acetyl group transferred to a nitrogen, either spontaneously or with the application of heat.

Figure 4.2 Synthesis of *N*-substituted *N'*-acyl- and *N'*-aroylthioureas from acyl or aroyl chlorides and *N*-substituted thioureas



For those pseudothiurea salts stable enough to be isolated and weighed, they recorded several yields in excess of 90%. Dixon and Taylor continued these investigations until 1912, and in the process successfully produced a variety of *N'*-acylthiurea derivatives²⁻⁴.

With the present day routine application of the Douglass and Dains synthesis, and with interest focused primarily on co-ordination chemistry and ligand behaviour of *N'*-aroylthiureas, these early achievements appear to have been overlooked and forgotten. However, in part, this oversight might also be linked to the fact that very few *N*-mono- and *N,N*-disubstituted thiureas are available commercially. Synthesis of these reagents should therefore be regarded as a prerequisite component of Dixon and Hawthorne's¹ method.

4.3.1 Experimental Approach

The acyl chloride – thiurea reaction was tested in the course of this project by combining butanoyl chloride with *N,N*-dimethyl-, *N*-propyl-, *N*-piperidyl-* and *N*-pyrrolidylthiureas*. These reagents were chosen because the reactions between butanoyl isothiocyanate and the analogous amines had only produced *N'*-butanoylthiureas in yields of 10% or less (see table 2.1, chapter 2). The acyl chloride - thiurea reaction was also applied in the synthesis of *N,N*-dimethyl-*N'*-acetylthiurea, the smallest *N,N*-dialkyl substituted acylthiurea.

The reactions were carried out by dissolving the thiurea in anhydrous acetone along with triethylamine base. The acyl chloride, also in anhydrous acetone, was then added at a dropwise rate to the thiurea solution. This mixture was boiled under reflux, then cooled to room temperature, and poured into a small volume of water to allow slow precipitation of solid products. As in the Douglass and Dains synthesis, the reactions were carried out under nitrogen. The addition of triethylamine base and the heating step were intended to ensure complete conversion of pseudothiurea salts to *N*-substituted *N'*-acylthiureas. Further experimental details are given in section 4.6.1.

4.3.2 Results and Discussion

The yields from the above reactions ranged between 62 and 85%, and as such, they all represented substantial improvements on the small fractions recovered previously from the analogous Douglass and Dains syntheses. For comparison, the results are listed in table 4.1 along with the yields recorded for the corresponding butanoyl isothiocyanate – amine reactions in chapter 2.

* According to IUPAC nomenclature^{12,13} these two compounds are formally named as piperidine-1-carbothioic acid amide and pyrrolidine-1-carbothioic acid amide respectively.

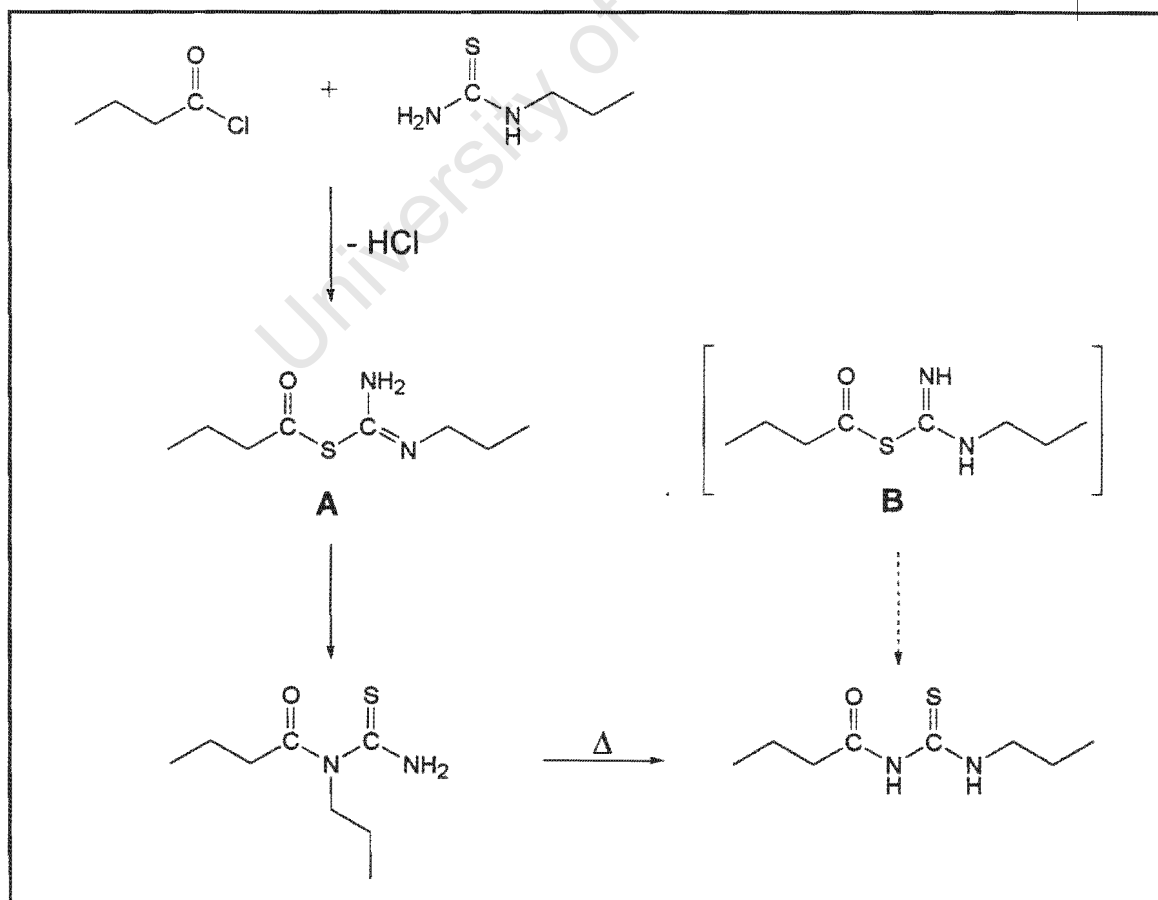
Table 4.1 Yields of *N*-substituted *N'*-butanoyl- and *N'*-acetylthiureas from the reactions of butanoyl and acetyl chlorides with *N*-substituted thioureas. (Corresponding *N'*-butanoylthiourea yields from the conventional Douglass and Dains reactions are listed for comparison)

Acyl chloride	Thiourea	Yield <i>N'</i> -acylthiourea (%)	<i>N'</i> -acylthiourea yield from Douglass and Dains reaction (%)
$\text{R}'-\text{C}(=\text{O})\text{Cl}$	$\text{H}_2\text{N}-\text{C}(=\text{S})-\text{NR}_2$	$\text{R}'-\text{C}(=\text{O})-\text{NH}-\text{C}(=\text{S})-\text{NR}_2$	(values from table 2.1)
$\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{Cl}$ +	$\text{H}_2\text{N}-\text{C}(=\text{S})-\text{N}(\text{CH}_3)_2$	80.2	(10.7)
	$\text{H}_2\text{N}-\text{C}(=\text{S})-\text{N}(\text{CH}_2)_5$	84.2	(8.5)
	$\text{H}_2\text{N}-\text{C}(=\text{S})-\text{N}(\text{CH}_2)_3$	77.6	(3.6)
	$\text{H}_2\text{N}-\text{C}(=\text{S})-\text{NHCH}_2\text{CH}_2\text{CH}_3$	68.5	(14.3)
$\text{CH}_3\text{C}(=\text{O})\text{Cl}$ +	$\text{H}_2\text{N}-\text{C}(=\text{S})-\text{N}(\text{CH}_3)_2$	62.0	-

N-piperidyl- and *N*-pyrrolidyl-*N'*-butanoylthiourea were recovered as precipitates and recrystallised. *N,N*-dimethyl-*N'*-butanoylthiourea, which is an oil at room temperature, appeared to be quite miscible with water, and was therefore extracted with chloroform and then purified by column chromatography. *N,N*-dimethyl-*N'*-acetylthiourea is a crystalline solid with a melting point between 102°C and 104°C. However, it also appeared to be relatively soluble in water, and had to be extracted with several portions of chloroform. It was also subsequently purified by column chromatography, but could be recrystallised from small volumes of water as well.

The synthesis of *N*-propyl-*N'*-butanoylthiourea produced a crystalline product that precipitated when the acetone reaction mixture was poured into water. However, thin layer chromatography indicated the presence of two closely associated compounds in this material: a minor component with an R_f value of 0.68, and a major one with an R_f of 0.63 (R_f values determined on silica gel plates with a 5% acetone in methylene chloride eluent). ^1H and ^{13}C NMR spectra of the mixture revealed the major compound to be a structural isomer of the desired product, in which the butanoyl and propyl groups were attached to the same nitrogen of the thiourea i.e. *N*-propyl-*N'*-butanoylthiourea. Minor peaks in these spectra corresponded to resonances expected for the targeted *N*-propyl-*N'*-butanoylthiourea. The C, H, N and S composition of the mixture was also determined and was found to match the composition expected for the pure forms of the isomers.

Figure 4.3 Synthesis of *N*-propyl-*N'*-butanoylthiourea and isomerisation to *N*-propyl-*N'*-butanoylthiourea



While this latter result appears to be an anomalous one in the above series of reactions, it was not entirely unexpected. Dixon and Hawthorne¹ observed that the initial S-acylation in *N*-monosubstituted thioureas was followed by a transfer of the acyl group to the substituted, rather than the unsubstituted, nitrogen. Evidently, the reaction proceeds via the S-substituted pseudothiourea isomer in which the proton is lost from the former site (isomer A in figure 4.3), and not the latter (isomer B). (With the *N,N*-disubstituted thioureas as reagents, only isomer B can form). Fortunately, however, by heating these *N,N*-substituted thioureas to slightly above their melting point temperatures, they were readily converted to the *N,N'* isomers. This also proved to be the case when the *N*-propyl-*N*-butanoylthiourea was melted (see figure 4.3).

The results in table 4.1 confirm that Dixon and Hawthorne's¹ acyl chloride – thiourea reaction provides a very useful pathway for the synthesis of *N*-substituted-*N'*-acylthioureas. Apart from the substantially improved yields, this reaction is no more complicated or time consuming than the Douglass and Dains procedure.

4.3.3 Synthesis of the *N*- and *N,N*-substituted thiourea reagents

Of the above mentioned *N*-substituted thiourea reagents, none were commercially available in South Africa, and they were thus especially prepared for the above investigation. These compounds have been synthesized by a variety of procedures in the past¹⁴⁻²¹. Some of the methods¹⁶⁻¹⁹ were, however, considered too complicated and time consuming to complement the simplicity of Dixon and Hawthorne's¹ reaction. Of the more convenient procedures, two were tested in the course of this project. These were a thermal isomerisation process, and an acid hydrolysis of *N*-substituted *N'*-acylthioureas.

4.3.2.1 Thermal isomerisation of amine thiocyanate salts

It is well known that certain amine thiocyanates will rearrange to thioureas when directly heated to 160°C for several hours, or when heated in organic solvents with high boiling points^{14,20,21}. Both are very simple procedures, but the degree of thiocyanate to thiourea conversion seems to depend on the particular amine thiocyanate that is used.

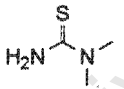
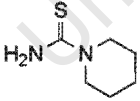
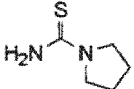
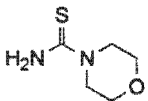
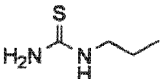
In this work, the necessary amine thiocyanates were formed by reacting amine hydrochloride salts with potassium thiocyanate or by adding amines directly to ammonium thiocyanate. In the latter process, a vigorous reaction ensued in which ammonia gas was evolved.

Thermal conversion of the amine thiocyanates was at first attempted by heating the salts under nitrogen to 160°C for five hours. After cooling, the solidified melt was washed with cold water to separate the *N*-substituted thiourea from the soluble thiocyanate salt that remained. The yields obtained are listed in

table 4.2. They ranged from 3.1% for *N*-piperidylthiourea to 27.4% for *N*-pyrrolidylthiourea, and as such proved to be disappointingly low.

The isomerisation of piperidine and dimethylamine thiocyanates was also attempted by heating the salts in boiling chlorobenzene (i.e. 132°C). The procedure is essentially an extraction process where the salts form dense, insoluble molten phases, and the isomerised thioureas, being more soluble, partition into the solvent. After boiling the mixtures under reflux, the hot chlorobenzene was decanted from the melt and allowed to cool. This brought about the rapid precipitation of a white, flaky material which, for the dimethylamine thiocyanate reaction, proved to be a pure form of the *N,N*-dimethylthiourea. However, the *N*-piperidylthiourea that was filtered from the other reaction was found to be less pure. It contained a significant fraction of piperidine thiocyanate that had to be washed out with cold water. It is possible that the contamination arose from the reverse isomerisation of the *N*-piperidylthiourea product, as this thiourea is particularly unstable and readily reverts to its thiocyanate form when it is heated to melting.

Table 4.2 Yields of *N*-substituted thioureas from the thermal conversion of amine thiocyanate salts at 160°C and in boiling chlorobenzene

Thiourea	Conversion yield (%)	
$\text{R}_2\text{NH.HSCN} \xrightarrow{\Delta} \text{H}_2\text{N}-\text{C}(=\text{S})-\text{NR}_2$	160°C	chlorobenzene (132°C, 0.1 M)
	6.0	30.3
	3.1	24.1
	27.4	-
	17.1	-
	26.1	-

The conversion yields depended on the volume of chlorobenzene and the quantity of salt used. 0.2 Molar solutions gave yields of 13.3% for *N*-piperidylthiourea and 17.0% for *N,N*-dimethylthiourea. These increased to 24.1% and 30.3% respectively, when 0.1 molar solutions were used. To obtain additional fractions of thiourea and to avoid waste, it is possible to re-heat the remaining thiocyanate salt in the filtered chlorobenzene. However, at least five extraction cycles were required to reach overall yields of 65%, even when working with the 0.1 M solutions.

Both conversions were repeated on other occasions. Boiling the mixtures for longer than an hour, rapidly quenching them with ice water after boiling, or using toluene (boiling point 111°C) instead of chlorobenzene, did not bring about any improvements. The fact that significantly more complex procedures have been developed for the synthesis of *N*-mono- and *N,N*-disubstituted thioureas in recent years suggests that the thermal conversion of amine thiocyanates has seldom proved efficient in the past. In this work, however, the concerted attempts at thermal conversion were also prompted by a publication from 1994, in which Kutbiddinov *et al.*²¹ reported that 80% to 90% yields of *N*-piperidylthiourea were obtained by heating piperidine thiocyanate in *n*-butanol for 90 minutes. Determined efforts were made to repeat this work, but these consistently failed to deliver more than 5% of the targeted compound. Unfortunately, the report by Kutbiddinov *et al.*²¹ includes only an incomplete description of the necessary experimental procedure. In recent personal communication, Dr Kutbiddinov confirmed to the author that certain experimental details were deliberately withheld. Nevertheless, the results in his report do suggest that the efficient thermal conversion of amine thiocyanates is indeed an attainable goal.

4.3.2.2 Acid Hydrolysis of *N*-substituted *N'*-acyl- and *N'*-aroylthioureas

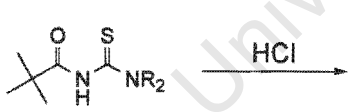
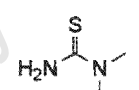
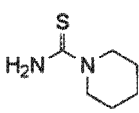
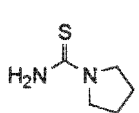
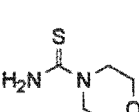
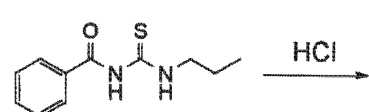
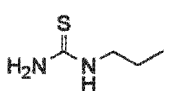
N-substituted thioureas are also produced when *N*-substituted *N'*-acyl- and *N'*-aroyl thioureas are broken down by acid hydrolysis. The process was reported as a formal synthesis for *N*-substituted thioureas in 1973 by Hartmann and Reuther¹⁵. They first produced several *N,N*-disubstituted *N'*-benzoyl- and *N'*-ethoxycarbonylthioureas using the Douglass and Dains method, and then proceeded to treat them with concentrated hydrochloric acid to obtain the *N,N*-dialkylthioureas. They remarked that exceptionally pure compounds were obtained from the *N'*-ethoxycarbonylthioureas because carbon dioxide and ethanol were the only other breakdown products.

A synthesis based on Hartmann and Reuther's¹⁵ procedure was first tested using *N*-propyl-*N'*-benzoylthiourea. According to directions, the appropriate amount of this compound was stirred into 100 ml of hot, concentrated hydrochloric acid. However, the vigorous reaction described by Hartmann and Reuther²¹ did not materialise. The *N'*-benzoylthiourea was hydrophobic, and visually, the process of dissolution and breakdown was obscured by the simultaneous precipitation of benzoic acid. As a result, a further 200 ml of hydrochloric acid was added and the period of heating and stirring extended to twenty four hours. After this, the benzoic acid precipitate was removed by filtration. The filtrate was neutralised by cautious addition of ammonia solution and then left to stand. On standing, however, only a small fraction of

the targeted *N*-propylthiourea precipitated. The bulk of this product was thus recovered by extraction with chloroform. In this way, an overall yield of 51.3% was obtained (see table 4.3). This was considered disappointingly low. The product also contained minor amounts of *N*'-benzoylthiourea starting material, which indicated that prolonged stirring and additional acid had been quite necessary.

Although Hartmann and Reuther's¹⁵ report does not make mention of similar difficulties, it is perhaps telling that only two of their hydrolysis reactions were carried out using *N*'-benzoylthioureas. Of the eleven *N,N*-dialkylthioureas, nine were derived from *N*'-ethoxycarbonylthiourea. It is thus tempting to suggest that hydrolysis of the appropriate *N*'-ethoxycarbonylthiourea may also be a more convenient approach to the synthesis of *N*-propylthiourea. Fortunately, it was also possible to identify a significantly more efficient approach to Hartmann and Reuther's¹⁵ synthesis of *N,N*-disubstituted thioureas in the course of this project. Based on the higher yields from the Douglass and Dains reactions, it seemed more appropriate to use as starting materials for the hydrolysis, the *N*-substituted *N*'-(2,2-dimethylpropanoyl)thioureas rather than the *N*'-benzoylthioureas (compare yields in tables 2.2 and 3.1a of chapters 2 and 3).

Table 4.3 Yields of *N*-substituted thioureas from the acid hydrolysis of *N*-substituted *N*'-(2,2-dimethylpropanoyl)thiourea and *N*-propyl-*N*'-benzoylthiourea

<i>N</i> '-acyl- or aroylthiourea hydrolysed	<i>N</i> -substituted Thiourea	Yield (%)
		86.8
		94.5
		89.2
		92.7
		51.3

After initial tests, it became evident that the choice also presented several other practical benefits. For one, dissolution and breakdown of the *N*'-(2,2-dimethylpropanoyl)thioureas was rapid and required just one hour of stirring in the hot acid. Furthermore, unlike benzoic acid, the 2,2-dimethylpropanoic acid by-product proved to be far more soluble in aqueous solution and did not have to be removed before recovery of the *N,N*-disubstituted thioureas. After neutralisation the solutions were simply left to cool and stand overnight, this usually bringing about the high yield precipitation of the pure *N,N*-disubstituted thioureas.

The method proved very effective, and for the synthesis of the *N,N*-dimethyl-, *N*-morpholino-, *N*-pyrrolidyl- and *N*-piperidylthioureas the yields all exceeded 85% (see table 4.3). As such, the overall conversion efficiency from amine and acyl chloride, via *N*'-acylthiourea, to *N,N*-disubstituted thiourea did not fall below 80%. This is a marked improvement on the 38% and 43% conversion rates that Hartmann and Reuther¹⁵ achieved for *N,N*-dimethyl and *N*-morpholino thioureas using the analogous *N*'-benzoylthioureas as intermediates. Using the *N*'-(2,2-dimethylpropanoyl)thioureas also holds a cost advantage because 2,2-dimethylpropanoyl chloride (i.e. trimethylacetyl chloride) is commercially slightly cheaper than benzoyl chloride^{22,23}.

4.4 Reactions of acyl and aroyl isothiocyanates with trimethylsilylamines

It has been shown on a number of occasions that trimethylsilyl protected amines will react with alkyl and phenyl isocyanates or isothiocyanates to form *N*-substituted silylureas and thioureas²⁴⁻²⁶. Such reactions have been carried out in a number of dry solvents, including acetone²⁴. Subsequent addition of water results in cleavage of the moisture sensitive N-Si bonds to yield trimethylsilanol and the urea or thiourea. Although it is said that silylamines are used relatively infrequently in organic synthesis^{27,28}, trimethylsilylamines are generally readily produced from the addition of amine and trimethylsilyl chloride²⁹. A surprising number of these reagents are also available commercially²².

As a substituent on *n*-alkyl- and secondary heterocyclic amines, the trimethylsilyl group provides substantial steric bulk. It has the same geometry as a tertiary butyl group, but is even larger²⁹. As a protecting group, it appeared to provide the kind of steric hindrance that was required in the Douglass and Dains synthesis, for preventing the amine nitrogen from reacting at the carbonyl carbon of acyl and aroyl isothiocyanates.

4.4.1 Experimental approach

Douglass and Dains type reactions with trimethylsilyl protected amines were initially studied using commercially available trimethylsilyldimethylamine. Unlike its parent amine, this reagent is a liquid at room temperature. Thus, in accordance with the typical procedure, it was first dissolved in anhydrous acetone and then added at a dropwise rate to the isothiocyanate solutions. This was followed by the usual

period of stirring and boiling under reflux. Desilylation of the products took place spontaneously when the reaction mixture was poured into water at the end of the synthesis. The products of the reaction were isolated and purified by column chromatography with silica gel.

The investigation was subsequently extended to include reactions of trimethylsilyl protected piperidine and propylamine as well. The latter was reacted with butanoyl isothiocyanate, while the reactivity of the silylated piperidine was tested using both butanoyl and benzoyl isothiocyanates. As neither amine could be purchased in silylated form in South Africa, they were prepared by the author for this study. Details of the preparations are summarized in section 4.6.4.

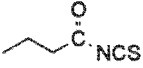
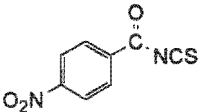
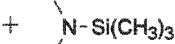
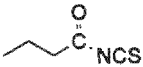
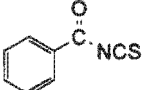
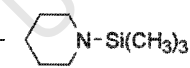
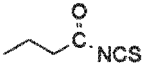
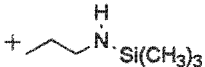
4.4.2 Results and Discussion

The results obtained for the five reactions are listed in table 4.4, along with pertinent data from chapters 2 and 3 for comparison (values in parentheses). The largest improvement over the conventional Douglass and Dains procedure, was observed for *N,N*-dimethyl-*N'*-butanoylthiourea, which increased in yield from 10.7% to 28.3% when the silyl protected dimethylamine was used. Although this was not regarded as a sufficient gain, it was significant enough to prompt further investigation with the other silylated amines. However, these subsequent reactions proved even more discouraging. Yields of *N'*-acyl- or *N'*-aroylthiourea improved only marginally when the silyl protected piperidine was used, and essentially remained unchanged for the synthesis of *N*-propyl-*N'*-butanoylthiourea with trimethylsilylpropylamine. Amidic products from all but the latter reaction were also recovered, and, as in the conventional Douglass and Dains synthesis, they essentially remained the dominant compounds. The results are a clear indication that the trimethylsilyl group did not fulfill the simple steric function for which it was intended.

To explain these disappointing results, it should be considered that a number of influences may have complicated and obscured the intended role of the trimethylsilyl group (i.e. to provide steric bulk). In particular, it must be pointed out that silyl groups are traditionally used as protecting groups for the hydroxyl function and it is well known that silicon is more oxaphilic than azaphilic²⁷. In the reactions with the acyl and aroyl isothiocyanates it is therefore quite possible that a transition state interaction occurs between the silicon of the silylated amine and the carbonyl oxygen of the acyl or aroyl group. The effect of this interaction would be to increase the electrophilic reactivity of the carbonyl carbon, a consequence that would promote, rather than inhibit amide formation. (It should also be added, that even reactions between alkyl or phenyl iso(thio)cyanates and silylated amines do not always proceed via nucleophilic attack of the amine nitrogen on the (thio)carbonyl carbon of the iso(thio)cyanate^{25,29}. In a more common pathway that has been observed with alkyl and phenyl isocyanates, the roles of the reagents are reversed. Nucleophilic attack is initiated by the isocyanate nitrogen and is directed at the silicon of the silylamine, which has 3d orbitals available for additional bonding^{25,29}. If this type of transition state interaction were to occur with the nitrogen of acyl and aroyl isothiocyanate reagents, the trimethylsilyl group would similarly affect the

steric environments of the adjacent carbonyl and thiocarbonyl carbons, and as such it might lose much of the directing steric effect originally intended for the nitrogen of the amine.)

Table 4.4 Yields of *N*-substituted *N'*-acyl and *N'*-aroylthioureas from the reactions of acyl and aroyl isothiocyanates with trimethylsilylated amines. (*N'*-acyl- and *N'*-aroylthiourea yields from the conventional Douglass and Dains reactions are listed for comparison)

Acyl or aroyl isothiocyanate	Silylated amine	Yield <i>N'</i> -acyl- or <i>N'</i> -aroylthiourea (%)	Yield amide (%)	<i>N'</i> -acyl- or <i>N'</i> -aroylthiourea yields from Douglass and Dains reaction (%)
$\text{R}'-\text{C}(=\text{O})\text{NCS}$	$\text{R}_2\text{N}-\text{Si}(\text{CH}_3)_3$	$\text{R}'-\text{C}(=\text{O})\text{NH}-\text{C}(=\text{S})\text{NR}_2$	$\text{R}'-\text{C}(=\text{O})\text{NR}_2$	(values from tables 2.1, 2.3, and 3.1a)
		28.3	64.7	(10.7)
	+ 	26.4	72.0	-
		12.1	85.9	(8.5)
	+ 	53.0	45.2	(41.8)
	+ 	14.7	-	(14.3)

4.5 Concluding Remarks

It is quite likely that a dedicated investigation would reveal further practical alternatives and useful modifications to the Douglass and Dains synthesis. More suitable protecting methodology may yet be identified for the amine – acyl isothiocyanate reaction, and with more effective activating agents it may also be possible to achieve success with the thiocarbamoyl chloride – amide addition.

The results from Dixon and Hawthorne's ¹ acyl chloride – thiourea reaction were by far the most encouraging. At present the only drawback in this approach is the need to first synthesise the *N*-substituted thiourea reagent. Although synthesis and hydrolysis of appropriately substituted *N*-(2,2-dimethylpropanoyl)thioureas proved effective in this regard, the overall procedure could be perceived as cumbersome. Dixon and Hawthorne's ¹ reaction would probably gain much wider acceptance if these reagents were commercially readily available.

4.6 Experimental Procedures and Characterisation

4.6.1 Synthesis of *N*-substituted *N*-acylthioureas from acyl chlorides and *N*-substituted thioureas

Working under a nitrogen atmosphere, *N*-substituted thiourea (0.03 mol) was dissolved in anhydrous acetone (150 ml) along with 1.1 equivalents (0.033 mol) of dried and distilled triethylamine. Acyl chloride (0.03 mol), also in anhydrous acetone (75 ml), was then added at a dropwise rate to the thiourea solution. The mixture was heated to reflux for an hour, and then allowed to cool to room temperature. It was subsequently poured into 75 ml of distilled water and left to stand to allow evaporation of the acetone.

N-piperidyl-*N'*-butanoylthiourea and *N*-pyrrolidyl-*N'*-butanoylthiourea precipitates were recovered by filtration and recrystallised from acetone – water or ethanol – water solutions. The mixture of *N'*- and *N*-propyl substituted *N'*-butanoylthiourea isomers was also recovered by filtration. The mixture was subsequently converted entirely to the *N*-propyl-*N'*-butanoylthiourea form by heating to 95°C for an hour under a nitrogen atmosphere.

N,N-dimethyl-*N'*-butanoylthiourea and *N,N*-dimethyl-*N'*-acetylthiourea were extracted with chloroform and purified on Silica Gel 60 columns. A 10% acetone in methylene chloride solution was used as eluent for the former and a 12% acetone in methylene chloride solution for the latter.

4.6.1.1 Characterisation

All the above mentioned products were thoroughly characterised by elemental analysis, ^1H and ^{13}C NMR spectroscopy, and melting point determinations. However, only the characterisation data of new compounds is listed below. The data of compounds also described in previous chapters, is not repeated.

***N,N*-dimethyl-*N'*-acetylthiourea:** 62.0% yield, mp 102 – 104°C, Calculated for $\text{C}_5\text{H}_{10}\text{N}_2\text{OS}$: C, 41.06; H, 6.91; N, 19.16; S, 21.93, Found: C, 41.42; H, 6.98; N, 19.36; S, 21.82, NMR $\delta(^1\text{H})$: 2.10 (s, 3H, $\text{CH}_3\text{C}(\text{O})-$), 3.16 + 3.41 (s + s, 3H + 3H, $-\text{N}(\text{CH}_3)_2$), 8.86 (br s, 1H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 23.93, 43.21, 44.13, 166.62, 179.71.

***N'*-propyl-*N'*-butanoylthiourea:** NMR $\delta(^1\text{H})$: 0.96 (m, 6H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, $>\text{N}'\text{CH}_2\text{CH}_2\text{CH}_3$), 1.71 (m, 4H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, $>\text{N}'\text{CH}_2\text{CH}_2\text{CH}_3$), 2.58 (t, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 4.20 (t, 2H, $>\text{N}'\text{CH}_2\text{CH}_2\text{CH}_3$), 7.35 + 10.62 (br s + br s, 1H + 1H, $-\text{NH}_2$), $\delta(^{13}\text{C})$: 10.92, 13.55, 18.30, 22.45, 39.13, 50.94, 177.26, 186.41.

4.6.2 Synthesis of *N*-substituted thioureas

4.6.2.1 By thermal conversion of amine thiocyanate salts

Amine thiocyanate salts were initially synthesized by combining amine hydrochloride and potassium thiocyanate. The amine hydrochloride was formed by mixing amine (0.05 mol) and one equivalent of concentrated hydrochloric acid (37%) in analytical grade acetone (50 ml). The potassium thiocyanate, also dissolved in acetone (50 ml), was added to this solution. The mixture was left to stir for fifteen minutes before the acetone was evaporated on a steam bath. The crystalline amine thiocyanate residue was then dried under vacuum. For the amines that were liquids at room temperature, the thiocyanate salts were also synthesized by direct mixing of amine (0.05 mol) and ammonium thiocyanate (0.05) in a 50 ml round bottomed flask. The addition resulted in a brief but vigorous exothermic reaction that was accompanied by evolution of ammonia gas. The amine thiocyanate formed in molten state. With gentle heating and stirring it was kept as a melt for a further ten minutes, to ensure that the reaction had proceeded to completion. On cooling, the melt solidified to a coarsely crystalline product.

For the thermal isomerisation at 160°C, the crystalline amine thiocyanate (0.05 mol) was placed in a round bottomed flask and heated on an oil bath, under nitrogen. After five hours the flask was removed from the bath and allowed to cool to room temperature. The solidified melt was broken up with a glass rod, and then stirred in 50 ml of cold water for five minutes to dissolve amine thiocyanate still remaining. The *N*-substituted thiourea products persisted as insoluble residues and were retrieved by filtration. (The aqueous filtrate was also extracted with chloroform, to ensure that all the thiourea had been recovered.)

For the solvent based isomerisation, the amine thiocyanate (0.05 mol) was added to 500 ml of analytical grade chlorobenzene in a round bottomed flask. The mixture was then vigorously stirred and brought to boil using a magnetic stirrer and an oil bath. The amine thiocyanate formed a dense molten phase. Stirring, and the turbulence of boiling ensured that this was broken up into fine droplets with a large surface area. After an hour, the mixture was removed from the oil bath. Without turbulence, the amine thiocyanate melt rapidly settled to the bottom of the flask. The hot chlorobenzene layer was promptly decanted into a beaker and allowed to cool. Precipitation of the *N*-substituted thiourea commenced almost immediately, and was virtually completed by the time the solvent had cooled to room temperature. Nevertheless, the reaction vessel was usually left to stand in a fridge for a further three hours. The thiourea was recovered by filtration, and dried under vacuum before it was washed with cold water to remove any residual amine thiocyanate.

4.6.2.2 By acid hydrolysis of *N*-substituted *N'*-(2,2-dimethylpropanoyl)thioureas

N-substituted *N'*-(2,2-dimethylpropanoyl)thiourea (0.05 mol) was placed in a beaker and dissolved in 100 ml of hot, concentrated hydrochloric acid (32%, analytical grade). The solution was then maintained at a temperature of 85°C and stirred for an hour. After this period it was allowed to cool to room temperature. (On cooling, a small amount of gel-like residue, possibly the 2,2-dimethylpropanoic acid, was deposited on the rim of the beaker. However, this material redissolved in the following step of the procedure and did not interfere with recovery of the thiourea product.) Then the solution was diluted with 100 ml of distilled water, and neutralised by *cautious*, dropwise addition of concentrated ammonia solution (25%, analytical grade). The neutralised solution was left to stand over night to allow precipitation of the *N,N*-disubstituted thiourea. This product was recovered by filtration, rinsed with cold water and dried. The filtrate was also extracted with three 50 ml aliquots of chloroform to retrieve any fraction of product that still remained in solution. Material that was not adequately pure was recrystallised from ethanol – water mixtures.

4.6.2.3 Characterisation

***N*-propylthiourea:** mp 109°C (lit¹⁹: 109°C), Calculated for C₄H₁₀N₂S: C, 40.63; H, 8.54; N, 23.70; S, 27.12, Found: C, 40.86; H, 8.65; N, 23.73; S, 27.20, NMR δ(¹H): 0.93 (t, 3H, -NHCH₂CH₂CH₃), 1.60 (m, 2H, -NHCH₂CH₂CH₃), 3.00 – 3.50 (v br unres m, 2H, -NHCH₂CH₂CH₃), 6.03 (br s, 2H, N'H₂C(S)-), 6.62 (br unres d, 1H, -NHCH₂CH₂CH₃), δ(¹³C): 11.39, 21.98, 46.23, 181.60.

***N*-piperidylthiourea:** mp 128 – 130°C (lit¹⁵: 128°C), Calculated for C₆H₁₂N₂S: C, 49.95; H, 8.40; N, 19.42; S, 22.23, Found: C, 50.04; H, 8.61; N, 19.61; S, 21.84, NMR δ(¹H): 1.60 (unres m, 6H, -N<(CH₂CH₂)₂>CH₂), 3.73 (unres t, 4H, -N<(CH₂CH₂)₂>CH₂), 5.99 (br s, 2H, N'H₂C(S)-), δ(¹³C): 23.79, 25.42, 49.39, 180.49.

***N*-pyrrolidylthiourea:** mp 193 – 195°C (lit¹⁵: 197 – 199°C), Calculated for C₅H₁₀N₂S: C, 46.11; H, 7.75; N, 21.51; S, 24.62, Found: C, 45.87; H, 7.82; N, 21.46; S, 24.39, NMR δ(¹H): 1.95 + 2.06 (m + m, 2H + 2H, -N<(CH₂CH₂)₂>), 3.36 + 3.81 (t + t, 2H + 2H, -N<(CH₂CH₂)₂>), 5.58 (br s, 2H, N'H₂C(S)-), δ(¹³C): 25.05, 26.50, 47.68, 52.32, 178.81.

***N,N*-dimethylthiourea:** mp 164 – 165°C (lit¹⁵: 166°C), Calculated for C₃H₈N₂S: C, 34.58; H, 7.75; N, 26.89; S, 30.78, Found: C, 34.83; H, 7.95; N, 27.20; S, 30.89, NMR δ(¹H): 3.26 (s, 6H, -N(CH₃)₂), 5.74 (br s, 2H, N'H₂C(S)-), δ(¹³C): 41.01, 182.42.

***N*-morpholinothiurea:** mp 170 – 172°C (lit¹⁹: 171°C), Calculated for C₅H₁₀N₂OS: C, 41.06; H, 6.91; N, 19.16; S, 21.93, Found: C, 41.46; H, 7.21; N, 19.35; S, 22.10, NMR δ(¹H): 3.77 (br unres m, 8H, -N<(CH₂CH₂)₂>O), 5.77 (br s, 2H, N'H₂C(S)-), δ(¹³C): 47.87, 65.98.

4.6.3 Synthesis of *N*-substituted-*N'*-acyl- and aroylthioureas using trimethylsilyl protected amines

The reactions with the silylated amines were carried out according to the same procedure that was used for the conventional Douglass and Dains synthesis with unprotected amines. The necessary experimental details have been described in section 2.6.1. For all the reactions, however, the thiourea and amidic products were separated using silica gel columns and acetone – methylene chloride eluents.

4.6.3.1 Characterisation

***N,N*-dimethyl-*N'*-*p*-nitrobenzoylthiourea:** 26.4% yield, mp 127 - 128°C, Calculated for $C_{10}H_{11}N_3O_3S$: C, 47.41; H, 4.39; N, 16.59; S, 12.66, Found: C, 47.85; H, 4.45; N, 16.75; S, 12.97, NMR $\delta(^1H)$: 3.26 + 3.49 (s + s, 3H + 3H, -N(CH₃)₂), 8.02 (d, 2H, $\phi(2,6)$), 8.31(d, 2H, $\phi(3,5)$), 8.76 (br s, 1H, >N'H), $\delta(^{13}C)$: 43.01, 44.28, 123.92, 129.15, 137.73, 150.31, 161.56, 179.24.

***N,N*-dimethyl-*p*-nitrobenzamide:** 72.0% yield, mp 96 - 97°C, Calculated for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.20; N, 14.43, Found: C, 55.92; H, 5.22; N, 14.63, NMR $\delta(^1H)$: 2.95 + 3.13 (s + s, 3H + 3H, -N(CH₃)₂), 7.55 (d, 2H, $\phi(2,6)$), 8.26 (d, 2H, $\phi(3,5)$), $\delta(^{13}C)$: 35.29, 39.23, 123.71, 127.98, 142.43, 148.23, 169.18.

4.6.4 Silylation of piperidine and propylamine with trimethylsilyl chloride

Trimethylsilylated piperidine and propylamine were prepared according to established methods reported in the literature²⁹. All necessary reagents and solvents were dried and distilled prior to use. The entire experimental procedure, including filtration steps, was conducted under a nitrogen atmosphere and prolonged exposure of the reagents to air was avoided. The products were also stored under nitrogen.

Under a nitrogen atmosphere, amine (0.25 mol) was dissolved in anhydrous methylene chloride (200 ml) along with one equivalent (0.25 mol) of triethylamine base. The mixture was cooled and maintained at 0°C while trimethylsilyl chloride (0.25 mol), also dissolved in methylene chloride (50 ml), was added at a dropwise rate. The solution was then allowed to warm to room temperature and stirred for a further twelve hours. Triethylamine hydrochloride salt that formed when the trimethylsilyl chloride was added to the amine was filtered off. Silylated amine still adsorbed in this salt residue was washed out with 150 ml methylene chloride and added to the filtrate. The methylene chloride was then carefully evaporated using a distillation apparatus with a Vigreux column. The remaining silylated amine was dissolved in 100 ml of dried hexane and again filtered to remove the last traces of triethylamine hydrochloride. After evaporation of the hexane, the silylated amine was distilled.

4.6.4.1 Characterisation

N-trimethylsilylpiperidine: 62.7% yield, bp 156°C (lit ²⁹: 156°C), NMR $\delta(^1\text{H})$: 0.01 (s, 9H, $(\text{CH}_3)_3\text{Si-}$), 1.50 (unres m, 6H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2 > \text{CH}_2$), 2.76 (t, 4H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2 > \text{CH}_2$).

N-trimethylsilylpropylamine: 65.1% yield, bp 100 – 102°C, NMR $\delta(^1\text{H})$: 0.02 (s, 9H, $(\text{CH}_3)_3\text{Si-}$), 0.85 (t, 3H, $-\text{NHCH}_2\text{CH}_2\text{CH}_3$), 1.37 (m, 2H, $-\text{NHCH}_2\text{CH}_2\text{CH}_3$), 2.64 (m, 2H, $-\text{NHCH}_2\text{CH}_2\text{CH}_3$).

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CHAPTER 5

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Pt(II) co-ordination chemistry of the *N*-substituted *N'*-acyl- and *N'*-benzoylthioureas

5.1 Introduction

Over the past thirty years it has been demonstrated on many occasions that *N,N*-dialkyl-*N'*-aroylthioureas form stable complexes with a large variety of transition metals ^{1,2}, and to date, crystal structures have been determined for complexes of Co(III) ³, Ni(II) ^{4,5}, Cu(II) ⁶, Rh(III) ⁷, Pd(II) ⁸, Ag(I) ⁹, Pt(II) ¹⁰⁻¹², Au(I) ¹³ and Hg(I) ¹⁴. Although their *N*-monosubstituted counterparts, the *N*-alkyl-*N'*-aroylthioureas, are also known to form complexes with the transition metals ², the *N,N*-dialkyl-*N'*-aroylthioureas are distinct as a group of ligands because they readily co-ordinate in bidentate or chelating fashion via the oxygen and sulphur atoms. Indeed, it is the chelating property of bidentate ligands which often gives rise to a particularly varied co-ordination chemistry ¹⁵. In this instance, oxygen, as a hard donor atom, may be expected to promote co-ordination with the harder metal ions like Co(III) and Ni(II), while sulphur, the soft donor, stabilises complexes with soft metals such as Pd(II) and Pt(II) ¹⁵.

The interest in transition metal complexes of the *N,N*-disubstituted *N'*-aroylthioureas, specifically the *N,N*-dialkyl-*N'*-benzoylthioureas, has not only been of an academic nature, but has also extended to practical application in the separation chemistry of these elements ^{2,16-24}. Solubilities of the ligands and complexes are such that separations have been achieved by employing relatively simple solvent extraction ^{2,17,25}, chromatography ^{16,18,24} and precipitation processes ^{17,19}. The mode of co-ordination and the stabilities of the resulting complexes vary from metal to metal, and are particularly sensitive to conditions of pH. Thus, with pH control it has been possible to carry out the separations with a high degree of selectivity, even from complicated matrices ^{16,17}. Stabilities and solubilities of the complexes are also influenced by the two *N*-alkyl substituents and by groups on the aromatic R' substituent of the ligand ^{16,17}, and this provides another avenue for optimising selectivity in a targeted separation.

Of the possibilities explored thus far, one of the most promising and exciting prospects for application has been in the purification and recovery of the platinum group metals (PGMs) ^{20-23,25}. As ligands, the *N,N*-dialkyl-*N'*-aroylthioureas exhibit an exceptional affinity for these noble metals and the resulting complexes are amongst the most stable. Co-ordination is maintained even in strongly acidic environments where complexes of the other transition elements dissociate, and accordingly, the PGMs can be isolated from matrices that might otherwise be considered potentially interfering ^{23,26}. Since these *N'*-aroylthioureas are chemically stable, and also selective under acidic conditions, they appear to be well suited to application in common PGM refining processes where mineral concentrates are often subjected to several cycles of acid treatment.

An ideal opportunity to study further Pt(II) complexes of the *N,N*-dialkyl-*N'*-acyl- and *N'*-benzoylthioureas arose in the course of this project because several new examples of these thioureas were produced during the investigations of the isothiocyanate – amine reactions (chapters 2 and 3). Although a number of *N'*-benzoylthiourea complexes of Pt(II), Pd(II) and Rh(III) are described in the literature, there is a singular lack of information on analogous metal complexes of the *N'*-acylthioureas. As such, little is known, even on a qualitative level, about the effects of the change from an aromatic R' group to an alkyl R' group on the ligand properties of this class of thioureas. (Recrystallisation of the *N'*-acylthioureas from acetone / water or ethanol / water mixtures provided some evidence that they were substantially more water soluble than the *N'*-benzoylthioureas, and this property in itself is important in selecting a ligand for a particular separation process). Thus, for this part of the project, one of the main objectives was to prepare a series of Pt(II) - *N,N*-dialkyl-*N'*-acylthiourea complexes along with some corresponding Pt(II) - *N,N*-dialkyl-*N'*-benzoylthioureas for comparison.

Although the Pt(II) - *N'*-acylthiourea complexes were of primary interest, a further three *N'*-benzoylthioureas were also synthesised for the co-ordination study. All three ligands were *N,N*-dialkyl-*N'*-(3,4,5-trimethoxybenzoyl)thiourea variants, specifically designed in an attempt to achieve *trans* bidentate co-ordination of the donor atoms around the Pt(II) metal centre. This goal represented an academic challenge. As is explained below, the bidentately co-ordinated *N,N*-dialkyl-*N'*-aroylthiourea complexes of Pt(II) have, with only one exception to date¹¹, all been of the *cis* isomeric form.

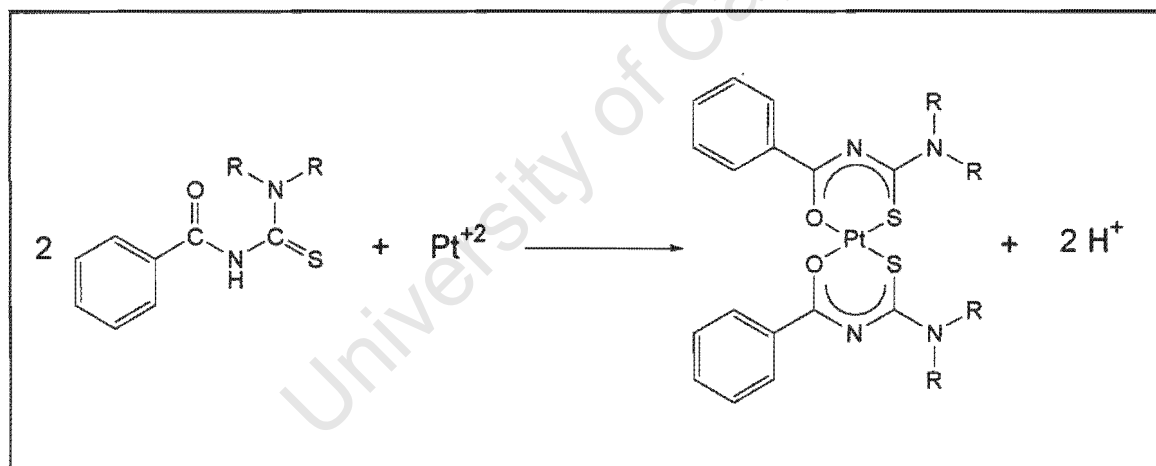
Unlike their *N,N*-disubstituted counterparts, the *N*-alkyl-*N'*-aroylthioureas have not enjoyed widespread application as ligands. They do not readily co-ordinate in a bidentate chelating fashion and thus far it has only been possible to isolate Pt(II) and Pd(II) complexes in which monodentate co-ordination via the sulphur atom has occurred²⁷⁻²⁹. Although this form of co-ordination has recently been studied by Wang²⁷, her investigation was also limited to ligands of the *N'*-benzoylthiourea variety. Hence, three of the *N*-monosubstituted *N'*-acylthioureas described in chapter 2 were also used to prepare Pt(II) complexes. However, because of the inherent difficulties associated with the synthesis of this particular group of *N'*-acylthioureas (see low yields in table 2.3, chapter 2), a comparison to the analogous *N'*-benzoylthiourea ligands and complexes was not intended. Instead, the three co-ordination reactions were carried out with the specific goal of inducing bidentate co-ordination to Pt(II).

The decision to focus only on Pt(II) as the metal centre, was based in part, on time constraint, and also on the fact that platinum is by far the most valuable PGM to the South African economy³⁰. For a qualitative assessment of the ligand properties of the new *N'*-acyl and *N'*-benzoylthioureas, it was also useful that Pt(II) co-ordination to *N*-substituted *N'*-benzoylthioureas has recently been studied^{10-12,28,29,31-34} in some detail. Furthermore, apart from the conventional methods of characterisation, it is possible to monitor Pt(II) chemistry by ¹⁹⁵Pt NMR spectroscopy. The +2 state is one of the principal oxidation states of platinum, along with oxidation states 0 and +4³⁵. Although both Pt(II) and Pt(IV) are encountered as anionic chlorides in hydrochloric acid solutions, the tetravalent platinum, in the form of PtCl₆²⁻, is easily reduced to the divalent state (as the PtCl₄²⁻ ion) with mild reducing agents³⁵.

5.2 Characteristic features of Pt(II) - *N*-substituted *N'*-benzoylthiourea complexes

Before continuing with a discussion of the experimental procedures and results, it is appropriate to provide an overview of what is currently known about Pt(II) complexes of *N*-substituted *N'*-benzoylthioureas. As pointed out, the mode of co-ordination depends on whether the *N'*-benzoylthioureas are *N*-mono- or *N,N*-disubstituted. With the latter group, bidentate *S,O* co-ordination is commonly observed when the facile sulphur to platinum co-ordination that is typical of thioureas is accompanied by co-ordination of the oxygen to the metal centre. This is made possible by the fact that the ligand conformation can change from the preferred *E,Z'* form to the chelating *Z,Z'* isomer (see figure 5.1), and because the *N'* proton is marginally acidic and readily dissociates in the presence of base². Dissociation of this proton is in fact a prerequisite for bidentate co-ordination, presumably because the ligand is converted to the charged and more nucleophilic O⁻ tautomeric form³⁴. When the oxygen does co-ordinate, a very stable, six-membered chelate ring with fairly extensive electronic delocalisation is formed¹⁰ (figure 5.1). For Pt(II), the reaction proceeds with 2 : 1 ligand to metal stoichiometry, so that the metal centre then effectively adjoins two such chelate rings. Since a proton is lost from each ligand, the complexes themselves are neutral.

Figure 5.1 Schematic illustration of a *N,N*-substituted *N'*-benzoylthiourea ligand (in preferred *E,Z'* conformation) reacting with Pt(II) to give the neutral *cis*-[Pt(L-*S,O*)₂] complex

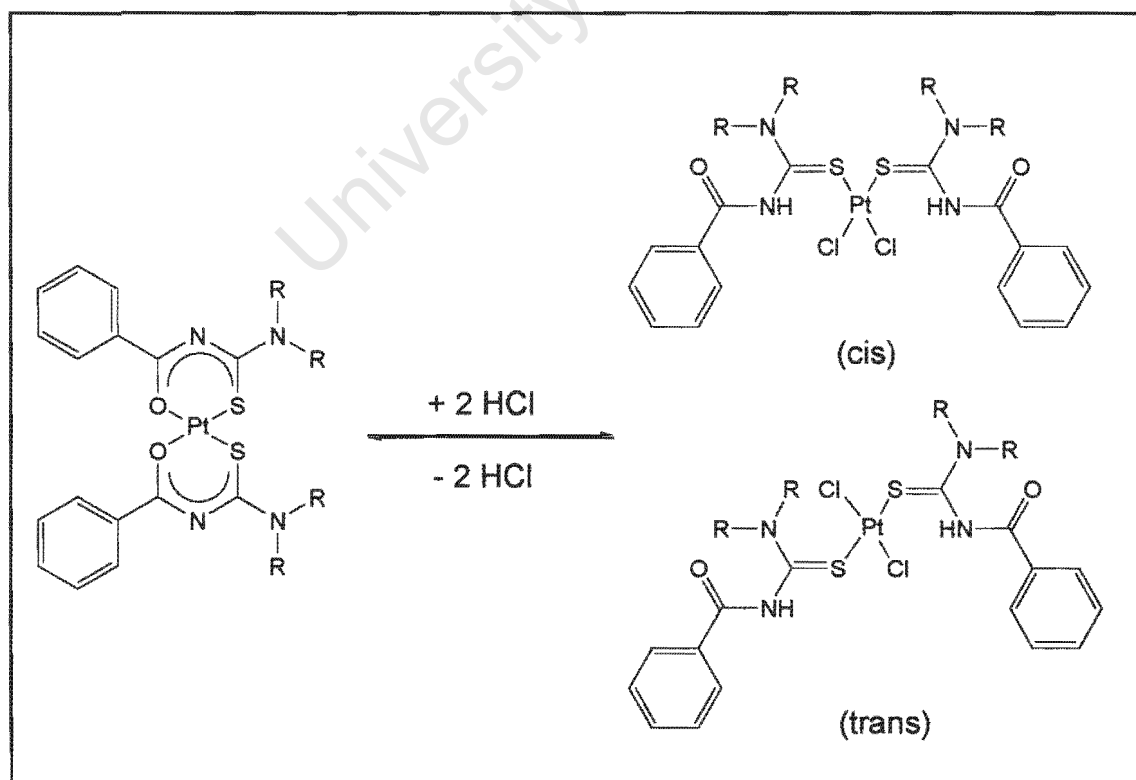


From crystal structure determinations^{10,36,37} it has been found that the four donor atoms (two from each ligand) essentially adopt a square planar conformation around the platinum and that the chelating rings on either side of the metal are essentially coplanar to each other. Square planar co-ordination is typical for a number of *d*⁸ metal ions³⁸ and the *N,N*-disubstituted *N'*-benzoylthiourea complexes of Pd(II) and Ni(II) exhibit very similar geometries^{4,5,8}. Also typical of these complexes is the overwhelming tendency of the four donor atoms to adopt a *cis* configuration around the metal centre. Although the reasons for this are not clearly understood, it has been pointed out¹⁰ that the phenomenon is in accord with the *trans* influence, a thermodynamically destabilising influence exerted when two highly polarisable donors like the sulphur atoms are in *trans* positions relative to each other^{10,38-40}. To indicate participation of the oxygen and sulphur

atoms in co-ordination, these complexes are commonly denoted as $cis-[M(L-S,O)_2]$ complexes, where M represents the metal, and L the deprotonated ligand (the unbound ligand with its acidic N' proton is denoted as HL).

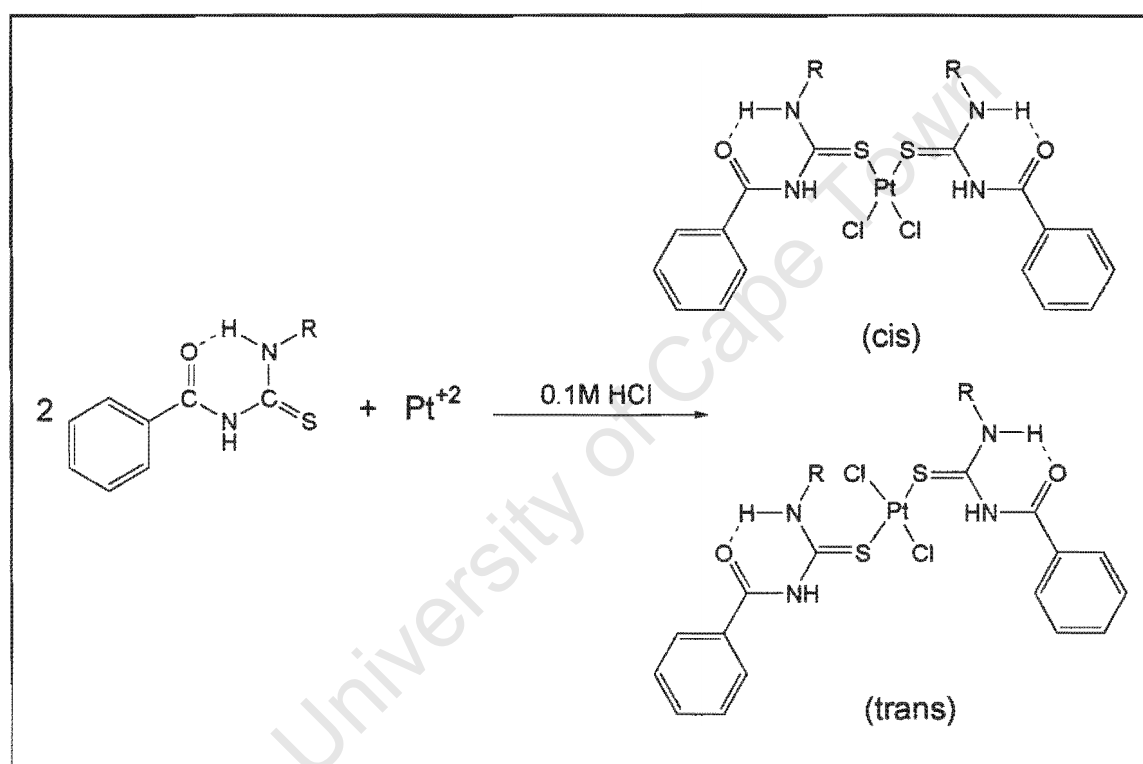
Co-ordination of the oxygen donors is reversible, and when chloroform solutions of the $cis-[Pt(L-S,O)_2]$ chelates are treated with concentrated HX mineral acids (where $X = Cl^-$, Br^- or I^-), it is possible to observe ring opening of the S,O -chelate^{12,34}. Under these conditions, the co-ordinated ligands may become protonated again, and in the process, the oxygen donors are displaced from the co-ordination sphere of the Pt(II) by halide ions. However, the two ligands remain bound to the platinum via the sulphurs, and with complete protonation complexes of the type $[Pt(HL-S)_2X_2]$ are formed (see figure 5.2). (Protonation and ring opening appear to be relatively slow, and with the aid of ^1H and ^{195}Pt NMR spectroscopy, partially protonated complexes of the type $[Pt(L-S,O)(HL-S)Cl]$ have also been identified³⁴). In contrast to the chelated parent complexes, the $[Pt(HL-S)_2X_2]$ species are obtained as a mixture of *cis* and *trans* isomers (the isomeric ratio will depend on the halide ions that displace the oxygen donors and on the solvent in which the reaction is carried out^{12,27}). Furthermore, it has also been demonstrated that the course of protonation is quite reversible. In the presence of sufficient base, the $[Pt(HL-S)_2X_2]$ complexes readily revert back to the original chelated $[Pt(L-S,O)_2]$ species. However, on deprotonation, even these *cis/trans* mixtures of $[Pt(HL-S)_2X_2]$ will only yield the *cis*- $[Pt(L-S,O)_2]$ isomers³⁴.

Figure 5.2 *cis* and *trans*- $[Pt(HL-S)_2Cl_2]$ complexes formed after protonation and ring opening of a *cis*-bis(*N,N*-dialkyl-*N'*-benzoylthioureato)platinum(II) complex



With *N*-monosubstituted *N'*-benzoylthioureas, the oxygen atom is prevented from participating in co-ordination because it is locked into a stable, six-membered ring, via an intramolecular hydrogen bond with the hydrogen that is found on the alkyl substituted *N* nitrogen^{28,29,32,36,41} (i.e. in the place of a second alkyl group). Nevertheless, these compounds still behave as monodentate sulphur ligands and also produce stable complexes with Pt(II) (figure 5.3). The co-ordination takes place readily and without dissociation of the *N'* proton. Thus, with H_2L to represent the undeprotonated ligand, the complexes that are typically derived with $PtCl_4^{2-}$ are of the type $[Pt(H_2L-S)_2Cl_2]$. As such, they are quite similar to the protonated $[Pt(HL-S)_2X_2]$ complexes of the *N,N*-disubstituted ligands, and they are also formed in a mixture of *cis* and *trans* isomers.

Figure 5.3 Diagram illustrating the intramolecular hydrogen bond and consequent monodentate co-ordination to Pt(II) of a *N*-alkyl-*N'*-benzoylthiourea, giving *cis* and *trans*- $[Pt(H_2L-S)_2Cl_2]$ complexes



5.3 Experimental Approach

The Pt(II) complexes of the *N,N*-dialkyl-*N'*-acyl- and *N'*-benzoylthioureas were prepared in a solvent mixture of water and acetonitrile. This was done to ensure that both the metal ion and the ligand remained soluble until the reaction had occurred. Typically, the ligand was dissolved along with 1.1 mole equivalents of sodium acetate. The latter was to serve as a mild base for deprotonation of the ligand. A water – acetonitrile solution containing 0.5 mole equivalents of Pt(II) (as $PtCl_4^{2-}$) was then added and the mixture stirred for 12 hours. To encourage and ensure complete precipitation of solid complexes the reaction mixtures were subsequently diluted with water and left to cool at 4°C overnight. On recovery, these

precipitates were recrystallised from chloroform - ethanol mixtures. In a few instances, however, the products were found to be oils, or included a water soluble fraction. Products such as these were extracted with chloroform and purified chromatographically with aluminium oxide stationary phase and methylene chloride eluent. The full experimental procedures and details of characterisation are given in section 5.6.

For the Pt(II) complexes with *N*-monosubstituted *N'*-acylthioureas, the *N*-propyl and *N*-butyl substituted *N'*-(2,2-dimethylpropanoyl)thioureas and the *N*-propyl-*N'*-butanoylthiourea were used as ligands. All three reactions were carried out by following exactly the method employed with the *N,N*-disubstituted ligands, and also included the addition of acetate base. Using a base with *N*-monosubstituted ligands has not been common practice, as the $[\text{Pt}(\text{LH}_2\text{-S})_2\text{Cl}_2]$ type complexes are normally prepared in the presence of acid to prevent deprotonation of the ligand^{27-29,32}. However, the deprotonation step was deliberately included to encourage *S,O* chelation, a form of co-ordination that has not yet been observed with the *N*-monosubstituted variety of *N'*-acyl- and *N'*-aroylthioureas.

The three *N,N*-dialkyl-*N'*-(3,4,5-trimethoxybenzoyl)thiourea ligands that were intended for the synthesis of *trans*- $[\text{Pt}(\text{L-S,O})_2]$ complexes, were produced by the method of Douglass and Dains (see section 2.6.1, chapter 2), and were all obtained in yields exceeding 80%. As above, the co-ordination reactions with these ligands were carried out in acetonitrile - water mixtures and with addition of acetate base. However, to help establish whether *trans* complexes had formed and to determine ratios of *cis* and *trans* isomers, the crude products were submitted for ^1H , ^{13}C and ^{195}Pt NMR spectroscopy before recrystallisation.

5.4 Results and Discussion

Melting points and yields for all the complexes and the three trimethoxy substituted benzoylthiourea ligands appear in section 5.6.2, along with the results from elemental C, H, N, S microanalysis, and ^1H and ^{13}C NMR resonances. For several of the complexes, ^{195}Pt NMR chemical shifts are given as well.

5.4.1 *cis*- $[\text{Pt}(\text{L-S,O})_2]$ complexes of the *N,N*-dialkyl-*N'*-acylthioureas ($\text{HL}^1 - \text{HL}^{14}$) and *N,N*-dialkyl-*N'*-benzoylthioureas ($\text{HL}^{15} - \text{HL}^{23}$)

5.4.1.1 General Observations

With only two exceptions, the co-ordination reactions with the *N,N*-dialkyl substituted ligands, including those of the *N'*-acylthiourea variety, all produced the $[\text{Pt}(\text{L-S,O})_2]$ type complexes in very high yields (i.e. > 80%). (The *N'*-acylthiourea complexes are listed as complexes $[\text{Pt}(\text{L}^1\text{-S,O})_2]$ to $[\text{Pt}(\text{L}^{14}\text{-S,O})_2]$ in table 5.1a along with the yields in which they were obtained and their melting points, while the *N'*-benzoylthiourea complexes $[\text{Pt}(\text{L}^{15}\text{-S,O})_2]$ to $[\text{Pt}(\text{L}^{23}\text{-S,O})_2]$ are listed in table 5.1b with their yields and melting points).

Table 5.1a A list of the yields and melting points of $[\text{Pt}(\text{L}-\text{S},\text{O})_2]$ complexes obtained from reactions of Pt(II) with the N,N -dialkyl- N' -acylthiourea ligands (HL^1 to HL^{14})

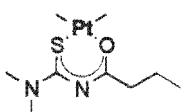
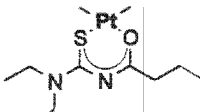
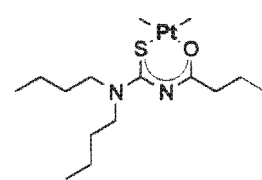
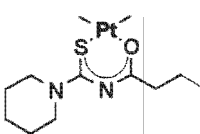
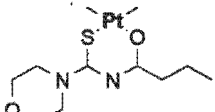
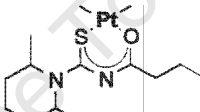
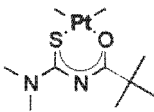
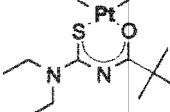
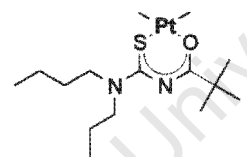
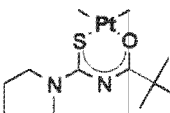
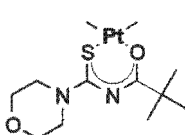
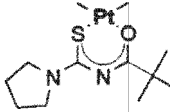
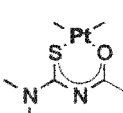
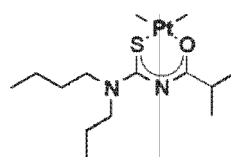
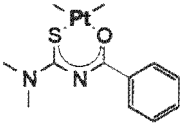
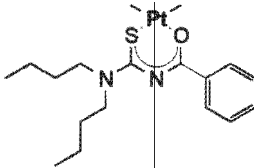
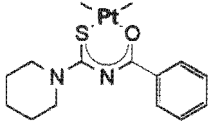
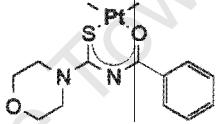
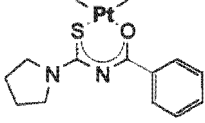
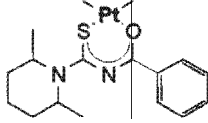
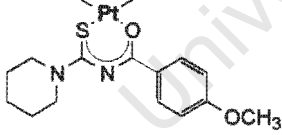
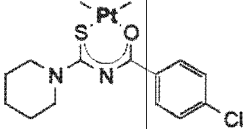
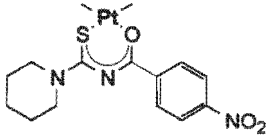
$[\text{Pt}(\text{L}-\text{S},\text{O})_2]$ complexes of the N,N -dialkyl- N' -acylthioureas	
 $[\text{Pt}(\text{L}^1-\text{S},\text{O})_2]$: 92.4%, mp: 156 – 159°C	 $[\text{Pt}(\text{L}^2-\text{S},\text{O})_2]$: 88.8%, mp: 90 – 91°C
 $[\text{Pt}(\text{L}^3-\text{S},\text{O})_2]$: 86.6%, oil	 $[\text{Pt}(\text{L}^4-\text{S},\text{O})_2]$: 23.8%, mp: 83 – 85°C
 $[\text{Pt}(\text{L}^5-\text{S},\text{O})_2]$: 85.7%, mp: 161 – 164°C	 $[\text{Pt}(\text{L}^6-\text{S},\text{O})_2]$: 88.7%, oil
 $[\text{Pt}(\text{L}^7-\text{S},\text{O})_2]$: 90.0%, mp: 219 – 220°C	 $[\text{Pt}(\text{L}^8-\text{S},\text{O})_2]$: 89.0%, mp: 162 – 165°C
 $[\text{Pt}(\text{L}^9-\text{S},\text{O})_2]$: 100%, mp: 149 – 152°C	 $[\text{Pt}(\text{L}^{10}-\text{S},\text{O})_2]$: 98.2%, mp: 211 – 214°C
 $[\text{Pt}(\text{L}^{11}-\text{S},\text{O})_2]$: 93.2%, mp: 215 – 217°C	 $[\text{Pt}(\text{L}^{12}-\text{S},\text{O})_2]$: 84.8%, mp: 227 – 229°C
 $[\text{Pt}(\text{L}^{13}-\text{S},\text{O})_2]$: 35.3%, mp: 201 – 204°C	 $[\text{Pt}(\text{L}^{14}-\text{S},\text{O})_2]$: 100%, mp: 64 – 66°C

Table 5.1b A list of the yields and melting points of $[\text{Pt}(\text{L-S},\text{O})_2]$ complexes obtained from reactions of Pt(II) with the *N,N*-dialkyl-*N'*-benzoylthiourea ligands (HL^{15} to HL^{23})

$[\text{Pt}(\text{L-S},\text{O})_2]$ complexes of the <i>N,N</i> -dialkyl- <i>N'</i> -benzoylthioureas	
 $[\text{Pt}(\text{L}^{15}\text{-S},\text{O})_2]$: 93.9%, mp: 212 – 214°C	 $[\text{Pt}(\text{L}^{16}\text{-S},\text{O})_2]$: 82.2%, mp: 161 – 162°C
 $[\text{Pt}(\text{L}^{17}\text{-S},\text{O})_2]$: 93.6%, mp: 195 – 198°C	 $[\text{Pt}(\text{L}^{18}\text{-S},\text{O})_2]$: 95.7%, mp: 214 – 216°C
 $[\text{Pt}(\text{L}^{19}\text{-S},\text{O})_2]$: 92.6%, mp: 209 – 210°C	 $[\text{Pt}(\text{L}^{20}\text{-S},\text{O})_2]$: 73.0%, mp: 176 – 180°C
 $[\text{Pt}(\text{L}^{21}\text{-S},\text{O})_2]$: 95.8%, mp: 199 – 200°C	 $[\text{Pt}(\text{L}^{22}\text{-S},\text{O})_2]$: 93.1%, mp: 210 – 211°C
 $[\text{Pt}(\text{L}^{23}\text{-S},\text{O})_2]$: 95.7%, mp: 211 – 212°C	

Although reactions of the *N'*-benzoylthioureas (and other ligands) are known to be noticeably slower with Pt(II) than with either Pd(II) or Ni(II)^{42,43}, it was almost always possible to detect the typical bright yellow colour of Pt(II) - thiourea complexes within 20 minutes of mixing metal and ligand solutions. As such, there was no time-dependent visual evidence to indicate any noticeable differences between the co-ordinating abilities of the *N'*-acyl- and *N'*-benzoylthioureas. Apart from the two anomalously low results (obtained with ligands HL⁴ and HL¹³), the yields and characterisation data also gave no indication to suggest that the bidentate mode of co-ordination is at all affected by replacing aromatic R' groups with alkyl groups, be they linear chains or bulky tertiary butyl substituents.

From a qualitative perspective, the only appreciable difference between the *N'*-acylthiourea complexes (complexes [Pt(L¹-S,O)₂] to [Pt(L¹⁴-S,O)₂]) and the *N'*-benzoylthiourea complexes (complexes [Pt(L¹⁵-S,O)₂] to [Pt(L²³-S,O)₂]), was that the former group appeared to be somewhat less stable to chromatographic separation on silica gel. When a pure *N'*-acylthiourea complex of the type [Pt(L-S,O)₂] was applied to a thin layer silica gel plate, it frequently happened that a significant proportion of the spot was not at all mobile with the commonly used eluents, chloroform and methylene chloride. Furthermore, in these instances the mobile fraction of complex did not travel as an isolated spot during elution, but gave a continuous streak of product on the plate. The explanation for this behaviour may be linked to the inherent acidity of silica gel. Under these circumstances the neutral complexes probably became protonated, and therefore charged and relatively immobile. A similar phenomenon has previously been observed with Ni(II) complexes of *N,N*-dialkyl-*N'*-benzoylthioureas^{16,36}. In acidic environments these complexes are much less stable than their Pt(II) counterparts and on silica gel plates they dissociate completely. For the Pt(II) - *N'*-acylthiourea complexes, however, the immobile baseline spot and the product streak maintained the yellow colour typical of Pt(II) - thiourea complexes and it was thus considered likely that at least monodentate co-ordination via the sulphur atoms was maintained and that complete dissociation was uncommon. Only in the chromatographic separation of the *cis*-bis(*N,N*-dimethyl-*N'*-acetylthioureaato)platinum(II) complex [Pt(L¹³-S,O)₂], was it possible to distinguish a minor component with the same mobility (i.e. R_f value) as the free ligand. The problems of protonation and streaking were overcome by using aluminium oxide columns or plates. With this stationary phase and methylene chloride or chloroform as eluent, the pure complexes were quantitatively isolated as well defined bands or spots.

The observed chromatographic differences between the *N'*-acylthiourea and *N'*-benzoylthiourea complexes appear to be consistent with the few comparisons that are documented in the literature. *N'* protons of *N,N*-diethyl-*N'*-acetylthiourea, *N,N*-diethyl-*N'*-ethanoylthiourea, and *N,N*-dimethyl-*N'*-acetylthiourea, for example, are reported to be an order of magnitude less acidic than the *N'* protons of the analogous *N'*-benzoylthioureas (i.e. $\Delta \text{pK}_a \approx 1$)^{16,44}. As bidentate ligands, these *N'*-benzoylthioureas have also been found to form the more stable metal complexes¹⁶. Complete dissociation of complexes on silica gel has only been observed for complexes of harder metal ions, and in part, this has been attributed to the competing ligand effect of the hard donor oxygens of the silica gel itself¹⁶. Thus, although *N'*-acylthiourea complexes may be more readily protonated, it is not unreasonable to expect that at least monodentate co-ordination via the sulphur is maintained with soft metal ions like Pt(II).

Of concern, were the two anomalously low yields recorded for the Pt(II) complexes of *N*-piperidyl-*N'*-butanoylthiourea [$\text{Pt}(\text{L}^4\text{-S},\text{O})_2$] and *N,N*-dimethyl-*N'*-acetylthiourea [$\text{Pt}(\text{L}^{13}\text{-S},\text{O})_2$] (see table 5.1a). Both reactions were left to proceed for forty eight rather than just twelve hours because they appeared to take place at an uncharacteristically slow rate. Although yellow precipitates were formed during this period, significant proportions of yellow complex also remained in solution (this was also unusual as high yield precipitation of the other [$\text{Pt}(\text{L-S},\text{O})_2$] complexes usually left the mother liquor colourless). These soluble fractions were extracted with chloroform and combined with the precipitated fractions for chromatographic separation on aluminium oxide columns. From both product mixtures, the [$\text{Pt}(\text{L-S},\text{O})_2$] species were readily eluted with methylene chloride. However, in each case a more polar band of yellow product was retained at the top of the column. Although these materials could be eluted with 10% methanol in methylene chloride solutions, they travelled as broad, diffuse bands and could not be separated to yield individual components. The ^1H and ^{13}C NMR spectra of these polar materials were also so complex that they were essentially uninterpretable. Although this does suggest that the materials were complicated mixtures, the spectra provided no conclusive information about any individual components. On the assumption that the *N'* protons of the two ligands HL^4 and HL^{13} are particularly weakly acidic, and therefore that they are not readily deprotonated during the co-ordination reactions, it could be proposed that the polar mixtures may have included at least [$\text{Pt}(\text{HL-S})(\text{L-S},\text{O})\text{Cl}$] species and *cis* and *trans*-[$\text{Pt}(\text{HL-S})_2\text{Cl}_2$] species. The possibility that other Pt(II) species were present as well, can also not be ruled out.

For the *N*-piperidyl-*N'*-butanoylthiourea (HL^4), in particular, the above co-ordination behaviour is unexpected and difficult to explain. The *N,N*-diethyl- (HL^2), *N*-morpholino- (HL^5) and *N*-cis-2,6-dimethylpiperidyl-*N'*-butanoylthioureas (HL^6), represent close relatives of this ligand that all reacted to give high yields of stable [$\text{Pt}(\text{L-S},\text{O})_2$] complexes. It is possible that yields may be improved if the reaction is carried out in the other solvents systems traditionally employed (such as dioxane – water mixtures), or in the presence of a stronger deprotonating base, and this in itself may provide further insight into the co-ordinating properties of this ligand.

5.4.1.2 ^1H and ^{13}C NMR Spectroscopy

^1H and ^{13}C NMR spectra of the [$\text{Pt}(\text{L-S},\text{O})_2$] complexes typically consisted of a single set of ligand resonance peaks and closely resembled the spectra of the unco-ordinated ligands. This is normal for the neutral [$\text{M}(\text{L-S},\text{O})_2$] type compounds and was found to apply for the Pt(II) - *N'*-acylthiourea complexes as well. Although it is therefore necessary to confirm the 2 : 1 ligand to metal stoichiometry by elemental microanalysis, it is possible to recognise in the spectra small, but consistent changes that are considered indicative of bidentate *S,O* co-ordination. For example, the absence of the distinctive $\text{N}'\text{H}$ singlet from the ^1H spectra, confirms that the ligands bound to the metal centre are deprotonated. Co-ordination also has a marked and characteristic effect on the α -methylene resonances of the two *N*-alkyl groups. Owing to restricted rotation about the thiocarbonyl to dialkyl nitrogen bond (i.e. $\text{C}(\text{S})\text{-NR}_2$)⁴⁵, both in the free ligand

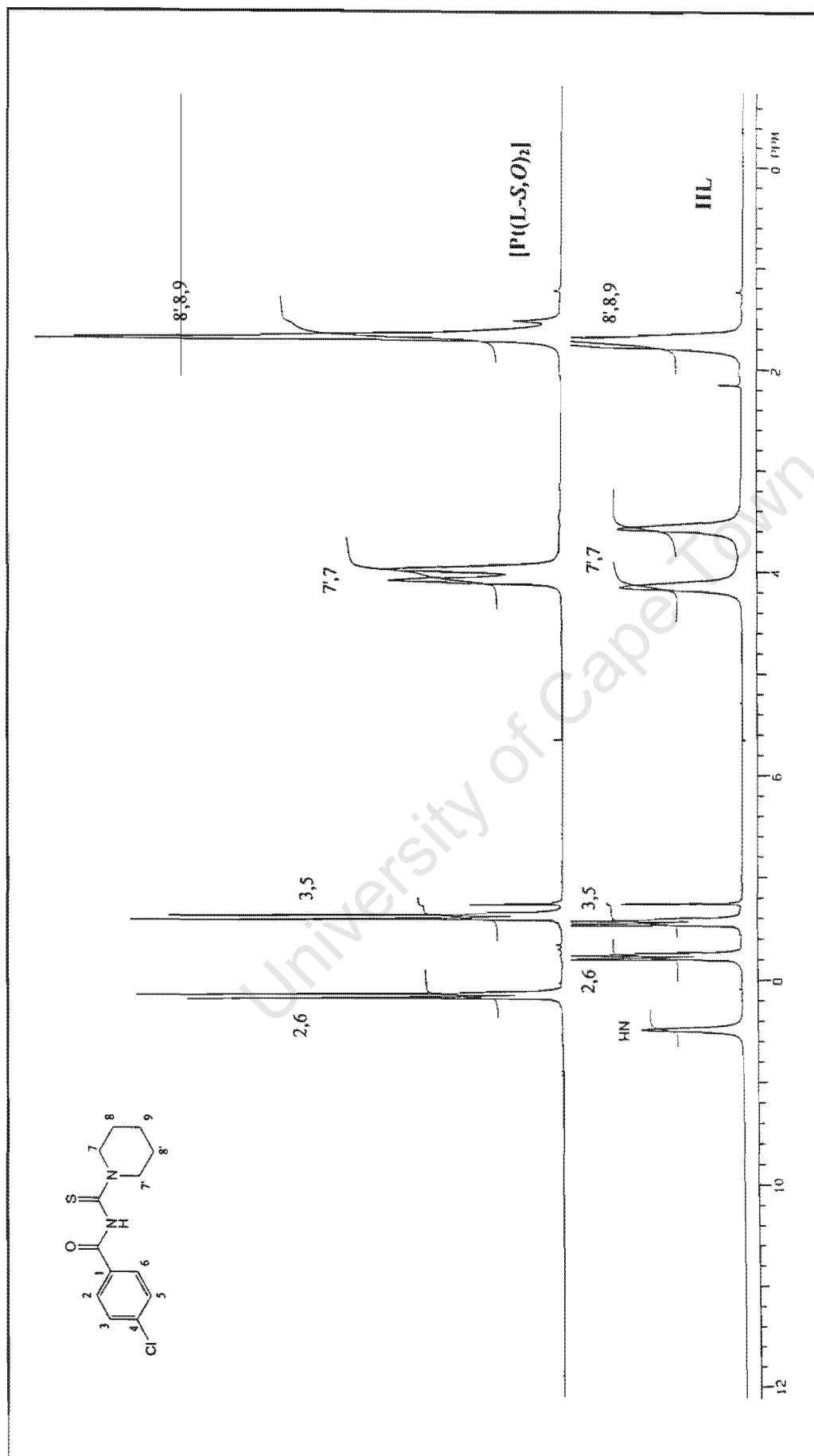


Figure 5.4 Representative ^1H NMR spectra showing the characteristic differences between the ^1H spectra of N -piperidyl- N' -(p -chlorobenzoyl)thiourea (HL^{22}) and its $[Pt(L^{22}-S,O)_2]$ complex

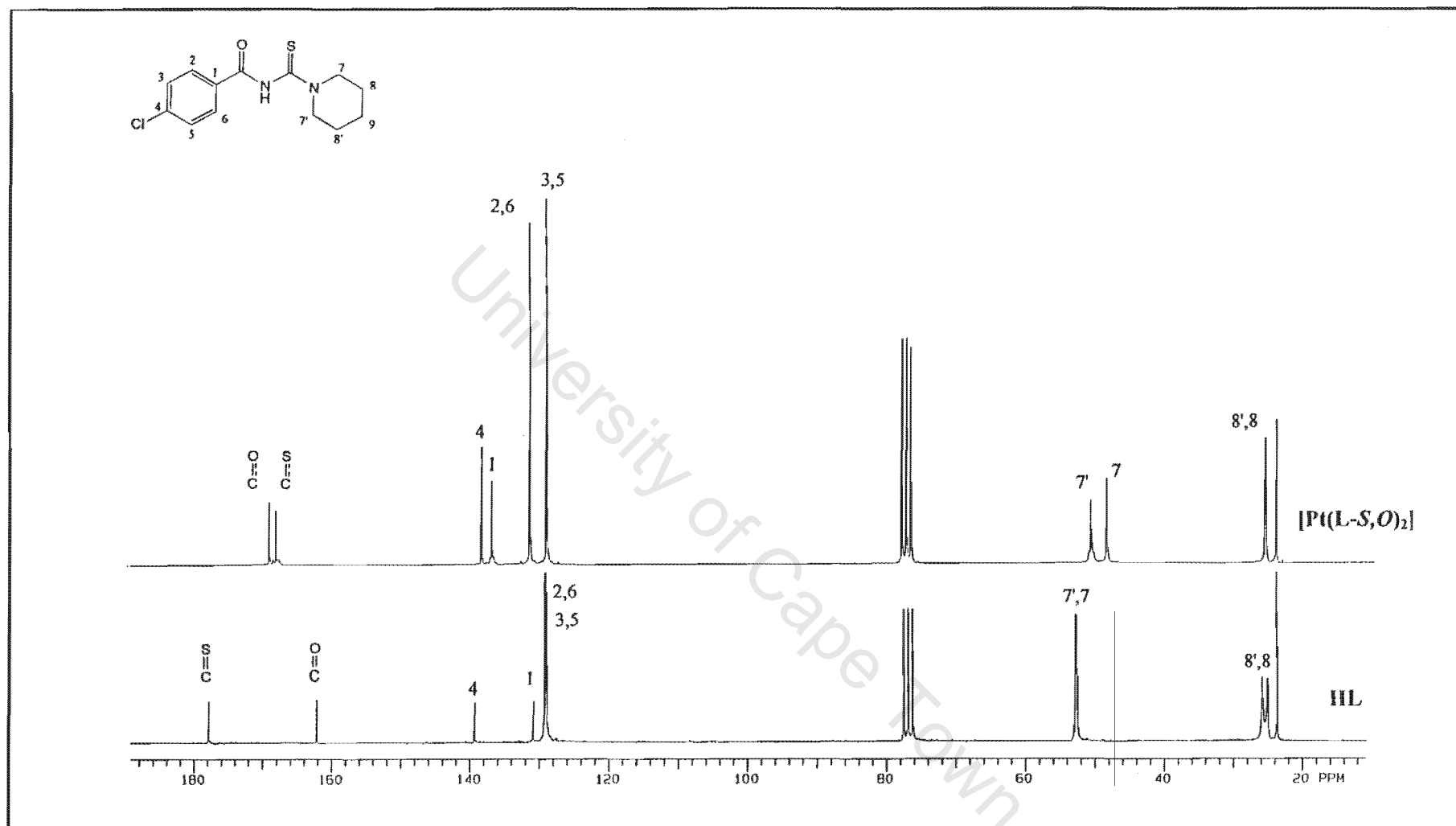


Figure 5.5 Representative ¹³C NMR spectra showing the characteristic differences between the ¹³C spectra of *N*-piperidyl-*N'*-(*p*-chlorobenzoyl)thiourea (HL²²) and its [Pt(L²²-S,O)₂] complex. Note the ¹⁹⁵Pt – ¹³C coupling satellites associated with peaks C=S, 1, and 7' in the spectrum of the complex

and in the complex, the *N*-dialkyl substituents produce a double set of ^1H and ^{13}C resonances. In the ^1H spectrum of the free ligand, the α -methylene resonances of these alkyl groups usually appear as two broad triplets, often unresolved, and relatively far apart from each other (eg. 3.5 and 4.2 ppm – see protons 7',7 in figure 5.4). However, with co-ordination to Pt(II) effecting a change from the *E,Z'* to the *Z,Z'* conformation for the ligand (see figure 5.1), and increasing the double bond character and barrier to rotation of the C(S)-NR₂ bond⁴⁵, the triplets typically become significantly sharper, and also shift closer together (to 3.9 and 4.1 ppm in figure 5.4).

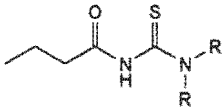
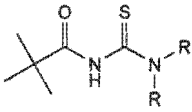
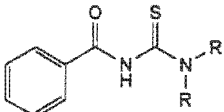
For the α fragment of the R' group on the other hand (i.e. on the carbonyl carbon side of the ligand), the effects of co-ordination are not particularly pronounced. α Methylene ^1H triplets of the butanoyl chain in *N'*-butanoylthioureas, for instance, are shifted by less than 0.2 ppm. However, the corresponding effect on the carbon nucleus of this fragment is a little more substantial, with typical downfield shifts of 5 ppm (i.e. from 37 to 42 ppm) recorded after co-ordination. (For the *N'*-benzoylthiourea ligands the corresponding effect of co-ordination is very similar i.e. the C1 resonance of the phenyl ring is shifted from 131 to 136 ppm – see figure 5.5).

As is to be expected from bidentate *S,O* co-ordination, the ^{13}C resonance peaks of the carbonyl and thiocarbonyl carbons are amongst the most noticeably shifted signals (see figure 5.5, and table 5.2 on the following page). Both peaks are relatively small and appear close to each other in the downfield region between 160 and 185 ppm. In the spectra of the unbound ligands, the thiocarbonyl carbon peak appears furthest downfield*. It is consistently found centered around 179 ppm (± 1.5 ppm), regardless of the R' and *N,N*-dialkyl substituents. Co-ordination to Pt(II) brings about a substantial and almost uniform *upfield* shift for this peak, usually to around 167 ppm. Again, the R' and *N,N*-dialkyl groups appear to have very little influence, and its new position seldom varies by more than 2 ppm (see table 5.2).

By comparison, the R' groups have a much greater influence on the position of carbonyl carbon resonance, which for the unbound ligand can be found anywhere between 160 and 175 ppm (table 5.2). The shift brought about by co-ordination is also substantial. However, in this instance it is in a *downfield* direction, and markedly dependant on whether R' is an aliphatic group (average downfield shift = 8.6 ± 0.8 ppm) or an aromatic group (average downfield shift = 5.5 ± 0.5 ppm). In both cases, though, the downfield shift is large enough for the carbonyl peak to end up downfield of the now more shielded thiocarbonyl resonance. This crossed-over shift pattern for the two peaks (see figure 5.5 for example) is not unusual and has also been observed on co-ordination of *N,N*-diethyl-*N'*-benzoylthiourea to other d^8 transition metal ions^{31,45}.

* The two peaks have been unambiguously assigned in the [Pt(L-*S,O*)₂] complex and unbound ligand ^{13}C NMR spectra of a *N'*-benzoylthiourea prepared with 45% ^{13}C isotopically enriched potassium thiocyanate³¹. For the *N'*-acylthioureas, the assignment was confirmed by comparing the carbonyl and thiocarbonyl ^{13}C - ^1H coupling patterns of *N*-piperidyl-*N'*-(2,2-dimethyl)-propanoylthiourea (HL¹⁰) and its Pt(II) complex. The fact that the R' group variations have a far more pronounced effect on the shift of the carbonyl carbon peak, and that ^{195}Pt - ^{13}C spin coupling satellites can only be observed for the thiocarbonyl carbon (see discussion below) also proved useful in this regard.

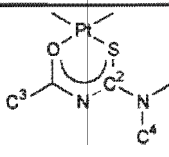
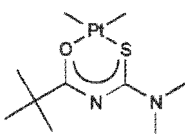
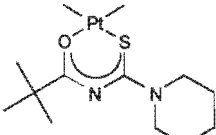
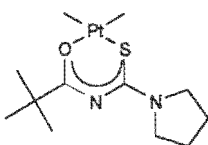
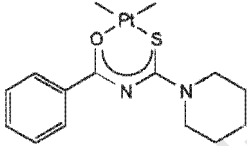
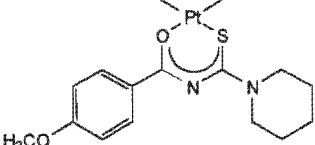
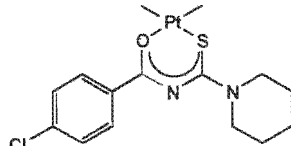
Table 5.2 Average ^{13}C chemical shifts for the carbonyl and thiocarbonyl carbons of *N,N*-dialkyl-*N'*-butanoyl-, *N'*-(2,2-dimethylpropanoyl)-, and *N'*-benzoylthioureas, and their Pt(II) complexes

Ligand group	$\delta \text{ } ^{13}\text{C}=\text{O}$ (ppm)		$\delta \text{ } ^{13}\text{C}=\text{S}$ (ppm)	
	HL	$\rightarrow$ [Pt(L-S, <i>O</i>) ₂]	HL	$\rightarrow$ [Pt(L-S, <i>O</i>) ₂]
	169.6 (± 0.3)	$\rightarrow$ + 8.4	178.0 (± 0.6)	179.3 (± 0.8) $\rightarrow$ -12.6 166.7 (± 0.6)
	174.4 (± 0.2)	$\rightarrow$ + 8.9	183.3 (± 0.6)	179.1 (± 1.3) $\rightarrow$ -12.4 166.7 (± 1.3)
	162.9 (± 0.8)	$\rightarrow$ + 5.5	168.4 (± 0.5)	178.5 (± 1.2) $\rightarrow$ -11.2 167.3 (± 1.3)

With adequate signal to noise ratios, it is also possible to observe at least three sets of $^{195}\text{Pt} - ^{13}\text{C}$ spin coupling satellites in the ^{13}C spectra (see figure 5.5 and table 5.3). Ligand atom spin-spin couplings to ^{195}Pt through one to four bonds are well known⁴⁶, and such interactions have previously been reported for complexes of the *N,N*-dialkyl-*N'*-benzoylthioureas as well. In the literature, average $^n\text{J} (^{195}\text{Pt} - ^{13}\text{C})$ coupling constants of 45 Hz, 25 Hz and 27 Hz are given for the thiocarbonyl carbon (^2J), the *R'* group α carbon (^3J), and the favourably oriented α carbon* of the *N*-alkyl chains respectively (^4J)³¹. Very similar values were recorded in the course of this project, not only for three *N'*-benzoylthiourea complexes ([Pt(L¹⁷-S,*O*)₂], [Pt(L²¹-S,*O*)₂], [Pt(L²²-S,*O*)₂]), but also for three *N'*-acylthiourea complexes (the *N'*-(2,2-dimethylpropanoyl)thiourea complexes [Pt(L⁷-S,*O*)₂], [Pt(L¹⁰-S,*O*)₂], [Pt(L¹²-S,*O*)₂] -see table 5.3). Evidently, in this respect, the effects of changing the *R'* and *N*-dialkyl groups also appear to be small. (With average values of 21.3 ± 1.2 Hz and 25.5 ± 0.3 Hz for the *N'*-acyl- and *N'*-benzoylthiourea complexes respectively, the $^3\text{J} (^{195}\text{Pt} - ^{13}\text{C})$ coupling constants showed the most substantial change. This is understandable considering that the carbons in question are the α carbon of the 2,2-dimethylpropanoyl group, and the C1 carbon of a phenyl ring.) Again in accordance with previous reports³¹, no coupling interaction was observed for the carbonyl carbon. Here the coupling interaction is thought to be too small to be resolved.

* It is reported that the four bond coupling in the latter case is only observed for the bond chain that assumes the 'W' configuration with respect to the Pt(II) centre^{31,32}

Table 5.3 $^nJ(^{195}\text{Pt} - ^{13}\text{C})$ coupling constants for the thiocarbonyl carbon, the R' group α carbon, and the favourably oriented α carbon of the *N*-alkyl chains

Complex			
	^2J (Hz)	^3J (Hz)	^4J (Hz)
 [Pt(L⁷-S,O)₂]	45.9	22.6	30.1
 [Pt(L¹⁰-S,O)₂]	44.7	21.0	31.2
 [Pt(L¹²-S,O)₂]	46.7	20.3	-
 [Pt(L¹⁷-S,O)₂]	44.6	25.3	28.8
 [Pt(L²¹-S,O)₂]	44.4	25.5	-
 [Pt(L²²-S,O)₂]	45.0	25.8	31.2

5.4.1.3 ^{195}Pt Chemical Shifts

^{195}Pt NMR spectroscopy is a useful tool in the study of platinum co-ordination chemistry because the ^{195}Pt chemical shift is very sensitive to donor atom variation in the co-ordination sphere of the metal, and to changes in the geometry of the complex^{46,47}. For example, two $[\text{PtX}_2\text{L}_2]$ stereoisomeric complexes with *cis* and *trans* arrangements of the ligands X' and L may produce ^{195}Pt resonance peaks several hundred ppm apart from each other (depending on the nature of X' and L)^{46,47}. Furthermore, any changes to the substituents of the ligands (eg. the lengthening of an alkyl chain, or changing a *para*-group on a phenyl ring) can also effect a shift of several tens of ppm to a ^{195}Pt resonance peak^{46,47}.

For *cis*- $[\text{Pt}(\text{L}-\text{S},\text{O})_2]$ type complexes of the *N,N*-dialkyl-*N'*-aroylthioureas, the ^{195}Pt spectra are reported to consist of a single, sharp resonance line* close to -2720 ppm (in CDCl_3 , and relative to external H_2PtCl_6 dissolved in 1.0 M HCl)^{31,32,36}. Shift variations depending on the two *N*-alkyl substituents and the R' group of the ligand appear to be relatively small and consistently fall within ± 35 ppm of this region. *Para*-substituents on the phenyl rings of *N*-benzoylthiourea complexes do, however, have a noticeable effect, with the change from a *p*-nitro to a *p*-methoxy group causing a downfield ^{195}Pt shift of 50 ppm, i.e. from -2738 ppm to -2688 ppm³¹. Far more dramatic ^{195}Pt shifts for the Pt(II) - *N,N*-dialkyl-*N'*-aroylthiourea complexes are brought about by protonation and ring opening of the metal to ligand chelate, since the oxygen donor atoms are displaced from the co-ordination sphere of the metal. This has been illustrated³⁴ by treating a CDCl_3 solution of neutral complex, directly in an NMR tube with concentrated HCl. Three new resonance peaks appeared around -2950, -3030 and -3210 ppm as a result. Of these, the first was assigned to the partially protonated $[\text{Pt}(\text{L}-\text{S},\text{O})(\text{HL}-\text{S})\text{Cl}]$ species, while the latter two were identified as the peaks of the *trans* and *cis*- $[\text{Pt}(\text{HL}-\text{S})_2\text{Cl}_2]$ species respectively. The three peaks are reported to appear even further upfield when HBr is used instead of HCl to protonate the neutral complex³⁴.

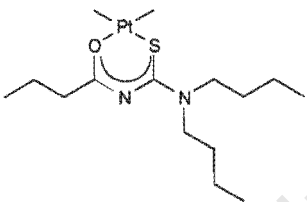
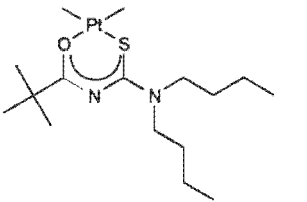
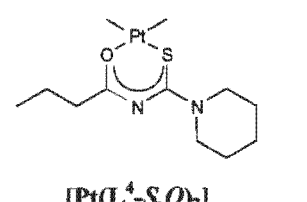
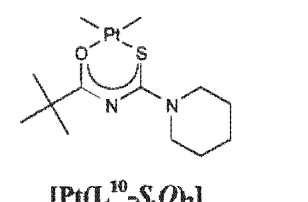
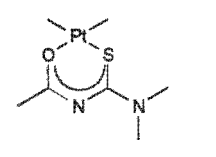
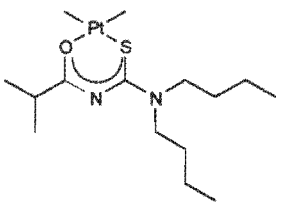
To continue with the comparison of the *N'*-acyl and *N'*-benzoylthiourea - Pt(II) complexes, ^{195}Pt spectra were recorded for six of the *N,N*-dialkyl-*N'*-acylthiourea complexes (see table 5.4). Included in this group was the bis(*N*-piperidyl-*N'*-(2,2-dimethylpropanoylthioureaato)platinum(II) sample ($[\text{Pt}(\text{L}^{10}-\text{S},\text{O})_2]$) for which the *cis* conformation was verified by X-ray crystallography (see section 5.4.1.4 below). In all regards the spectra appeared to be very similar to those described for the *cis*- $[\text{Pt}(\text{L}-\text{S},\text{O})_2]$ *N'*-aroylthiourea complexes. Here too, they consisted of single, sharp resonance lines, with the only minor difference being a slightly more upfield distribution at around -2750 ppm (see table 5.4). Shifts resulting from R' and *N*-alkyl group variations were also small and did not exceed ± 20 ppm. In this regard, however, it was of interest to note that the most substantial ^{195}Pt shift changes (i.e. from around -2745 ppm to -2760 ppm) arose when the ligands with *N,N*-dimethyl or *N,N*-dibutyl groups ($[\text{Pt}(\text{L}^3-\text{S},\text{O})_2]$, $[\text{Pt}(\text{L}^9-\text{S},\text{O})_2]$, $[\text{Pt}(\text{L}^{14}-\text{S},\text{O})_2]$, and $[\text{Pt}(\text{L}^{13}-\text{S},\text{O})_2]$) were replaced by the ligands with the *N*-piperidyl group ($[\text{Pt}(\text{L}^4-\text{S},\text{O})_2]$, $[\text{Pt}(\text{L}^{10}-\text{S},\text{O})_2]$).

* A single line is observed if the two *N*-alkyl groups of the ligand are equivalent. However, for complexes of ligands like *N*-butyl-*N*-methyl-*N'*-benzoylthiourea, three closely spaced lines appear in the ^{195}Pt spectrum. These are assigned to the EE', E'Z / Z'E and Z'Z isomers which can be distinguished due to the restricted rotation of the C(S)-NR¹R² bond³².

Somewhat surprisingly, a much smaller and, in some instances, almost negligible peak shift was effected by changing the acyl R' groups of the ligands. For example, the ^{195}Pt resonances of the *N,N*-dibutyl substituted *N'*-butanoyl- and *N'*-(2,2-dimethylpropanoyl)thiourea – Pt(II) complexes ($[\text{Pt}(\text{L}^3\text{-S},\text{O})_2]$ and $[\text{Pt}(\text{L}^9\text{-S},\text{O})_2]$) were found at –2745 and –2748 ppm respectively. Similarly, for the two complexes with the *N*-piperidyl substituted ligands, the change from an *N'*-butanoyl group to the *N'*-(2,2-dimethylpropanoyl) only caused the ^{195}Pt resonance to shift from –2760 ppm to –2764 ppm. (It is of interest to note that these marginal effects from the acyl R' group are in contrast to the significantly more pronounced ^{195}Pt shifts caused by *para* substituents on the benzoyl R' group of the $[\text{Pt}(\text{L-S},\text{O})_2]$ complexes of *N'*-benzoylthioureas³¹).

Although the ^{195}Pt resonances essentially highlight similarities between the *N'*-acyl- and *N'*-benzoylthiourea – Pt(II) complexes, they also indicate that some differences do exist. In this respect, a ^{195}Pt study based on protonation experiments may prove more informative. With time and acid concentration as controlled variables, such experiments may provide for a semi-quantitative comparison of the relative complex stabilities.

Table 5.4 ^{195}Pt chemical shifts recorded for some of the *cis*-bis(*N,N*-substituted-*N'*-acylthioureaato)-platinum(II) complexes

$[\text{Pt}(\text{L-S},\text{O})_2]$	$\delta^{195}\text{Pt}$	$[\text{Pt}(\text{L-S},\text{O})_2]$	$\delta^{195}\text{Pt}$
 $[\text{Pt}(\text{L}^3\text{-S},\text{O})_2]$	–2745 ppm	 $[\text{Pt}(\text{L}^9\text{-S},\text{O})_2]$	–2748 ppm
 $[\text{Pt}(\text{L}^4\text{-S},\text{O})_2]$	–2760 ppm	 $[\text{Pt}(\text{L}^{10}\text{-S},\text{O})_2]$	–2764 ppm
 $[\text{Pt}(\text{L}^{13}\text{-S},\text{O})_2]$	–2745 ppm	 $[\text{Pt}(\text{L}^{14}\text{-S},\text{O})_2]$	–2746 ppm

5.4.1.4 Crystal Structure determination of *bis*(*N*-piperidyl-*N'*-(2,2-dimethylpropanoyl)thioureato)-platinum(II) ([Pt(L¹⁰-S,O)₂])

From an overview of the pertinent literature, it became apparent that no crystal structures of metal – *N'*-acylthiourea complexes have been published to date. It was thus pleasing to find that, when allowed to recrystallise from chloroform – ethanol mixtures over a period of several days, most of the Pt(II) – *N'*-acylthiourea complexes readily formed crystals suitable for single crystal X-ray diffraction. Of these, a crystal of *bis*(*N*-piperidyl-*N'*-(2,2-dimethylpropanoyl)thioureato)platinum(II) ([Pt(L¹⁰-S,O)₂]) was submitted for structure analysis. This complex crystallised in the monoclinic space group P2₁/c with 4 molecules per unit cell. The structure was solved and refined using SHELXS-97 and SHELXL-97^{48,49}. Hydrogen atoms were placed in calculated positions during later stages of the refinement. The molecular structure is shown in figure 5.6 and the important bond lengths and bond angles associated with the metal – ligand chelate ring are summarised in table 5.5. Included for comparison in this table are analogous measurements previously determined from *N,N*-dialkyl-*N'*-aroylthiourea complexes and free ligands. The full sets of experimental and refinement parameters are given in Appendix 2 along with the fractional coordinates, bond lengths, bond angles and torsion angles of all the non-hydrogen atoms.

Figure 5.6 Perspective view of the molecular structure of *cis*-*bis*(*N*-piperidyl-*N'*-(2,2-dimethylpropanoyl)thioureato)platinum(II) ([Pt(L¹⁰-S,O)₂]), showing the atom numbering scheme for the non-hydrogen atoms. Hydrogen atoms are omitted for clarity

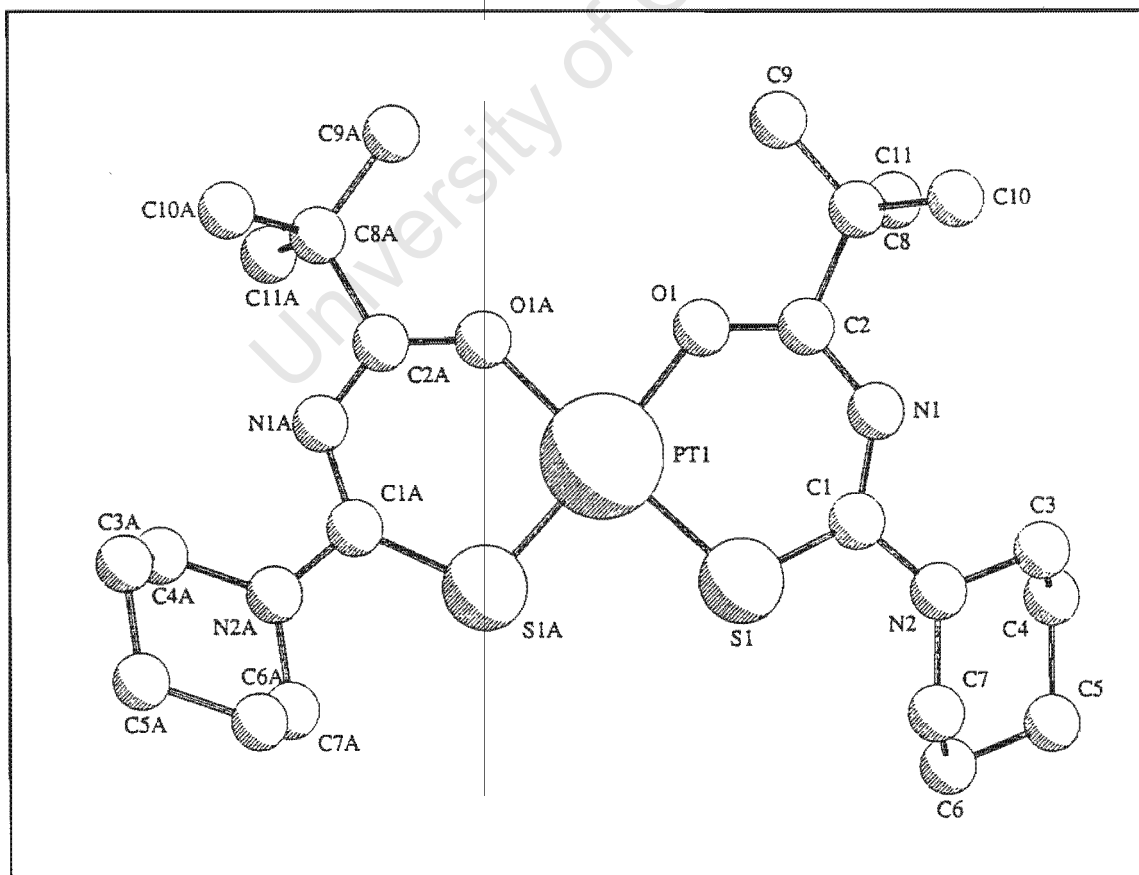
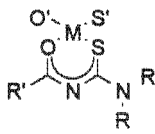


Table 5.5 Average bond lengths and bond angles associated with the bidentate chelating moieties in *cis*-bis(*N*-piperidyl-*N'*-(2,2-dimethylpropanoyl)thioureato)platinum(II) (*cis*-[Pt(L¹⁰-S,O)₂]). Included for comparison are the average bond lengths from various *N,N*-dialkyl-*N'*-aroylthiourea ligands (HL)^{4,32,33,36} and average bond lengths and angles from other *cis* square planar Ni(II)^{4,5}, Pd(II)³⁷ and Pt(II)^{10,36} complexes ([M(L-S,O)₂]) of *N,N*-dialkyl-*N'*-aroylthioureas (standard deviations* appear in parentheses)

Bond / Angle 	Bond Lengths (Å) / Angles (°)		
	<i>cis</i> -[Pt(L ¹⁰ -S,O) ₂]	[M(L-S,O) ₂] average	HL average
R'—C(O)	1.535 (± 0.006)	1.487 (± 0.015)	1.498 (± 0.002)
C=O	1.258 (± 0.005)	1.261 (± 0.009)	1.213 (± 0.004)
(O)C=N'	1.313 (± 0.006)	1.318 (± 0.011)	1.374 (± 0.011)
N'=C(S)	1.348 (± 0.005)	1.342 (± 0.006)	1.409 (± 0.016)
C=S	1.735 (± 0.004)	1.724 (± 0.010)	1.666 (± 0.006)
(S)C—NR ₂	1.341 (± 0.006)	1.341 (± 0.010)	1.327 (± 0.006)
O—M	2.021 (± 0.003)	2.016 (± 0.008) [†]	-
S—M	2.236 (± 0.001)	2.226 (± 0.006) [†]	-
O—M—O'	82.0 (± 0.1)	82.6 (± 0.6) [†]	-
S—M—S'	88.6 (± 0.4)	88.4 (± 0.2) [†]	-
O—M—S/O'—M—S'	94.7 (± 0.8)	94.5 (± 0.3) [†]	-

* the standard deviations listed for the *cis*-[Pt(L¹⁰-S,O)₂] complex, are experimental deviations recorded for the measurements during the crystallographic data collection

† the average values of bond lengths and angles involving the metal centres were calculated using only the values reported for *cis*-[Pt(L-S,O)₂] structures i.e. values from references 10 and 36

The molecular structure in figure 5.6 shows that co-ordination occurred, as anticipated, in the *cis* square planar conformation. Indeed, as far as the chelate rings around the metal centre are concerned, the complex appears to be virtually identical to Pt(II) complexes of the *N,N*-dialkyl-*N'*-aroylthioureas^{10,36}. As observed in previous work^{4,5,10,36,37}, the chelate rings themselves are planar (the maximum deviation from planarity is 0.15 Å). From the bond angles O-Pt-S, O'-Pt-S', O-Pt-O', and S-Pt-S' in table 5.5 it is evident that the arrangement of donor atoms is somewhat distorted from an ideal square. However, a very similar degree of distortion is observed in the Pt(II) – *N'*-aroylthiourea complexes^{10,36}. The donor atom to Pt(II) bond lengths are also essentially invariant from the values that have previously been reported for the Pt(II) – *N'*-aroylthiourea complexes^{10,36}.

Much the same can be said about the rest of the chelate ring i.e. the four bonds of the S1(A)-C1(A)-N1(A)-C2(A)-O1(A) moiety in figure 5.6 (here the similarities even extend to *N*-aroylthiourea complexes of Ni(II) and Pd(II)). In all the *N'*-aroylthiourea complexes, this part of the chelate ring is associated with extensive electron delocalisation¹⁰. At average lengths of 1.258 (±0.005) Å and 1.735 (±0.004) Å respectively, the C[≡]O and C[≡]S bonds are longer than the C=O and C=S double bonds in the free ligands, but shorter than the 1.34 Å and 1.75 Å typical of analogous single bonds⁵⁰. This also applies to the N[≡]C(S) and (O)C[≡]N' bonds (C1(A)-N1(A) and N1(A)-C2(A) in figure 5.6), which at 1.348 (±0.005) Å and 1.313 (±0.006) Å respectively, are too short to be considered typical single bonds (1.38 Å⁵⁰), and too long for normal C=N double bonds (1.28 Å⁵⁰). That these four bond lengths are essentially replicated in the *N'*-acylthiourea complex is significant because it indicates that changing R' from an aromatic to an aliphatic group does not have a noticeable effect on the electronic distribution in the chelate ring. For the *N'*-benzoylthiourea [Pt(L-S,O)₂] complexes the implication is that very little resonance interaction occurs between the phenyl and chelate rings, despite the fact that they are reported to be nearly coplanar (the angle between the least squares plane of each ring is usually close to 10°^{8,51}).

In the molecular structure of figure 5.5, the other bonds of interest are the ones linking the chelate rings to the tertiary butyl and *N*-piperidyl groups. Of these, the latter (C1(A)-N2(A)) also conforms closely to the values determined previously for the *N'*-aroylthiourea complexes. At an average length of 1.341(±0.006) Å, this bond is clearly also a partial double bond. (As far as the average values for the *N'*-aroylthioureas are concerned (table 5.5), it is of interest to note that the length of this bond actually increases, from 1.33 Å to 1.34 Å, after co-ordination. Although the difference is marginal, it appears to contradict the NMR finding that the bond order and barrier to rotation of this bond increase after co-ordination⁴⁵.) At 1.535 (±0.006) Å the carbonyl carbon to tertiary butyl bond, R'-C(O) (or C2(A)-C8(A) in figure 5.6), is the only bond that is significantly longer than its counterparts in the *N'*-aroylthiourea complexes (1.49 Å). However, this is not surprising because bonds from *sp*³ carbons are usually longer than bonds from *sp*² carbons⁵⁰.

In deciding on which *N'*-acylthiourea – Pt(II) complex to submit for structure analysis, it was considered important to select from the compounds with the most bulky R' groups on the ligands (i.e. the tertiary butyl group). This was to confirm that *cis* square planar chelation was indeed also the favoured conformation for the *N'*-acylthioureas, even when *trans* co-ordination might have more effectively alleviated any steric

crowding of substituents. On this basis, and bearing in mind the overall similarities of the NMR characteristics, particularly the chemical shifts of the ^{195}Pt resonance peaks, it would seem reasonable to assume that the other *N*-acylthiourea complexes also co-ordinated with *cis* orientation of the donor atoms.

5.4.2 *trans*-[Pt(L-S,O)₂] complexes of *N,N*-dialkyl-*N'*-aroylthioureas

5.4.2.1 Introduction

The overwhelming tendency of the *N,N*-dialkyl-*N'*-aroylthioureas to form only the *cis* co-ordinated [M(L-S,O)₂] type complexes with the square planar d^8 metal ions Pt(II), Pd(II) and Ni(II) is well known. This conformation is thought to be more stable since it ensures that the two sulphur atoms (i.e. the donors with the larger *trans* influence) are not co-ordinated *trans* to each other, but *trans* to the oxygens (donor atoms with a lower *trans* influence)^{10,38-40}. Only one example of a [M(L-S,O)₂] type complex in *trans* conformation has been described thus far. The compound was a bis(*N,N*-dibutyl-*N'*-naphthoylthioureato)platinum(II) complex, and its *trans* configuration was confirmed by Koch *et al.* using X-ray crystallography¹¹. It was isolated by fractional crystallisation as the minor component from an 85% : 15% mixture of *cis* and *trans*-[Pt(L-S,O)₂] species, after ^1H and ^{195}Pt NMR suggested the presence of the two isomeric products (in the ^{195}Pt NMR spectrum a major and a minor peak were found at -2707.9 and -3037.6 ppm respectively). At the time, it was speculated that steric effects in the transition state of complex formation had given rise to the *trans* isomer. However, in subsequent work, a ligand with an upper rim-modified calix(4)arene as the aroyl R' group was synthesized and added to Pt(II)⁵². Despite the considerable bulk of this R' group, the ligand reacted to give only the *cis*-[Pt(L-S,O)₂] species, a result confirmed by ^{195}Pt NMR spectroscopy and from an X-ray crystal structure determination.

In their report on the structure of the *trans* complex¹¹, Koch *et al.* pointed out that the naphthyl R' moieties were coplanar with the six membered chelate rings on either side of the metal centre. They drew attention to the fact that, due to steric constraints, this orientation would be unlikely in the *cis* complex and suggested that the naphthyl moieties might be forced perpendicular to the square plane of co-ordination. To a degree, this was verified by Grimbacher³⁶ who subsequently determined the crystal and molecular structure of the closely related *cis*-bis(*N*-morpholino-*N'*-naphthoylthioureato)platinum(II) complex. She found one of the naphthyl rings oriented at an angle of 16.8° and the other at an angle of 52.8° relative to the co-ordination plane of the metal. Significantly, it appears that a small fraction of this complex also formed as the *trans* isomer, since a crude sample produced a ^{195}Pt spectrum with two distinct peaks, a major one at -2708 ppm and a minor peak at -3027 ppm.

Although the overall similarities of the chelating moieties in the *N'*-acylthiourea and *N'*-benzoylthiourea [Pt(L-S,O)₂] crystal structures suggest otherwise (see section 5.4.1.4), it was tempting to consider that an element of resonance interaction between the carbonyl group and an aroyl R' group does persist in the *N*-aroylthiourea complexes when the aroyl R' group is coplanar with the six-membered chelate ring and plane

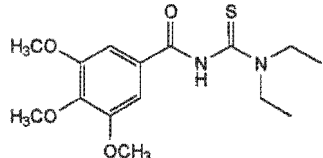
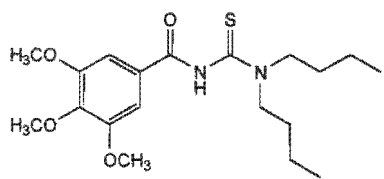
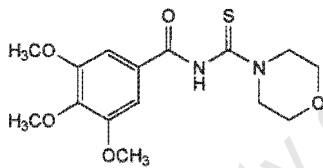
of co-ordination. On this basis, an electron rich aryl group, like the naphthyl moiety, might be expected to have a 'softening' effect on the oxygen donor atom of the ligand (i.e. increase its polarisability). The implication, in terms of the *trans* influence, is that the stabilising effect of having the oxygen of one ligand, *trans* to the sulphur donor of the other (as is the case in the *cis* complexes), would be less pronounced, and the incidence of *trans*-[Pt(L-S,O)₂] complex formation thereby increased (i.e. with a less significant difference between the respective *trans* influences of the sulphur and oxygen donors resulting if the latter were 'softer' than usual, the thermodynamic stability differences between the *cis* and *trans*-[Pt(L-S,O)₂] isomers would be smaller). Considering that methoxy groups are recognised as resonance donating substituents (even in the *meta* position, they are considered mildly resonance donating⁵³) the trio of *N*-(3,4,5-trimethoxybenzoyl)thiourea ligands mentioned earlier (ligands HL²⁴ to HL²⁶, see table 5.6) was specifically prepared to test this crude hypothesis.

5.4.2.2 Results and Discussion

As pointed out earlier, the three ligands were reacted with Pt(II) in the conventional manner. However, the complexes obtained, were submitted for ¹H, ¹³C and ¹⁹⁵Pt NMR spectroscopy before recrystallisation. Although all three reactions gave high yields of the characteristically yellow [Pt(L-S,O)₂] complex, the NMR spectra, which were of primary interest, initially appeared discouraging. A first glance at the ¹H and ¹³C spectra in particular, suggested that the crude materials were relatively pure complexes, but only of one isomeric form. The ¹⁹⁵Pt spectra of the *N,N*-diethyl- ([Pt(L²⁴-S,O)₂]) and *N,N*-dibutyl-*N*-(3,4,5-trimethoxy)benzoylthiourea ([Pt(L²⁵-S,O)₂]) complexes also showed only single peaks, which at shifts of -2731 ppm and -2723 ppm, were attributed to the respective *cis* isomers. However, for the complex with the *N*-morpholino substituted ligand ([Pt(L²⁶-S,O)₂]), the ¹⁹⁵Pt spectrum showed, in addition to a major peak at -2733 ppm, a very small, but distinct peak at -3051 ppm. Because the latter appeared in the same region as the minor peaks previously attributed to the *trans* *N*-naphthoylthiourea - Pt(II) complexes^{11,36,37}, the investigations were carried a little further. At first, attempts were made to isolate any *trans* complex by thin layer chromatography using silica gel and aluminium oxide plates, and chloroform and methylene chloride as eluents. When these attempts failed, the crude materials were each subjected to a prolonged cycle of fractional recrystallisation. In this way, each sample was separated into five sequential batches of crystalline material. The individual fractions were then re-submitted for ¹H and ¹³C NMR spectroscopy. This proved fruitful, because two of the fractions were found to contain more than one [Pt(L-S,O)₂] species.

One such result was obtained from the second batch of bis(*N,N*-dibutyl-*N*-(2,2-dimethylpropanoyl)thiourea)platinum(II) crystals ([Pt(L²⁵-S,O)₂]). This batch produced a ¹H NMR spectrum similar to that acquired from the crude material (see figure 5.7). However, two important differences were noticed at the resonance peaks of the protons closest to the chelating moieties. The first concerned the equivalent triplet pair expected from the α-carbon protons of the *N*-butyl groups (3.69 and 3.76 ppm – peaks 7,7' in figure 5.7). Of these, the downfield triplet was masked by the appearance of an

Table 5.6 Proportions of *cis* and *trans*-[Pt(L-S,O)₂] complexes obtained from the co-ordination of *N,N*-substituted *N'*-(3,4,5-trimethoxybenzoyl)thiourea ligands to Pt(II)

Ligand (HL ⁿ)		[Pt(L ⁿ -S,O) ₂] Yields	
HL ²⁴		<i>cis</i>	90.5 %
		<i>trans</i>	-
HL ²⁵		<i>cis</i>	88.2 %
		<i>trans</i>	4.2 %
HL ²⁶		<i>cis</i>	90.1 %
		<i>trans</i>	7.0 %

additional multiplet. The signal intensity of this multiplet was more than twice that of the upfield triplet. The other, potentially more diagnostic difference, was the appearance of an extra singlet at 7.34 ppm. This signal was of considerable interest because it appeared 0.21 ppm upfield of the characteristic singlet (at 7.55 ppm) produced by the two phenyl ring protons (positions 2 and 6 on the ring – peak 2,6 in figure 5.7) of the *cis* complex. Again, the extra singlet was significantly more intense than the assigned singlet. These two phenyl ring protons and their resonance signal are of particular interest because they are analogous to the naphthyl ring α proton (i.e. the ring proton closest to the R'-C(O) bond) in the *N,N*-dibutyl-*N'*-naphthoylthiourea complex described by Koch *et al.*¹¹ Significantly, the resonance signal of this proton (a doublet) was reported to be shifted upfield by 0.20 ppm, from 8.15 ppm in the ¹H NMR spectrum of the *cis*-[Pt(L-S,O)₂] complex, to 7.95 ppm in the spectrum of the *trans*-[Pt(L-S,O)₂] complex.

The ¹³C spectrum acquired from this second batch of [Pt(L²⁵-S,O)₂] crystals proved even more interesting (see figure 5.8). This quite clearly consisted of two sets of peaks, one set matching exactly the ¹³C spectra

from the other pure *cis*-[Pt(L²⁵-S,O)₂] samples, and the other set, appearing to be a more intense and slightly shifted duplicate. In the downfield region for example, an extra pair of peaks were found at 169.1 and 170.2 ppm. This was close to the carbonyl and thiocarbonyl peaks (167.8 and 167.4 ppm) recognised from the spectra of the crude material and the pure *cis*-[Pt(L²⁵-S,O)₂] samples. (The close proximity of the two pairs was considered important, because it essentially ruled out the possibility that the second set of peaks were the resonances of any unusual *N,S* co-ordinated [PtL₂] species – see section 5.4.3.2 below for an example). As obvious as the extra pair of downfield resonances, were neighbouring peaks in even closer proximity to each of the *cis*-[Pt(L²⁵-S,O)₂] peaks from the phenyl ring carbons, the 3 and 5 methoxy group carbons, and the α and β carbons of the *N*-butyl groups.

From the relative peak intensities in the ¹H and ¹³C spectra, it appeared that the unknown component was the dominant product in the second batch of crystals. This was important, because a sample was also submitted for elemental microanalysis. The C, H, N, and S contents were found to match, well within experimentally acceptable limits, the values calculated for the [Pt(L-S,O)₂] complex. This effectively ruled out that the sample contained appreciable amounts of unbound ligand or species such as the protonated [Pt(HL-S)₂Cl₂] and [Pt(L-S,O)(HL-S)Cl] complexes. In this respect, it was also reassuring to observe the melting properties of the sample. Significantly, only a portion of the crystals placed on the melting point apparatus melted sharply between 125 – 127°C. (This was the temperature region in which the crude sample and the first batch of *cis*-[Pt(L²⁵-S,O)₂] crystals had been found to melt, and was well above the 100 – 102°C melting point of the free ligand.) The remaining crystals persisted in the molten phase, and only began melting gradually once a temperature of 170°C had been reached. Based on the overall evidence it is reasonable to conclude that the unknown second component was indeed the *trans*-[Pt(L-S,O)₂] species. By comparing the relative intensities of the ¹H peaks at 7.34 and 7.55 ppm, it was estimated that this species made up about 60% of the second crystal batch. However, as the batch had been very small (33 mg) and only made up 7% of the total product, the effective overall yield of *trans* complex was less than 4.5%.

The other batch of crystalline material that appeared to contain an appreciable amount of the *trans*-[Pt(L-S,O)₂] species, was the third fraction of the complex derived from the *N*-morpholino-*N'*-(3,4,5-trimethoxybenzoyl)thiourea ligand (HL²⁶). (This was reassuring since the crude reaction product had produced the ¹⁹⁵Pt spectrum with the additional minor peak at -3051 ppm.) Again, the ¹³C spectrum of this crystal batch was found to consist of two sets of resonances, one corresponding to the peaks of the *cis*-[Pt(L²⁶-S,O)₂] samples, and the other, a slightly shifted duplicate. Furthermore, an extra singlet also reappeared in the ¹H spectrum (7.29 ppm), and as before, it was located just upfield (0.22 ppm) of the characteristic peak usually assigned to the phenyl ring protons (7.51 ppm). In this instance, the relative peak intensities indicated that the *trans* species made up approximately 30% of the third crystal fraction, and hence 7% of the overall product. For the complex with *N,N*-diethyl- *N'*-(3,4,5-trimethoxybenzoyl)thiourea ligand (HL²⁴) none of the crystal fractions were found to contain detectable amounts of the *trans*-[Pt(L-S,O)₂] species.

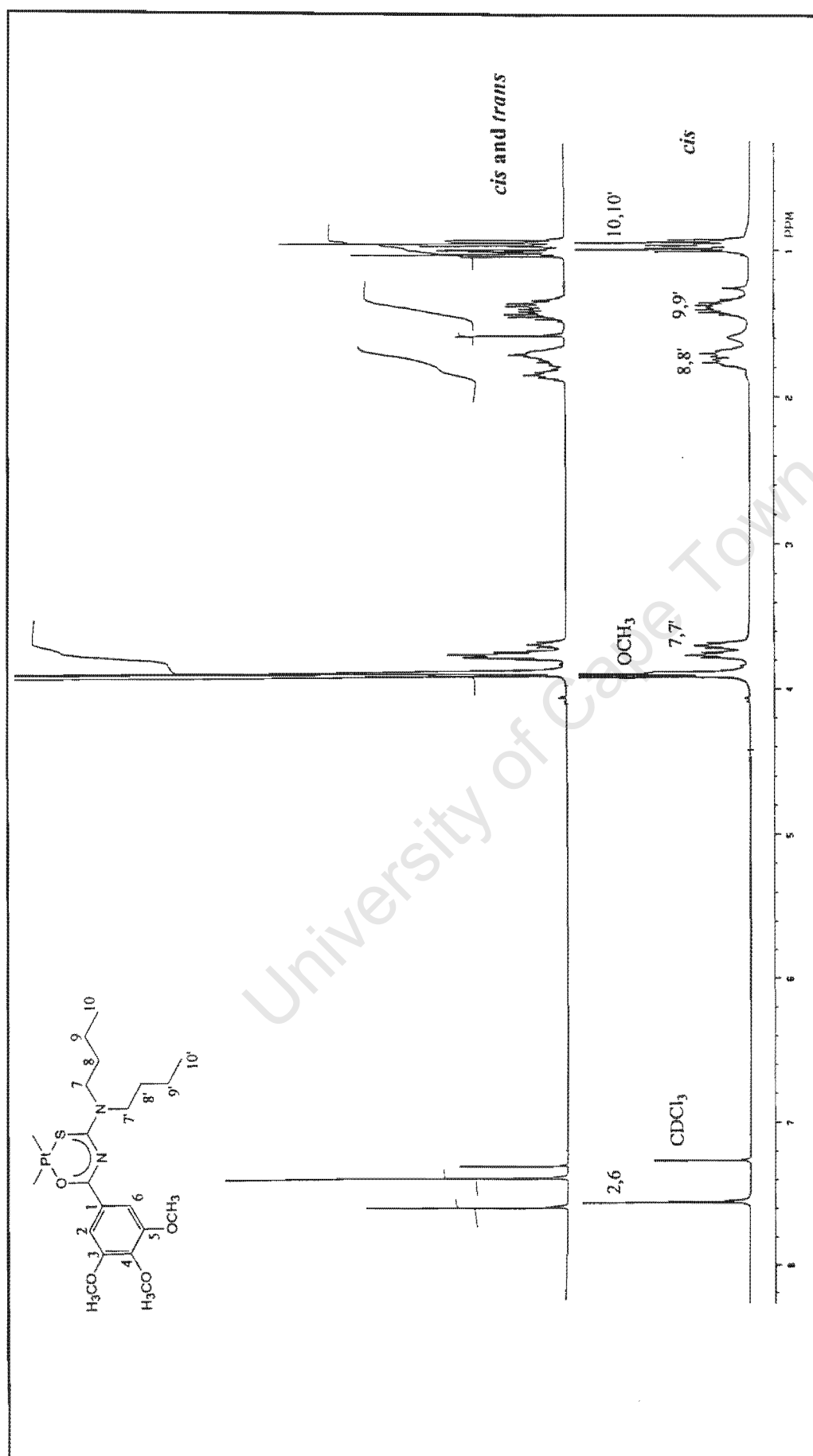


Figure 5.7 ^1H NMR spectra of the crude, predominantly *cis*-bis(*N,N*-dibutyl-*N'*-(3,4,5-trimethoxy)benzoylthiourea)platinum(II) product ($[\text{Pt}(\text{L}^{25}\text{-S}_2\text{O}_2)_2]$) and of the crystal fraction thought to consist of a mixture of the *cis* and *trans* isomers

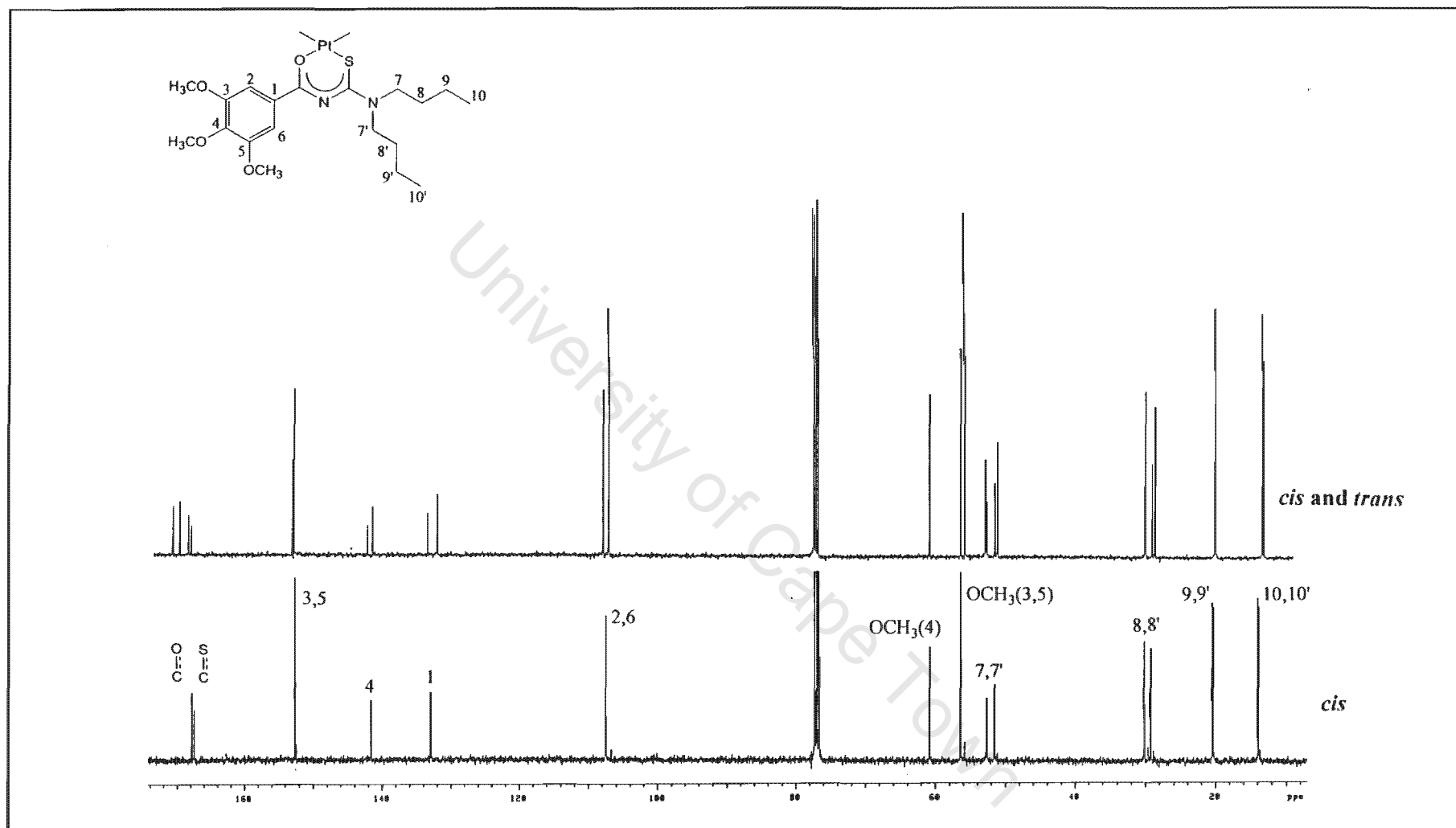


Figure 5.8 ^{13}C NMR spectra of the crude, predominantly *cis*-bis(*N,N*-dibutyl-*N'*-(3,4,5-trimethoxy)benzoylthioureato)platinum(II) product ($[\text{Pt}(\text{L}^{25}\text{-S},\text{O})_2]$) and of the crystal fraction thought to consist of a mixture of the *cis* and *trans* isomers

To complete this discussion, it must be pointed out that the *trans* complexes were not indefinitely stable when dissolved in chloroform. This was discovered by chance when the second fraction of the $[\text{Pt}(\text{L}^{25}\text{-S,O})_2]$ complex was submitted for ^{195}Pt NMR. Owing to the very limited amount of material, the sample submitted for ^1H and ^{13}C NMR was kept in the NMR tube, dissolved in CDCl_3 , until the opportunity arose to run the ^{195}Pt spectrum. This only presented itself two months later, by which stage almost all the solvent had evaporated. After more CDCl_3 was added, the ^{195}Pt spectrum that was obtained, was found to contain only the characteristic peak of the *cis* isomer (-2723 ppm). The sample was thus immediately re-submitted for ^1H and ^{13}C NMR spectroscopy. This confirmed that the isomeric composition of the sample had changed completely, and that the *trans* isomer content had decreased from the initial 60% to less than 10%. It thus appears that over time the *trans*- $[\text{Pt}(\text{L-S,O})_2]$ species isomerised to the *cis* complex. Although the change would appear to be consistent with the dictates of the *trans* influence, the mechanism for the isomerisation process is not clear at this stage. One possibility considered was that the process was linked to residual traces of HCl known to occur in chloroform and other chlorinated organic solvents. Through a small scale cycle of protonation and chelate ring opening this residual HCl may have brought about the conversion.

Although the *trans* complexes were obtained in two instances, it would be premature to conclude that the proposal concerning the softening effect of an R' group on the carbonyl moiety, had been proved correct. These preliminary results, however, do warrant further attention and a more detailed investigation could be extended to include a host of other electron rich N' -aroylthioureas as ligands. The slow isomerisation from the *trans* to the *cis* species that seemed to occur with the second fraction of $[\text{Pt}(\text{L}^{25}\text{-S,O})_2]$ complex also requires further explanation and should therefore be studied under more controlled conditions.

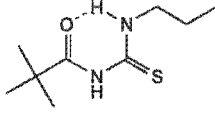
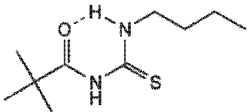
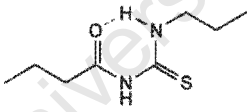
5.4.3 Pt(II) co-ordination chemistry of the N' -monosubstituted N' -acylthioureas

5.4.3.1 General Observations

On the occasions when the N' -monosubstituted N' -benzoylthioureas (H_2L) have been used as ligands for Pt(II), the reactions have commonly been carried out in 1 : 2 mixtures of 0.1 M HCl and acetonitrile or dioxane^{27,28}. According to reports, these reactions usually proceed fairly rapidly and good yields of bright yellow $[\text{Pt}(\text{H}_2\text{L-S})_2\text{Cl}_2]$ are obtained within an hour of mixing metal and ligand solutions²⁸. In the water – acetonitrile solutions with sodium acetate, however, the reactions of the N' -propyl- and N' -butyl substituted N' -(2,2-dimethylpropanoyl)thioureas (H_2L^{27} , H_2L^{28} – table 5.7) were found to be very much slower. These preparations were thus left to proceed for forty eight hours. Although the reaction solutions had turned an orange colour after this period, no precipitate had been formed. On dilution with an equivalent volume of water, an orange coloured suspension appeared. This material, however, was too fine to be recovered by ordinary filtration or centrifugation, and was extracted with chloroform after most of the acetonitrile fraction in the solution had been allowed to evaporate. With N' -propyl- N' -butanoylthiourea (H_2L^{29}), the reaction initially appeared to proceed somewhat faster. In this instance, a fine yellow precipitate appeared

after an hour of mixing the ligand and metal solutions. However, as the yield of this product appeared to be low, the reaction was also left to proceed for forty eight hours. Again, the solution itself turned an orange colour and yielded an orange suspension after dilution with water. Here too, the products were extracted with chloroform. In all three cases, evaporation of the chloroform left a solidified orange oil (i.e. a glassy product). None of these materials could be separated into individual components on silica gel or aluminium oxide plates, but gave continuous product streaks.

Table 5.7 A list of products obtained from the reactions of the *N*-monosubstituted *N'*-acylthioureas with Pt(II)

Ligand (H_2L)	Reaction products	Yield (%)
H_2L^{27} 	unidentified orange oil	-
H_2L^{28} 	unidentified orange oil	-
H_2L^{29} 	unidentified orange oil <i>trans</i> -[Pt(HL- <i>N,S</i>) ₂]	- 34.7

For the *N*-propyl- (H_2L^{27}) and the *N*-butyl-*N'*-(2,2-dimethylpropanoyl)thiourea (H_2L^{28}) derived oils, attempts at recrystallisation from chloroform – ethanol mixtures also proved fruitless as only the solidified oil reappeared after the bulk of the solvent had evaporated.

For the *N*-propyl-*N'*-butanoylthiourea (H_2L^{29}) derived material, however, recrystallisation yielded, in addition to the orange coloured oil, a set of pale yellow crystals. These formed long before the reappearance of the oil, and at 34.7% yield, they constituted a substantial fraction of the product mixture. They were presumed to have formed from the fine yellow precipitate which, it was pointed out above, was observed soon after the $PtCl_4^{2-}$ and H_2L^{29} ligand solutions were mixed. When separated from the mother liquor the crystals were found to be air stable and of a quality suitable for single crystal X-ray diffraction analysis. This was fortuitous because a structure determination of this compound revealed it to be a highly unusual

complex of the form *trans*-[Pt(HL-*N,S*)₂] i.e. a complex in which two deprotonated ligands were co-ordinated to the Pt(II) centre, not in the expected *cis* bidentate *S,O* manner, but in *trans* bidentate fashion via the sulphur and *N'* nitrogen atoms.

5.4.3.2 Characterisation and crystal structure determination of an unusual *trans*-[Pt(HL-*N,S*)₂] complex of *N*-propyl-*N'*-butanoylthiourea (*H₂L*²⁹)

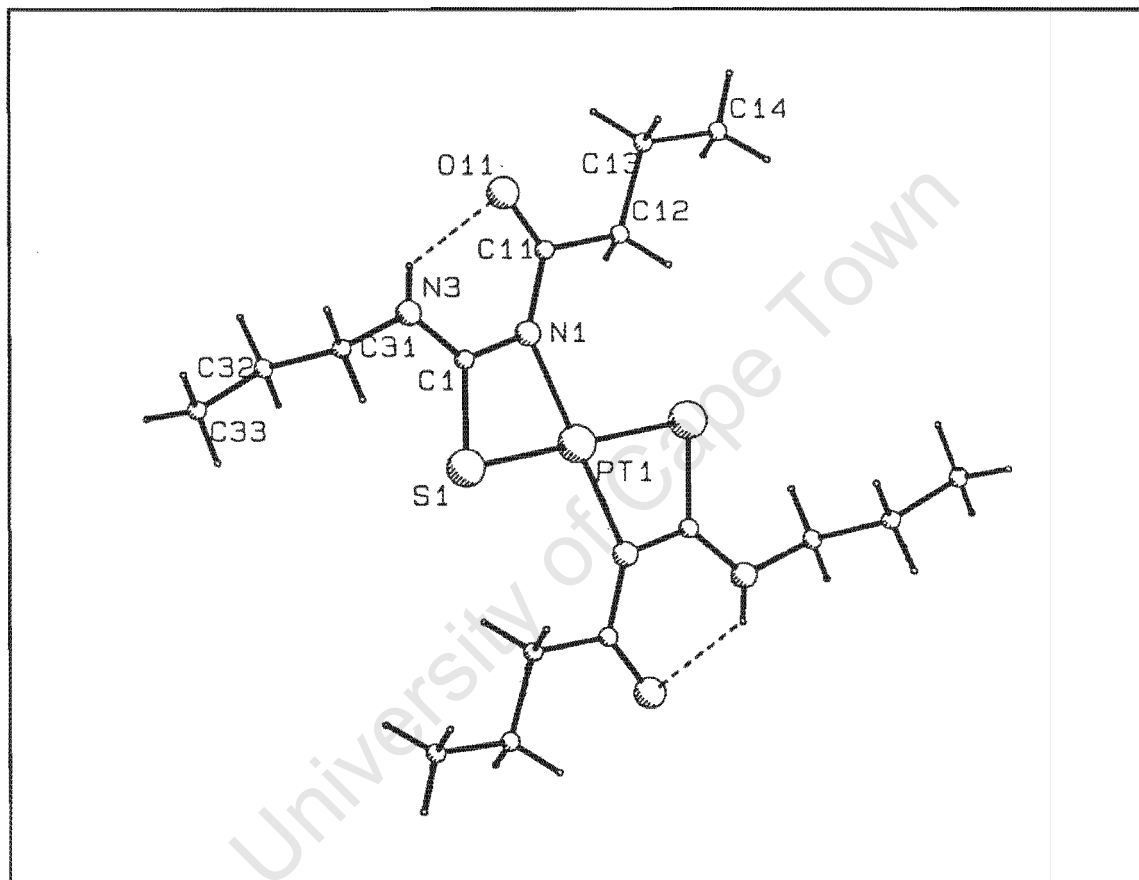
The yellow crystalline compound isolated from the reaction of the *N*-propyl-*N'*-butanoylthiourea ligand (*H₂L*²⁹) was found to have a sharp melting point (173 – 175°C). From elemental microanalysis it was established that the C, H, N and S content of this material matched the values calculated for a complex with Pt(HL²⁹)₂ stoichiometry. Although this indicated that the co-ordinated ligands were in deprotonated form, it was initially assumed that the ligands were co-ordinated, as intended, in the conventional bidentate *S,O* fashion to produce the [Pt(HL²⁹-*S,O*)₂] complex. The ¹H NMR spectrum of this compound bore a close resemblance to the spectrum of the unbound ligand, but particularly significant, was the absence of the characteristic singlet for the *N'*H proton.

Assignment of the resonance signals in the ¹³C spectrum also appeared to be straightforward at first, since the product gave only a single set of sharp ligand peaks. In this instance, however, it was of some concern to note that instead of shifting in opposite directions, both the carbonyl carbon and the thiocarbonyl carbon peaks had shifted substantially downfield, the latter from 179.6 ppm (in the spectrum of the unbound ligand) to 191.1 ppm. (This was quite unlike the crossed-over ¹³C shift pattern that had typified *S,O* co-ordination of the *N,N*-dialkyl-*N'*-acyl- and *N'*-benzoylthiourea ligands to Pt(II) - see section 5.4.1.2). Of further interest, was that ¹⁹⁵Pt – ¹³C spin coupling interaction had increased significantly, even to the point that the spin satellites of the carbonyl carbon peak were well resolved. A *J*(¹⁹⁵Pt – ¹³C) coupling constant of 122 Hz was measured at the thiocarbonyl resonance, thus well above the average ²*J*(¹⁹⁵Pt – ¹³C) value of 45.2 Hz for the [Pt(L-*S,O*)₂] complexes of the *N,N*-dialkyl-*N'*-acyl- and *N'*-benzoylthioureas (see table 5.2). At the carbonyl carbon peak, the *J*(¹⁹⁵Pt – ¹³C) coupling constant was 35 Hz. It was also surprising to find in the ¹⁹⁵Pt NMR spectrum of the crystalline product, that a single ¹⁹⁵Pt resonance appeared at a chemical shift of –2451 ppm i.e. approximately 300 ppm downfield of the resonance peaks of the *N,N*-dialkyl-*N'*-acylthiourea *cis*-[Pt(L-*S,O*)₂] complexes (–2750 ppm – see section 5.4.1.3). Considering the relatively small shifts brought about by R' and *N*-alkyl group variations in the latter, it seemed unreasonable to attribute the large shift difference solely to the absence of a second *N*-alkyl group in the ligand. Fortunately, the reasons for the unusual ¹³C and ¹⁹⁵Pt chemical shifts became clear after the crystal and molecular structure were solved by X-ray diffraction analysis.

The crystal submitted for X-ray diffraction analysis was found to be of the triclinic space group *P* $\bar{1}$ with one molecule per unit cell. The structure was solved and refined using SHELXS-97 and SHELXL-97^{49,54}. The final model included anisotropic refinement of all non-hydrogen atoms. The hydrogen involved in hydrogen bonding was located in the difference electron density map and refined independently from the

other hydrogens. The latter were placed in geometrically calculated positions during later stages of refinement. Data solution and refinement parameters are given in Appendix 3, along with fractional atomic co-ordinates, bond lengths and bond angles, bond torsion angles, anisotropic temperature factors and hydrogen bonding parameters.

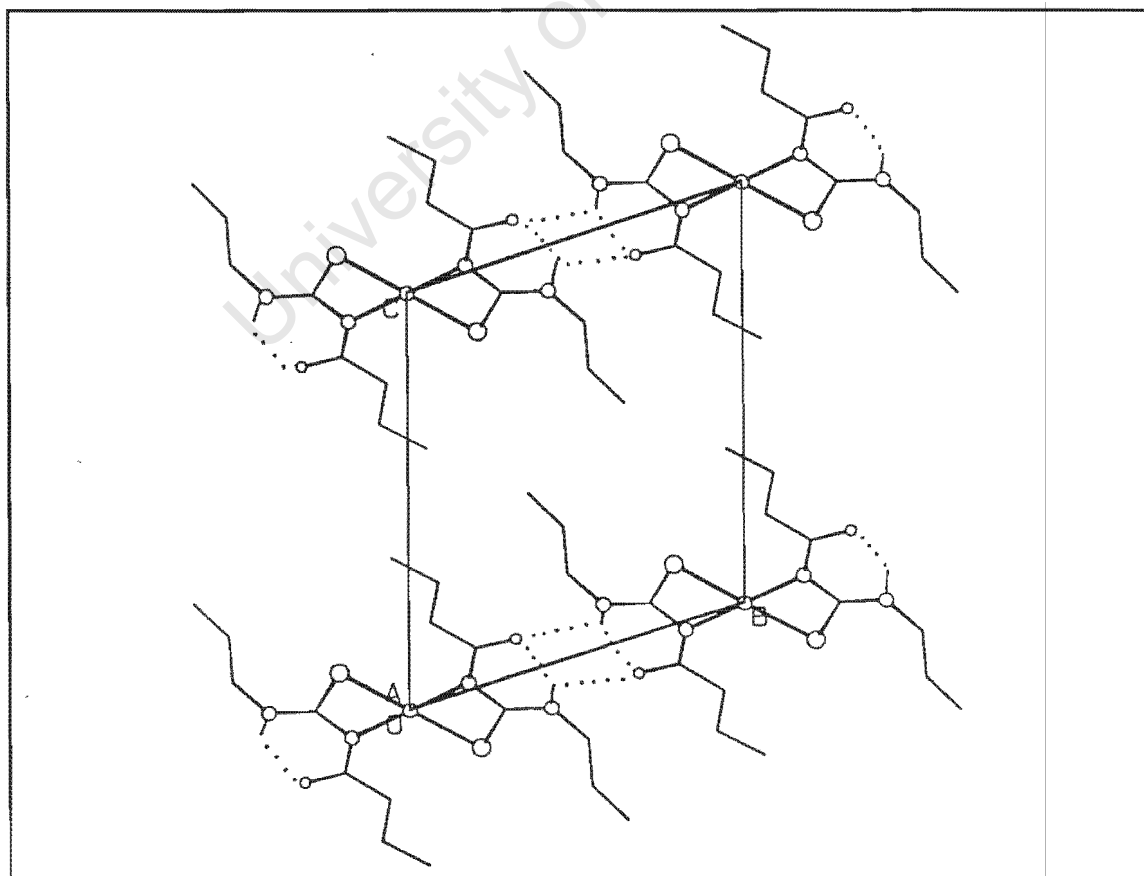
Figure 5.9 Perspective view of the molecular structure of the *trans*-[Pt(HL²⁹-*N,S*)₂] complex of *N*-propyl-*N'*-butanoylthiourea, showing the atom numbering scheme for the non-hydrogen atoms, and the intermolecular hydrogen bond



The molecular structure (see figure 5.9) confirmed that the complex was a neutral [Pt(HL)₂] species, and that the two ligands around the metal centre had indeed been deprotonated at the *N'* nitrogens (N1 in figure 5.9). However, the structure also revealed that the hydrogen bonds between the protons of the *N*-alkyl nitrogens (N3) and the carbonyl oxygens (i.e. N3-H···O11 = 2.096(5) Å) had remained intact, and that as a result, the oxygen atoms were not co-ordinated to the metal centre. Instead, and quite unexpectedly, it was the deprotonated *N'* nitrogens that were found to be participating with the sulphur atoms in bidentate co-ordination to the Pt(II) centre. Of further surprise, was that the four donor atoms had co-ordinated in a *trans* configuration around the metal.

With only two bonds separating the donor atoms on each ligand (S1-C1-N1), the *N,S* chelating bite was relatively small, and the resulting chelate ring only of four-membered size. Nevertheless, the rings were found to be planar (standard deviation from planarity of 0.02 Å), as was the co-ordination geometry around the metal centre. At the latter, however, there was considerable distortion from an ideal square, with angles of 110.58 (10)° and 69.42 (10)° between the bond diagonals subtended at the Pt (i.e. the bond angles N-Pt-S). It was also of interest to note a significant degree of electron delocalisation associated with the three bonds around each thiocarbonyl carbon (at 1.346 (5) Å, 1.321 (5) Å, and 1.732 (4) respectively the C1-N1, C1-N3 and C1-S1 bonds were all markedly shorter than analogous single bonds⁵⁰). Very much less π character, on the other hand, was evident of the bond between the *N'* nitrogen and the carbonyl carbon (N1-C11), which was found to be 1.385 (5) Å in length. This is quite unlike the analogous bond in the *N,N'*-dialkyl-*N'*-benzoylthioureas, which typically decreases from 1.37 Å to 1.32 Å on *S,O* chelation to Pt(II), Pd(II) or Ni (II) (see table 5.5). Planar geometry was not just confined to the vicinity of the metal centre, but essentially extended over the entire structure. Contributing to this were the six-membered rings maintained by the intramolecular hydrogen bonds. Apart from being planar (standard deviation from planarity of 0.04 Å), these rings were also found to be coplanar to the adjacent four-membered chelate rings (the angle between the least squares planes of the two rings was 3.8 (7)°). The crystal structure also showed

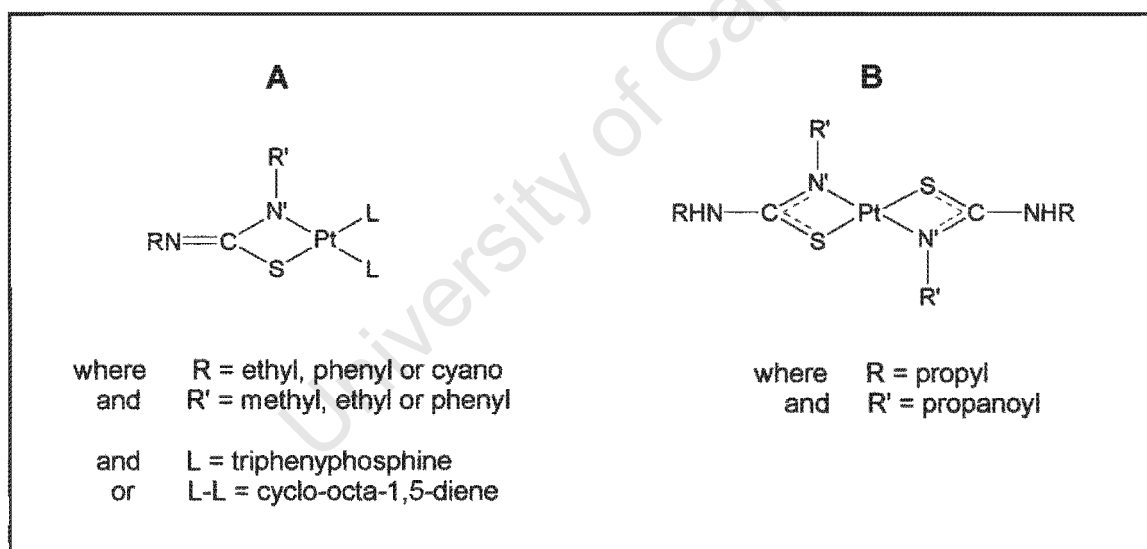
Figure 5.10 Molecular packing diagram of the *trans*-[Pt(HL²⁹-*N,S*)₂] complex showing the intra- and inter-molecular hydrogen bonds



evidence of a long (2.602(5) Å), and hence weak, intermolecular contact between the N-H moiety and the oxygen atom on an adjacent molecule. This resulted in layers of molecules packing parallel to the *ab* face, with the weak hydrogen bonds between adjacent molecules parallel to (110) (see figure 5.10).

The molecular structure is remarkable, not only because *trans N,S* chelation represents an unprecedented form of co-ordination for the *N*-substituted *N'*-acyl- and *N'*-aroylthiourea ligands, but also because confirmed structures with four-membered *N,S* chelate rings around Pt(II) and Pd(II) centres appear to be extremely rare. A comprehensive literature survey revealed only four crystal structures with this type of co-ordinating moiety, one derived from a carbon disulphide⁵⁵, and three with *N,S* co-ordinated *N,N'*-substituted thioureas (*N,N'*-diphenylthiourea⁵⁶, *N,N'*-diethylthiourea⁵⁷, and *N*-methyl-*N'*-cyanothiourea⁵⁸). Significantly, in all four cases, the compounds were mixed ligand complexes, with the *N,S* chelate sharing the metal centre with either triphenylphosphine or cyclo-octadiene ligands (i.e. $[\text{Pt}(\text{L}^{\text{a}}-\text{N},\text{S})(\text{L}^{\text{b}})_2]$ - see complex A in figure 5.11). Symmetrical structures with two *N,S* co-ordinated thiourea ligands on the metal centre (i.e. of the type $[\text{Pt}(\text{L}-\text{N},\text{S})_2]$) have not been described to date.

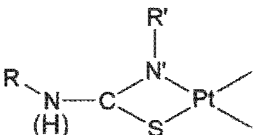
Figure 5.11 Schematic representation to compare the dianionic, *N,S* co-ordinated *N,N'*-substituted thioureas of the mixed ligand $[\text{Pt}(\text{L}^{\text{a}}-\text{N},\text{S})(\text{L}^{\text{b}})_2]$ complexes (A)⁵⁶⁻⁵⁸, with the monoanionic *N*-propyl-*N'*-butanoylthiourea ligands of the symmetrical *trans*- $[\text{Pt}(\text{HL}^{29}-\text{N},\text{S})_2]$ complex (B)



The *trans*- $[\text{Pt}(\text{HL}^{29}-\text{N},\text{S})_2]$ complex also differs from the three mixed ligand Pt(II) - thiourea complexes because the *N,N'*-substituted thiourea ligands of the latter were doubly deprotonated and therefore formally dianionic (i.e. both the *N'* and the *N* nitrogens of these thioureas were deprotonated). In the *trans*- $[\text{Pt}(\text{HL}^{29}-\text{N},\text{S})_2]$ complex, on the other hand, the two ligands are monoanionic since only the *N'* nitrogens are deprotonated. From the comparative list of bond lengths in table 5.8, it can be seen that this difference does have an effect on some of the bonds associated with the *N,S* chelating moieties. The most noticeably influenced appear to be the thiocarbonyl carbon to sulphur bonds (C-S in table 5.8). In the mixed ligand

$[\text{Pt}(\text{L}^{\text{a}}\text{-N,S})(\text{L}^{\text{b}})_2]$ complexes, this bond has an average value of 1.78 Å and it is therefore regarded as a single bond⁵⁶⁻⁵⁸. However, at 1.732 Å the analogous bond in the *trans*- $[\text{Pt}(\text{HL}^{29}\text{-N,S})_2]$ complex is significantly shorter, and should thus be considered a partial double bond. In the reports on the mixed ligand $[\text{Pt}(\text{L}^{\text{a}}\text{-N,S})(\text{L}^{\text{b}})_2]$ complexes, it is also noted that there is usually a distinct difference between the bond lengths from the thiocarbonyl carbon to the *N* and *N'* nitrogens⁵⁶⁻⁵⁸. It is pointed out that the bond to the unco-ordinated *N* nitrogen has greater double bond character (it is usually represented as a double bond - see complex A in figure 5.11) and is therefore noticeably shorter than the bond to the co-ordinated *N'* nitrogen (compare the average values of 1.31 Å and 1.36 Å for bonds C-N and C-N' in table 5.8). In the *trans*- $[\text{Pt}(\text{HL}^{29}\text{-N,S})_2]$ complex the analogous difference between the C-N and C-N' bonds is not quite as pronounced (compare the respective values of 1.321 Å and 1.346 Å in table 5.8). Interestingly, however, the pair of bonds to the metal centre in the *trans*- $[\text{Pt}(\text{HL}^{29}\text{-N,S})_2]$ complex (i.e. S-Pt and N'-Pt) appear to very similar to the analogous bonds of the mixed ligand $[\text{Pt}(\text{L}^{\text{a}}\text{-N,S})(\text{L}^{\text{b}})_2]$ complexes. This indicates that they are not noticeably affected by change from dianionic to monoanionic thiourea ligand.

Table 5.8 Average bond lengths and bond angles associated with the bidentate *N,S* chelating moieties of the thioureas in the mixed ligand $[\text{Pt}(\text{L}^{\text{a}}\text{-N,S})(\text{L}^{\text{b}})_2]$ ⁵⁶⁻⁵⁸ complexes and the *trans*- $[\text{Pt}(\text{HL}^{29}\text{-N,S})_2]$ complex (standard deviations appear in parentheses*)

Bond / Angle	Bond Lengths (Å) / Angles (°)	
	<i>trans</i> - $[\text{Pt}(\text{HL}^{29}\text{-N,S})_2]$	$[\text{Pt}(\text{L}^{\text{a}}\text{-N,S})(\text{L}^{\text{b}})_2]$ average
		
C—S	1.732 (± 0.004)	1.78 (± 0.01)
C—N'	1.346 (± 0.005)	1.36 (± 0.06)
C—N	1.321 (± 0.005)	1.31 (± 0.03)
Pt—S	2.328 (± 0.001)	2.325 (± 0.012)
Pt—N'	2.039 (± 0.003)	2.036 (± 0.027)
S—Pt—N'	69.4 (± 0.1)	70.8 (± 0.4)

* the standard deviations listed for the *trans*- $[\text{Pt}(\text{HL}^{29}\text{-N,S})_2]$ complex, are experimental deviations recorded for the measurements during the crystallographic data collection

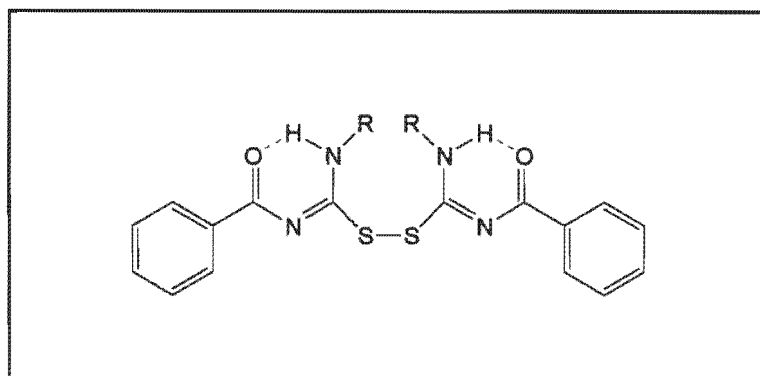
It is somewhat unfortunate that similar *trans*-[Pt(HL-*N,S*)₂] species could not be isolated from the orange oil products of the *N*-propyl- and *N*-butyl-*N'*-(2,2-dimethylpropanoyl)thiourea (**H₂L²⁷** and **H₂L²⁸**) reactions, although this is not to say that they were absent. With small yields, and the tertiary butyl R' group of these two ligands possibly disrupting the overall molecular planarity, it is quite conceivable that crystallisation may have been inhibited. As far as obtaining any *trans*-[Pt(HL-*N,S*)₂] species in more detectable yields is concerned, it may also be significant, that acetate base was added to the ligand solution prior to addition of the metal. With delayed and more controlled addition of base, and with further work to optimise other reaction conditions, it may well be possible to obtain these types of complexes in significantly higher yields.

5.4.3.3 The orange oil products recovered from the co-ordination reactions of the *N*-monosubstituted *N'*-acylthioureas (**H₂L²⁷** – **H₂L²⁹**)

The solidified orange oils obtained from the reactions of all three ligands proved to be remarkably similar to each other. None exhibited sharp melting points and all transformed gradually from a solid to a viscous oil over a 20 to 30°C temperature range. Except for the consistent presence of two broad, but distinct singlets between 7.6 and 9.0 ppm, the ¹H NMR spectra of these materials were complex and poorly resolved. Although two broad downfield signals also appeared in the spectra of the free ligands, only the characteristic resonance of the acidic N'H proton appeared between 8 and 9.5 ppm (the broad peak of the hydrogen bonded -NHR proton was always found much further downfield, usually around 10.6 ppm). Further differences from the parent ligands were evident in the ¹³C NMR spectra of the three oils. Though not noticeably shifted, the ¹³C peaks of the R' and *N*-alkyl group carbons were significantly broader than usual. Furthermore, the thiocarbonyl carbon peak, which invariably appeared at 180 ppm in the spectra of the unbound ligands, in all cases appeared to be shifted upfield by 26 ppm, to 154 ppm. The positions of carbonyl carbon peaks, however, appeared unaffected, remaining at 174 ppm for the *N'*-butanoylthiourea (**H₂L²⁹**) derived oil, and at 179 ppm for the oils from the two *N'*-(2,2-dimethylpropanoyl)thioureas (**H₂L²⁷** and **H₂L²⁸**).

The two downfield ¹H singlets and the shift of the thiocarbonyl carbon ¹³C peak are of particular interest, because they appear to conform to NMR features of a side-product previously isolated from a co-ordination reaction of a *N*-monosubstituted *N'*-benzoylthiourea. This product, thought to be a disulfide derived from the oxidation of the *N'*-benzoylthiourea (see figure 5.12), was described by Grimbacher³⁶ after an attempt to synthesize a [M(HL)₂] type complex with Cu(II). Although *N,N*-disubstituted *N'*-benzoylthioureas readily form neutral [Cu(L-*S,O*)₂] complexes when added to DMF – water solutions of Cu(II) acetate, Grimbacher isolated a yellow complex with a 1 : 1 metal to ligand stoichiometry from a reaction with the monosubstituted *N*-tetradecyl-*N'*-benzoylthiourea. This product was found to be a neutral complex, consisting of a deprotonated ligand, bound to a Cu centre in the +1 oxidation state i.e. Cu(LH). At 45%, however, the yield of this complex was considered low and the disulfide was isolated after subsequent

Figure 5.12 The disulfide product derived from the oxidation of a *N*-substituted *N'*-benzoylthiourea [TG, B16]



evaporation, under reduced pressure, of the reaction solvents. In discussing the ^1H and ^{13}C NMR spectra of this compound, Grimbacher³⁶ pointed out the similarities to the spectra of the parent ligand, but also mentioned the two broad ^1H signals between 8 and 9 ppm, and the downfield ^{13}C resonances at 168 and 154 ppm. Attention was drawn to the fact that the peak at 154 ppm corresponded favourably with the ^{13}C peak at 153 ppm of a $-\text{N}=\text{C}-\text{S}-$ thiazole type moiety³⁹, whereas the peak at 168 ppm was typical of the carbonyl carbon peak of the free ligand. Reference was also made to a previous study by Harris⁶⁰, who showed that *N'*-benzoylthioureas were readily oxidised to the corresponding disulfides in the presence of bromine.

Comparisons of the elemental microanalysis results are also of interest. For the *N*-propyl- and *N*-butyl-*N'*-(2,2-dimethylpropanoyl)thiourea (H_2L^{27} and H_2L^{28}) derived oils, the elemental C, H, N, and S contents match, within experimental error, the values calculated for the intended $[\text{Pt}(\text{HL}-\text{S},\text{O})_2]$ type complex. However, since a disulfide molecule is proposed to consist of two deprotonated *N'*-acylthiourea molecules linked via the sulphur atoms, these calculated values are also correct for a $[\text{PtL}]$ type complex in which the disulfide is the ligand L. On the basis of C, H, and N elemental microanalysis, Grimbacher³⁶ speculated that the white disulfide powder that was isolated was in the form of a hydrochloride salt i.e. $\text{L}\cdot 2\text{HCl}$. However, considering that copper (II) acetate was used as the metal source, and that the reaction was carried out in a DMF – water mixture, the origin of the HCl is not at all certain. Surprisingly, it appears to have been overlooked that a CuL type complex of the disulfide would have a very similar C, H and N content to the $\text{L}\cdot 2\text{HCl}$ disulfide salt that the product was proposed to be. (Compositional differences between $\text{C}_{44}\text{H}_{70}\text{N}_4\text{S}_2\text{O}_2\text{Cu}$ and $\text{C}_{44}\text{H}_{70}\text{N}_4\text{S}_2\text{O}_2\cdot 2\text{HCl}$ amount to 0.7% for the C content, and 0.1% each for the H and N contents.) If Grimbacher's product were indeed a CuL disulfide complex, the metal centre was probably in the +1 oxidation state, since most Cu(I) compounds are colourless³⁵ (i.e. white in powdery form).

Despite the parallels, the characterisation of the orange oils is far from complete. Neither the NMR nor the elemental microanalysis data shed any light on the oxidation state of the Pt, if indeed the latter did form part of a complex with the proposed disulfide. In a neutral complex, a charged Pt centre would have to be co-

ordinated to a deprotonated disulfide ligand. This would involve dissociation of the hydrogen bonded *N* protons, a step that would certainly be considered highly unusual for the parent *N*-alkyl-*N'*-acylthioureas. Furthermore, the experimentally determined H content of the *N*-propyl- and *N*-butyl-*N'*-(2,2-dimethylpropanoyl)thiourea (H_2L^{27} , H_2L^{28}) derived oils tended to be marginally higher, not lower than the values calculated for the proposed [PtL] disulfide complexes. Of course, it is also possible that the neutral [PtL] complexes consisted of a disulfide co-ordinated to Pt(0) metal centre. The co-ordination chemistry of Pt(0) is reasonably extensive³⁵, and a reduction of the metal would also be in accord with the Cu(II) to Cu(I) reduction observed by Grimmacher³⁶. Attempts to obtain a ^{195}Pt spectrum from the *N*-propyl-*N'*-(2,2-dimethylpropanoyl)thiourea (H_2L^{27}) derived product yielded little further information on the constitution of the orange oils, since no resonance peaks were observed in the spectral window between -2200 to -3400 ppm. Although the absence of a resonance peak may indicate that the Pt is in the paramagnetic +1 oxidation state, a significant paramagnetic shift and broadening would then also be expected for the ^1H and ^{13}C resonance signals of the compound. Since the chemical shift range of ^{195}Pt resonances is approximately 13000 ppm⁴⁷, a more likely explanation is that the resonance peak(s) occurred outside the observed spectral region.

More uncertainties about the constituents of the orange oils arose on elemental microanalysis of the oil derived from the *N*-propyl-*N'*-butanoylthiourea (H_2L^{29}) (the ligand that also reacted to give the significant fraction of yellow [*trans*-Pt(HL²⁹-*N,S*)₂] complex - see section 5.4.3.2). In appearance, and from the NMR spectra this material seemed very similar to the oils derived from the other two ligands. However, in this instance, the C, H, and N contents were found to be well below the values calculated for a [Pt(HL²⁹-*S,O*)₂] type complex or the values calculated for the proposed [PtL] complex of the disulfide. At 28.7%, the carbon content, for example, was found to be 5% below the expected value. The sulphur content, on the other hand, was found to be 1.1% higher than the 11.3% calculated for the complexes. These results suggest that the common product that always gave rise to the characteristic downfield ^{13}C peaks at 154 and 179 ppm in the NMR spectra of the oils was not a simple [PtL] disulfide complex. Evidently, further work will have to be carried out to isolate and identify all the components from these reactions.

5.5 Concluding Remarks

At the beginning of this chapter it was pointed out that the co-ordination reactions between *N,N*-disubstituted *N'*-benzoylthioureas and transition metal ions have been studied in considerable detail. It was therefore to be anticipated that most of the *N,N*-dialkyl-*N'*-benzoylthioureas prepared during the course of this project would form *cis*-[M(L-*S,O*)₂] type complexes with Pt(II). Furthermore, it is unlikely to be considered any more surprising that their *N'*-acylthiourea counterparts were also found to co-ordinate in the same bidentate fashion. However, the differences between the two groups of ligands appeared to be more subtle, affecting properties such as the water solubility and pH stability of the complexes. This is an aspect that may have important implications as far as potential application in the recovery of the platinum group metals from aqueous systems is concerned, and accordingly, warrants further investigation.

The work on the *trans*-[Pt(L-S,O)₂] complexes and the co-ordination of the *N*-monosubstituted *N'*-acylthioureas is far from complete, and it was therefore with some reluctance that it was included in this report. However, the results of these investigations serve to illustrate that the co-ordination chemistry of these ligands is potentially quite variable and therefore cannot yet be classified as completely predictable. The work with the *N*-monosubstituted ligands, for example, could be extended to include a host of analogous *N'*-benzoylthioureas. These are easier to synthesise in reasonable yields and may well be used to obtain further variants of the unusual *trans*-[M(HL-*N*,S)₂] complex. It would also be of interest to determine whether *trans* S,O co-ordination is prevalent with other *N,N*-disubstituted *N'*-aroylthioureas as this would provide more substantial insight into the mechanism of co-ordination and the factors affecting conformation.

5.6 Experimental Procedures and Characterisation

5.6.1 General procedure for reacting Pt(II) with *N*-substituted *N'*-acyl- and *N'*-aroylthioureas

N-substituted *N'*-acyl- or *N'*-aroylthiourea ligand (1.0 mmol) was dissolved in acetonitrile (20 ml). Sodium acetate (1.1 mmol) dissolved in water (10 ml) was then added to the ligand solution. The Pt(II) solution was prepared by dissolving potassium tetrachloroplatinate (0.5 mmol) in water (15 ml). This was diluted with an equivalent volume of acetonitrile (15 ml) before it was added dropwise to the ligand solution. The mixture was left to stir for 12 hours, after which it was diluted with an equivalent volume of water (60 ml). It was then placed in a fridge and left to cool at 4°C for at least another 12 hours.

The complexes that formed solid precipitates were recovered by centrifugation and decanting the reaction solution. They were subsequently rinsed in a cold 50 : 50 mixture of acetonitrile and water, and dried. For purification, these compounds were recrystallised from a 2 : 1 mixture of chloroform and ethanol. Oils and products soluble in the acetonitrile – water mixture were extracted with chloroform, but only after most of the acetonitrile portion had been allowed to evaporate. Where possible, these products were further purified, using aluminium oxide (0.063 – 0.200 mm particle size) as stationary phase (50g / g of product) and pure chloroform or methylene chloride as eluent.

5.6.2 Product characterisation

All melting points and elemental C, H, N, and S microanalyses, and most of the ¹H and ¹³C NMR spectra were determined or recorded using the instrumentation and conditions described in chapter 2 (section 2.6.2). For the crystal fractions of the *N'*-(3,4,5-trimethoxybenzoyl)thiourea complexes, however, the ¹H and ¹³C spectra were recorded using a Varian UNITY-400 spectrometer operating at 400 and 100 MHz respectively. All the ¹⁹⁵Pt spectra were also recorded using this instrument. For this purpose the operating frequency was 85.7 MHz and the temperature set to 30°C. The chemical shifts are all quoted relative to external H₂PtCl₆ (500 mg/ml in 30% vol / vol D₂O / 1M HCl) and are estimated to be accurate to ± 2 ppm.

5.6.2.1 *cis*-[Pt(L-S,O)₂] complexes

cis-bis(*N,N*-dimethyl-*N'*-butanoylthioureato)platinum(II) ([Pt(L¹-S,O)₂] - table 5.1a): 92.4% yield, mp 156 – 159°C, Calculated for C₁₄H₂₆N₄O₂PtS₂: C, 31.04; H, 4.84; N, 10.34; S, 11.84, Found: C, 30.97; H, 5.04; N, 10.02; S, 11.68, NMR δ(¹H): 0.92 (t, 6H, CH₃CH₂CH₂C(O)-), 1.66 (m, 4H, CH₃CH₂CH₂C(O)-), 2.30 (t, 4H, CH₃CH₂CH₂C(O)-), 3.21 (s, 12H, -N(CH₃)₂), δ(¹³C): 13.84, 19.91, 40.30, 41.51, 42.58, 167.42, 178.00.

cis-bis(*N,N*-diethyl-*N'*-butanoylthioureato)platinum(II) ([Pt(L²-S,O)₂] - table 5.1a): 88.8% yield, mp 90 – 91°C, Calculated for C₁₈H₃₄N₄O₂PtS₂: C, 36.16; H, 5.74; N, 9.37; S, 10.73, Found: C, 35.69; H, 5.68; N, 9.46; S, 10.83, NMR δ(¹H): 0.92 (t, 6H, CH₃CH₂CH₂C(O)-), 1.13 + 1.25 (t + t, 12H, -N(CH₂CH₃)₂), 1.65 (m, 4H, CH₃CH₂CH₂C(O)-), 2.30 (t, 4H, CH₃CH₂CH₂C(O)-), 3.63 + 3.66 (q + q, 4H + 4H, -N(CH₂CH₃)₂), δ(¹³C): 12.18, 12.67, 13.66, 19.61, 42.28, 45.16, 46.33, 165.97, 177.50.

cis-bis(*N,N*-dibutyl-*N'*-butanoylthioureato)platinum(II) ([Pt(L³-S,O)₂] - table 5.1a): 86.6% yield, oil, Calculated for C₂₆H₅₀N₄O₂PtS₂: C, 43.98; H, 7.11; N, 7.89; S, 9.03, Found: C, 44.77; H, 7.30; N, 7.95; S, 9.05, NMR δ(¹H): 0.93 (unres m, 18H, CH₃CH₂CH₂C(O)-, -N(CH₂CH₂CH₂CH₃)₂), 1.31 (m, 8H, -N(CH₂CH₂CH₂CH₃)₂), 1.60 (unres m, 12H, CH₃CH₂CH₂C(O)-, -N(CH₂CH₂CH₂CH₃)₂), 2.30 (t, 4H, CH₃CH₂CH₂C(O)-), 3.59 (t, 8H, -N(CH₂CH₂CH₂CH₃)₂), δ(¹³C): 13.86, 19.82, 20.20, 29.27, 29.84, 42.47, 50.89, 52.16, 166.57, 177.49, δ(¹⁹⁵Pt): -2745.

cis-bis(*N*-piperidyl-*N'*-butanoylthioureato)platinum(II) ([Pt(L⁴-S,O)₂] - table 5.1a): 23.8% yield, mp 83 – 85°C, Calculated for C₂₀H₃₄N₄O₂PtS₂: C, 38.63; H, 5.52; N, 9.01; S, 10.32, Found: C, 38.68; H, 5.69; N, 8.83; S, 9.77, NMR δ(¹H): 0.93 (t, 6H, CH₃CH₂CH₂C(O)-), 1.64 (unres m, 16H, CH₃CH₂CH₂C(O)-, -N<(CH₂CH₂)₂>CH₂), 2.31 (t, 4H, CH₃CH₂CH₂C(O)-), 3.90 (br unres t, 8H, -N<(CH₂CH₂)₂>CH₂), δ(¹³C): 13.84, 19.94, 24.49, 25.87, 42.61, 47.89, 50.34, 166.15, 178.42, δ(¹⁹⁵Pt): -2760.

cis-bis(*N*-morpholino-*N'*-butanoylthioureato)platinum(II) ([Pt(L⁵-S,O)₂] - table 5.1a): 85.7% yield, mp 161 – 164°C, Calculated for C₁₈H₃₀N₄O₄PtS₂: C, 34.55; H, 4.84; N, 8.96; S, 10.25, Found: C, 34.48; H, 4.60; N, 8.69; S, 10.18, NMR δ(¹H): 0.93 (t, 6H, CH₃CH₂CH₂C(O)-), 1.66 (m, 4H, CH₃CH₂CH₂C(O)-), 2.32 (t, 4H, CH₃CH₂CH₂C(O)-) 3.68 + 3.72 + 3.95 + 4.00 (br unres t + br unres t + br unres t + br unres t, 4H + 4H + 4H + 4H, -N<(CH₂CH₂)₂>O), δ(¹³C): 13.76, 19.81, 42.60, 46.75, 49.14, 66.10, 66.48, 167.39, 179.11.

cis-bis(*N*-cis-2,6-dimethylpiperidyl-*N'*-butanoylthioureato)platinum(II) ([Pt(L⁶-S,O)₂] - table 5.1a): 88.7% yield, oil, Calculated for C₂₄H₄₂N₄O₂PtS₂: C, 42.52; H, 6.26; N, 8.27; S, 9.46, Found: C, 42.77; H, 6.43; N, 8.16; S, 9.29, NMR δ(¹H): 0.92 (t, 6H, CH₃CH₂CH₂C(O)-), 1.19 + 1.33 (d + d, 6H + 6H, -N<(CH(CH₃)CH₂)₂>CH₂), 1.60 (br unres m, -N<(CH(CH₃)CH₂)₂>CH₂), 1.65 (m, CH₃CH₂CH₂C(O)-), 2.32 (t, 4H, CH₃CH₂CH₂C(O)-), 5.05 + 5.36 (m + m, 2H + 2H, -N<(CH(CH₃)CH₂)₂>CH₂), δ(¹³C): 13.95 (br), 19.72 (br), 30.25 (br), 42.57, 48.76, 51.14, 166.61, 177.61.

cis-bis(*N,N*-dimethyl-*N'*-(2,2-dimethylpropanoyl)thioureato)platinum(II) ([Pt(L⁷-S,O)₂] - table 5.1a): 90.0% yield, mp 219 – 220°C, Calculated for C₁₆H₃₀N₄O₂PtS₂: C, 33.73; H, 5.32; N, 9.84; S, 11.26, Found: C, 34.21; H, 5.39; N, 9.62; S, 11.21, NMR δ(¹H): 1.20 (s, 18H, (CH₃)₃CC(O)-), 3.22 (s, 12H, -N(CH₃)₂), δ(¹³C): 28.32, 40.43, 41.52, 42.27, 167.83, 183.27.

cis-bis(*N,N*-diethyl-*N'*-(2,2-dimethylpropanoyl)thioureato)platinum(II) ([Pt(L⁸-S,O)₂] - table 5.1a): 89.0% yield, mp 162 – 165°C, Calculated for C₂₀H₃₈N₄O₂PtS₂: C, 38.38; H, 6.13; N, 8.95; S, 10.25, Found: C, 38.77; H, 6.26; N, 8.24; S, 10.24, NMR δ(¹H): 1.19 (s, 18H, (CH₃)₃CC(O)-), 1.14 + 1.26 (t + t, 6H + 6H, -N(CH₂CH₃)₂), 3.64 (unres m, 8H, -N(CH₂CH₃)₂), δ(¹³C): 12.41, 12.83, 28.19, 42.05, 45.48, 46.59, 166.59, 182.93.

cis-bis(*N,N*-dibutyl-*N'*-(2,2-dimethylpropanoyl)thioureato)platinum(II) ([Pt(L⁹-S,O)₂] - table 5.1a): 100% yield, mp 149 – 152°C, Calculated for C₂₈H₅₄N₄O₂PtS₂: C, 45.56; H, 7.39; N, 7.59; S, 8.69, Found: C, 45.78; H, 7.62; N, 7.73; S, 8.71, NMR δ(¹H): 0.90 + 0.94 (t + t, 6H + 6H, -N(CH₂CH₂CH₂CH₃)₂), 1.20 (s, 18H, (CH₃)₃CC(O)-), 1.32 (m, 8H, -N(CH₂CH₂CH₂CH₃)₂), 1.56 + 1.69 (m + m, 4H + 4H, -N(CH₂CH₂CH₂CH₃)₂), 3.58 (t, 8H, -N(CH₂CH₂CH₂CH₃)₂), δ(¹³C): 13.86, 20.28, 28.23, 29.26, 29.82, 42.07, 51.19, 52.28, 167.01, 182.77, δ(¹⁹⁵Pt): -2748.

cis-bis(*N*-piperidyl-*N'*-(2,2-dimethylpropanoyl)thioureato)platinum(II) ([Pt(L¹⁰-S,O)₂] - table 5.1a): 98.2% yield, mp 211 – 214°C, Calculated for C₂₂H₃₈N₄O₂PtS₂: C, 40.66; H, 5.91; N, 8.62; S, 9.87, Found: C, 40.76; H, 5.98; N, 8.70; S, 9.80, NMR δ(¹H): 1.20 (s, 18H, (CH₃)₃CC(O)-), 1.61 (unres m, 12H, -N<(CH₂CH₂)₂>CH₂), 3.92 (br unres t, 8H, -N<(CH₂CH₂)₂>CH₂), δ(¹³C): 24.53, 25.83, 28.30, 42.27, 48.01, 50.39, 166.67, 183.66, δ(¹⁹⁵Pt): -2764.

cis-bis(*N*-morpholino-*N'*-(2,2-dimethylpropanoyl)thioureato)platinum(II) ([Pt(L¹¹-S,O)₂] - table 5.1a): 93.2% yield, mp 215 – 217°C, Calculated for C₂₀H₃₄N₄O₄PtS₂: C, 36.74; H, 5.25; N, 8.57; S, 9.81, Found: C, 37.13; H, 5.28; N, 8.64; S, 9.90, NMR δ(¹H): 1.19 (s, 18H, (CH₃)₃CC(O)-), 3.69 (br unres t, 8H, -N<(CH₂CH₂)₂>O), 3.97 (br unres t, 8H, -N<(CH₂CH₂)₂>O), δ(¹³C): 28.23, 42.43, 46.84, 49.27, 66.33, 167.98, 184.37.

cis-bis(*N*-pyrrolidyl-*N'*-(2,2-dimethylpropanoyl)thioureato)platinum(II) ([Pt(L¹²-S,O)₂] - table 5.1a): 84.8% yield, mp 227 – 229°C, Calculated for C₂₀H₃₄N₄O₂PtS₂: C, 38.63; H, 5.52; N, 9.01; S, 10.31, Found: C, 38.77; H, 5.59; N, 9.05; S, 10.16, NMR δ(¹H): 1.19 (s, 18H, (CH₃)₃CC(O)-), 1.93 (m, 8H, -N<(CH₂CH₂)₂), 3.54 + 3.64 (t + t, 4H + 4H, -N<(CH₂CH₂)₂), δ(¹³C): 24.72, 25.30, 42.13, 49.99, 164.31, 182.92.

cis-bis(*N,N*-dimethyl-*N'*-acetylthioureato)platinum(II) ([Pt(L¹³-S,O)₂] - table 5.1a): 35.3% yield, mp 201 – 204°C, Calculated for C₁₀H₁₈N₄O₂PtS₂: C, 24.74; H, 3.74; N, 11.54; S, 13.21, Found: C, 25.03; H, 3.71; N, 11.60; S, 13.34, NMR δ(¹H): 2.10 (s, 6H, CH₃C(O)-), 3.21 (s, 12H, -N(CH₃)₂), δ(¹³C): 27.92, 40.39, 41.58, 167.40, 175.38, δ(¹⁹⁵Pt): -2745.

cis-bis(*N,N*-dibutyl-*N'*-(2-methylpropanoyl)thioureato)platinum(II) ([Pt(L¹⁴-S,O)₂] - table 5.1a): 100% yield, mp 64 – 66°C, Calculated for C₂₆H₅₀N₄O₂PtS₂: C, 43.98; H, 7.11; N, 7.89; S, 9.03, Found: C, 44.17; H, 7.29; N, 8.01; S, 8.99, NMR δ(¹H): 0.90 + 0.94 (t + t, 6H + 6H, -N(CH₂CH₂CH₂CH₃)₂), 1.15 (d, 12H,

$\text{CH}_3\text{CH}(\text{CH}_3)\text{C}(\text{O})-$, 1.30 (m, 8H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.56 + 1.69 (m + m, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 2.60 (m, 2H, $\text{CH}_3\text{CH}(\text{CH}_3)\text{C}(\text{O})-$), 3.60 (unres t + t, 8H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), $\delta(^{13}\text{C})$: 13.81, 13.87, 20.24, 29.28, 29.70, 29.84, 39.18, 51.02, 52.25, 166.91, 181.26, $\delta(^{195}\text{Pt})$: -2746.

cis-bis(*N,N*-dimethyl-*N'*-benzoylthioureato)platinum(II) ([Pt(L¹⁵-S,O)₂] - table 5.1b): 93.9% yield, mp 212 - 214°C, Calculated for C₂₀H₂₂N₄O₂PtS₂: C, 39.40; H, 3.64; N, 9.19; S, 10.52, Found: C, 39.58; H, 3.64; N, 8.94; S, 10.45, NMR $\delta(^1\text{H})$: 3.33 + 3.42 (s + s, 6H + 6H, $-\text{N}(\text{CH}_3)_2$), 7.45 (m, 6H, $\text{O}(3,4,5)$), 8.29 (d, 4H, $\text{O}(2,6)$), $\delta(^{13}\text{C})$: 40.82, 41.90, 128.07, 129.41, 131.48, 137.48, 168.40, 168.68.

cis-bis(*N,N*-dibutyl-*N'*-benzoylthioureato)platinum(II) ([Pt(L¹⁶-S,O)₂] - table 5.1b): 82.2% yield, mp 161 - 162°C (lit ³⁶: 164 - 166°C), Calculated for C₃₂H₄₆N₄O₂PtS₂: C, 49.40; H, 5.97; N, 7.20; S, 8.24, Found: C, 49.63; H, 6.03; N, 7.01; S, 8.46, NMR $\delta(^1\text{H})$: 0.94 + 0.97 (t + t, 12H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.39 (m, 8H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.72 (m, 8H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 3.68 + 3.78 (t + t, 8H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 7.42 (m, 6H, $\text{O}(3,4,5)$), 8.25 (d, 4H, $\text{O}(2,6)$), $\delta(^{13}\text{C})$: 13.87, 20.31, 29.28, 29.99, 51.51, 52.61, 128.01, 129.37, 131.29, 137.61, 167.40, 168.29.

cis-bis(*N*-piperidyl-*N'*-benzoylthioureato)platinum(II) ([Pt(L¹⁷-S,O)₂] - table 5.1b): 93.6% yield, mp 195 - 198°C, Calculated for C₂₆H₃₀N₄O₂PtS₂: C, 45.27; H, 4.39; N, 8.12; S, 9.30, Found: C, 45.39; H, 4.39; N, 8.24; S, 9.16, NMR $\delta(^1\text{H})$: 1.72 (br unres m, 12H, $-\text{N}(\text{CH}_2\text{CH}_2)_2>\text{CH}_2$), 3.99 + 4.19 (unres t + unres t, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2)_2>\text{CH}_2$), 7.44 (m, 6H, $\text{O}(3,4,5)$), 8.25 (d, 4H, $\text{O}(2,6)$), $\delta(^{13}\text{C})$: 24.50, 25.97, 48.39, 50.67, 128.07, 129.46, 131.40, 137.68, 167.14, 169.22.

cis-bis(*N*-morpholino-*N'*-benzoylthioureato)platinum(II) ([Pt(L¹⁸-S,O)₂] - table 5.1b): 95.7% yield, mp 214 - 216°, Calculated for C₂₄H₂₆N₄O₄PtS₂: C, 41.55; H, 3.79; N, 8.08; S, 9.25, Found: C, 41.79; H, 3.70; N, 8.11; S, 9.19, NMR $\delta(^1\text{H})$: 3.78 (t, 8H, $-\text{N}(\text{CH}_2\text{CH}_2)_2>\text{O}$), 4.05 + 4.18 (br unres t + br unres t, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2)_2>\text{O}$), 7.42 (dd, 4H, $\text{O}(3,5)$), 7.54 (t, 2H, $\text{O}(4)$), 8.23 (d, 4H, $\text{O}(2,6)$), $\delta(^{13}\text{C})$: 47.24, 49.42, 66.28, 66.52, 128.21, 129.47, 131.82, 137.20, 168.46, 169.73.

cis-bis(*N*-pyrrolidyl-*N'*-benzoylthioureato)platinum(II) ([Pt(L¹⁹-S,O)₂] - table 5.1b): 92.6% yield, mp 209 - 210°C, Calculated for C₂₄H₂₆N₄O₂PtS₂: C, 43.56; H, 3.97; N, 8.47; S, 9.69, Found: C, 43.94; H, 3.95; N, 8.37; S, 9.72, NMR $\delta(^1\text{H})$: 2.03 (m, 8H, $-\text{N}(\text{CH}_2\text{CH}_2)_2$), 3.65 + 3.88 (t + t, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2)_2$), 7.40 (dd, 4H, $\text{O}(3,5)$), 7.51 (t, 2H, $\text{O}(4)$), 8.32 (d, 4H, $\text{O}(2,6)$), $\delta(^{13}\text{C})$: 24.84, 25.32, 50.42, 50.52, 128.02, 129.42, 131.41, 137.53, 164.81, 168.25.

cis-bis(*N*-(*cis*-2,6-dimethylpiperidyl)-*N'*-benzoylthioureato)platinum(II) ([Pt(L²⁰-S,O)₂] - table 5.1b): 73.0% yield, mp: 176 - 180°C, Calculated for C₃₀H₃₈N₄O₂PtS₂: C, 48.30; H, 5.15; N, 7.51; S, 8.60 Found: C, 47.62; H, 4.98; N, 7.23; S, 9.00, NMR $\delta(^1\text{H})$: 1.38 (dd, 12H, $-\text{N}(\text{CH}(\text{CH}_3)\text{CH}_2)_2>\text{CH}_2$), 1.70 (br unres m, 12H, $-\text{N}(\text{CH}(\text{CH}_3)\text{CH}_2)_2>\text{CH}_2$), 5.15 + 5.57 (unres m + unres m, 4H, $-\text{N}(\text{CH}(\text{CH}_3)\text{CH}_2)_2>\text{CH}_2$), 7.44 (dd,

4H, $\delta(3,5)$), 7.51 (t, 2H, $\delta(4)$), 8.24 (d, 4H, $\delta(2,6)$), $\delta(^{13}\text{C})$: 14.05, 19.99, 20.08, 30.35, 49.44, 51.50, 128.08, 129.46, 131.30, 137.91, 167.62, 168.53.

cis-bis(*N*-piperidyl-*N'*-(*p*-methoxybenzoyl)thioureato)platinum(II) ([Pt(L²¹-S,O)₂] - table 5.1b): 95.8% yield, mp 199 - 200°C, Calculated for C₂₈H₃₄N₄O₄PtS₂: C, 44.84; H, 4.58; N, 7.47; S, 8.55, Found: C, 44.81; H, 4.59; N, 7.39; S, 8.51, NMR $\delta(^1\text{H})$: 1.69 (br unres m, 12H, -N<(CH₂CH₂)₂>CH₂), 3.86 (s, 6H, δ -OCH₃) 3.98 + 4.09 (unres t + unres t, 4H + 4H, -N<(CH₂CH₂)₂>CH₂), 6.91 (d, 4H, $\delta(3,5)$), 8.20 (d, 4H, $\delta(2,6)$), $\delta(^{13}\text{C})$: 24.52, 25.96, 48.21, 50.52, 55.36, 113.30, 130.18, 131.41, 162.37, 166.77, 168.99.

cis-bis(*N*-piperidyl-*N'*-(*p*-chlorobenzoyl)thioureato)platinum(II) ([Pt(L²²-S,O)₂] - table 5.1b): 93.1% yield, mp 210 - 211°C, Calculated for C₂₆H₂₈ClN₄O₂PtS₂: C, 41.16; H, 3.73; N, 7.39; S, 8.45, Found: C, 41.10; H, 3.72; N, 7.01; S, 8.34, NMR $\delta(^1\text{H})$: 1.70 (br m, 12H, -N<(CH₂CH₂)₂>CH₂), 3.98 + 4.08 (unres t + unres t, 4H + 4H, -N<(CH₂CH₂)₂>CH₂), 7.37 (d, 4H, $\delta(3,5)$), 8.14 (d, 4H, $\delta(2,6)$), $\delta(^{13}\text{C})$: 24.42, 25.91, 26.00, 48.47, 50.74, 128.33, 130.72, 136.14, 137.64, 167.14, 168.14.

cis-bis(*N*-piperidyl-*N'*-(*p*-nitrobenzoyl)thioureato)platinum(II) ([Pt(L²³-S,O)₂] - table 5.1b): 95.7% yield, mp 211 - 212°C, Calculated for C₂₆H₂₈N₆O₆PtS₂: C, 40.04; H, 3.63; N, 10.78; S, 8.22, Found: C, 40.04; H, 5.53; N, 10.54; S, 7.98, NMR $\delta(^1\text{H})$: 1.74 (br unres m, 12H, -N<(CH₂CH₂)₂>CH₂), 4.00 + 4.10 (unres t + unres t, 4H + 4H, -N<(CH₂CH₂)₂>CH₂), 8.30 (q, 8H, $\delta(3,5,2,6)$), $\delta(^{13}\text{C})$: 24.31, 25.85, 26.04, 48.79, 50.99, 123.30, 130.09, 143.45, 149.45, 166.73, 167.37.

5.6.2.2 *N,N*-substituted *N'*-(3,4,5-trimethoxybenzoyl)thiourea ligands and Pt(II) complexes

***N,N*-diethyl-*N'*-(3,4,5-trimethoxybenzoyl)thiourea (HL²⁴ - table 5.6):** 89.5% yield, mp 158 - 161°C, Calculated for C₁₅H₂₂N₂O₄S: C, 55.18; H, 6.81; N, 8.58; S, 9.82, Found: C, 55.11; H, 6.95; N, 8.67; S, 9.62, NMR $\delta(^1\text{H})$: 1.30 (unres t, 6H, -N(CH₂CH₃)₂), 3.54 + 3.97 (unres q + unres q, 2H + 2H, -N(CH₂CH₃)₂), 3.85 (s, 3H, δ -OCH₃(4)), 3.87 (s, 6H, δ -OCH₃(3,5)), 7.04 (s, 2H, $\delta(2,6)$), 8.82 (br s, 1H, >N'H), $\delta(^{13}\text{C})$: 11.41, 13.29, 47.55, 47.70, 56.38, 60.91, 105.22, 127.36, 142.04, 153.13, 163.33, 179.61.

***N,N*-dibutyl-*N'*-(3,4,5-trimethoxybenzoyl)thiourea (HL²⁵ - table 5.6):** 96.2% yield, mp 100 - 102°C, Calculated for C₁₉H₃₀N₂O₄S: C, 59.64; H, 7.92; N, 7.32; S, 8.38, Found: C, 59.58; H, 8.30; N, 7.36; S, 8.04, NMR $\delta(^1\text{H})$: 0.89 + 0.97 (t + t, 3H + 3H, -N(CH₂CH₂CH₂CH₃)₂), 1.28 + 1.43 (m + m, 2H + 2H, -N(CH₂CH₂CH₂CH₃)₂), 1.64 + 1.77 (m + m, 2H + 2H, -N(CH₂CH₂CH₂CH₃)₂), 3.50 + 3.96 (t + t, 2H + 2H, -N(CH₂CH₂CH₂CH₃)₂), 3.88 (s, 9H, δ -OCH₃(3,4,5)), 7.04 (s, 2H, $\delta(2,6)$), 8.68 (br s, 1H, >N'H), $\delta(^{13}\text{C})$: 13.69, 13.82, 19.98, 28.41, 30.08, 52.81, 53.03, 56.37, 60.89, 105.16, 127.44, 142.07, 153.17, 163.11, 179.93.

***N*-morpholino-*N'*-(3,4,5-trimethoxybenzoyl)thiourea (HL²⁶ - table 5.6):** 84.6% yield, mp 98 - 101°C, Calculated for C₁₅H₂₀N₂O₅S: C, 52.92; H, 5.93; N, 8.23; S, 9.42, Found: C, 53.15; H, 5.91; N, 8.34; S, 9.28,

NMR $\delta(^1\text{H})$: 3.81 (br unres t, 4H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2 > \text{O}$), 3.62 + 4.21 (br unres t + br unres t, 2H + 2H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2 > \text{O}$), 3.88 (s, 9H, $\text{O}-\text{OCH}_3(3,4,5)$), 7.03 (s, 2H, $\text{O}(2,6)$), 8.67 (br s, 1H, $>\text{N}^{\text{H}}$), $\delta(^{13}\text{C})$: 51.54, 52.37, 60.94, 66.17, 105.21, 127.10, 142.39, 153.27, 162.92, 179.27.

cis-bis(*N,N*-diethyl-*N'*-(3,4,5-trimethoxybenzoyl)thioureato)platinum(II) ($[\text{Pt}(\text{L}^{24}-\text{S},\text{O})_2]$ - table 5.6): 93.9% yield, mp 218 - 220°C, Calculated for $\text{C}_{30}\text{H}_{42}\text{N}_4\text{O}_8\text{PtS}_2$: C, 42.59; H, 5.01; N, 6.62; S, 7.58, Found: C, 42.94; H, 5.06; N, 6.60; S, 7.48, NMR $\delta(^1\text{H})$: 1.30 + 1.33 (t + t, 3H + 3H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.79 (m, 4H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.88 (s, 6H, $\text{O}-\text{OCH}_3(3,5)$), 3.90 (s, 3H, $\text{O}-\text{OCH}_3(4)$), 7.57 (s, 2H, $\text{O}(2,6)$), $\delta(^{13}\text{C})$: 12.51, 13.16, 46.07, 47.12, 56.41, 60.84, 107.52, 132.96, 141.69, 152.69, 166.97, 167.98, $\delta(^{195}\text{Pt})$: -2731.

cis-bis(*N,N*-dibutyl-*N'*-(3,4,5-trimethoxybenzoyl)thioureato)platinum(II) ($[\text{Pt}(\text{L}^{25}-\text{S},\text{O})_2]$ - table 5.6): 92.4% yield, mp 125 - 127°C, Calculated for $\text{C}_{38}\text{H}_{58}\text{N}_4\text{O}_8\text{PtS}_2$: C, 47.63; H, 6.11; N, 5.85; S, 6.72, Found: C, 47.45; H, 6.36; N, 5.86; S, 6.47, NMR $\delta(^1\text{H})$: 0.92 + 0.97 (t + t, 6H + 6H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.37 (m, 8H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.71 (m, 8H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 3.71 (unres t + t, 8H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 3.87 (s, 12H, $\text{O}-\text{OCH}_3(3,5)$), 3.89 (s, 6H, $\text{O}-\text{OCH}_3(4)$), 7.54 (s, 4H, $\text{O}(2,6)$), $\delta(^{13}\text{C})$: 13.81, 13.96, 20.26, 20.46, 29.29, 30.18, 51.59, 52.72, 56.42, 60.82, 107.49, 132.97, 141.66, 152.68, 167.47, 167.88, $\delta(^{195}\text{Pt})$: -2723.

cis-bis(*N*-morpholino-*N'*-(3,4,5-trimethoxybenzoyl)thioureato)platinum(II) ($[\text{Pt}(\text{L}^1-\text{S},\text{O})_2]$ - table 5.6): 97.1% yield, mp 222 - 224°C, Calculated for $\text{C}_{30}\text{H}_{38}\text{N}_4\text{O}_{10}\text{PtS}_2$: C, 41.23; H, 4.39; N, 6.41; S, 7.34, Found: C, 40.88; H, 4.31; N, 6.26; S, 7.49, NMR $\delta(^1\text{H})$: 3.80 (unres t, 8H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2 > \text{O}$), 4.10 (br unres t, 8H, $-\text{N} < (\text{CH}_2\text{CH}_2)_2 > \text{O}$), 3.89 (s, 12H, $\text{O}-\text{OCH}_3(3,5)$), 3.90 (s, 6H, $\text{O}-\text{OCH}_3(4)$), 7.50 (s, 4H, $\text{O}(2,6)$), $\delta(^{13}\text{C})$: 47.23, 49.47, 56.60, 60.86, 66.40, 107.86, 132.50, 142.24, 152.80, 168.44, 169.35, $\delta(^{195}\text{Pt})$: -2733.

5.6.2.3 *N*-monosubstituted *N'*-acylthiourea products

Orange oil product from *N*-propyl-*N'*-(2,2-dimethylpropanoyl)thiourea (H_2L^{27} - table 5.7): mp 60 – 85°C, Found: C, 35.71; H, 5.87; N, 9.01; S, 10.14, (Calculated for $[\text{Pt}(\text{LH})_2]$ (i.e. $\text{C}_{18}\text{H}_{34}\text{N}_4\text{O}_2\text{PtS}_2$): C, 36.16; H, 5.74; N, 9.37; S, 10.73).

Orange oil product from *N*-butyl-*N'*-(2,2-dimethylpropanoyl)thiourea (H_2L^{28} - table 5.7): mp 50 – 70°C, Found: C, 37.75; H, 6.21; N, 8.71; S, 10.06, (Calculated for $\text{Pt}(\text{LH})_2$ (i.e. $\text{C}_{20}\text{H}_{38}\text{N}_4\text{O}_2\text{PtS}_2$): C, 38.38; H, 6.13; N, 8.95; S, 10.25).

Orange oil product from *N*-propyl-*N'*-butanoylthiourea (H_2L^{29} - table 5.7): mp 75 – 100°C, Found: C, 28.69; H, 4.66; N, 8.04; S, 12.43, (Calculated for $\text{Pt}(\text{LH})_2$ (i.e. $\text{C}_{16}\text{H}_{30}\text{N}_4\text{O}_2\text{PtS}_2$): C, 33.73; H, 5.32; N, 9.84; S, 11.26).

N,S co-ordinated *trans*-bis(*N*-propyl-*N'*-butanoylthioureato)platinum(II) ([Pt(HL)²⁹-*N,S*]₂) - table 5.7): 34.7% yield, mp 173 – 175°C, Calculated for C₁₆H₃₀N₄O₂PtS₂: C, 33.73; H, 5.32; N, 9.84; S, 11.26, Found: C, 34.16; H, 5.25; N, 9.89; S, 11.24, NMR δ(¹H): 0.90 (t, 6H, CH₃CH₂CH₂C(O)-), 0.96 (t, 6H, -NHCH₂CH₂CH₃), 1.60 (m, 8H, CH₃CH₂CH₂C(O)-, -NHCH₂CH₂CH₃), 2.99 (t, 4H, CH₃CH₂CH₂C(O)-), 3.27 (m, 4H, -NHCH₂CH₂CH₃), 10.58 (br s, 2H, -NHCH₂CH₂CH₃), δ(¹³C): 11.26, 13.71, 18.14, 22.07, 39.20, 43.80, 180.98, 191.13, δ(¹⁹⁵Pt): -2451.

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CHAPTER 6

University of Cape Town

Bipodal *N*-substituted *N'*-acyl- and *N'*-benzoylthioureas

General Introduction

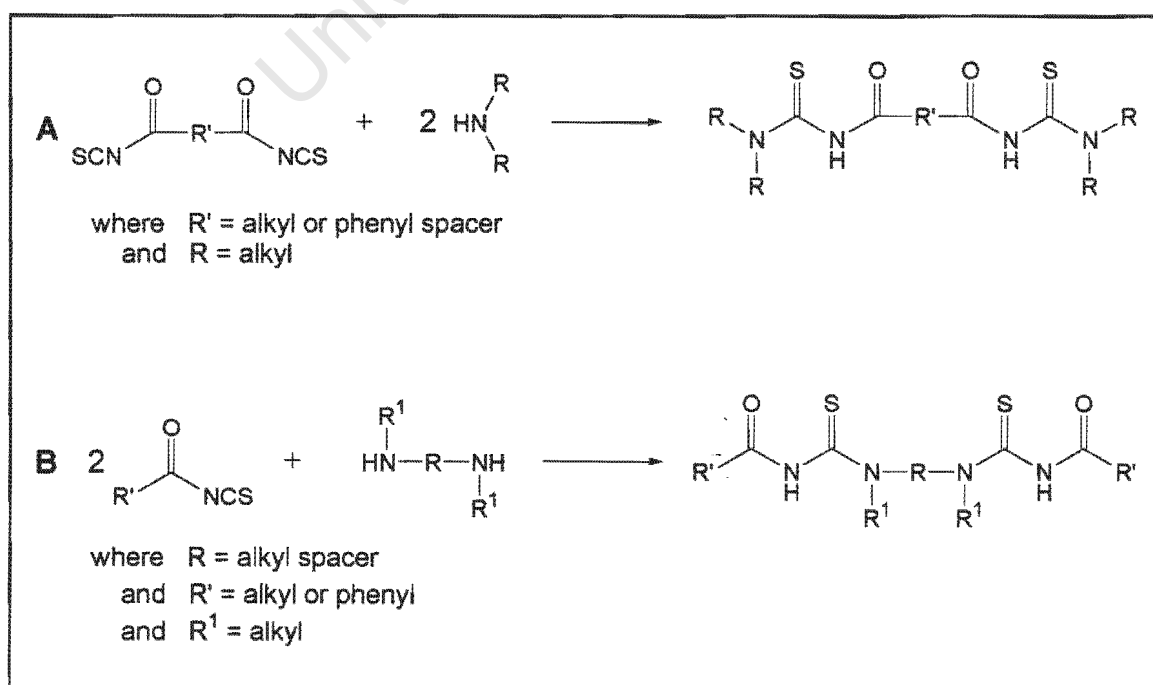
It was pointed out in chapter 1, that an early goal for this project was to test a variety of novel bipodal *N'*-acyl and *N'*-aroylthioureas as selective chelating ligands for the solvent extraction and chromatographic separation of Pt, Pd, and possibly, the other PGMs. However, with the unexpected failure to obtain the desired ligands from the reactions of adipoyl isothiocyanate with piperidine and pyrrolidine, the overall investigation became focused on the synthesis of the simple *N'*-acyl and *N'*-aroylthioureas instead. Once the variables affecting these reactions were better understood, it seemed necessary and appropriate to study the synthesis of the bipodal ligands on a more methodical basis as well. The results of this study are presented and discussed in Part A below. Testing the ligand properties of these compounds, however, was undertaken on a much smaller scale than originally intended, and was again restricted to an investigation of the Pt(II) and, in this instance, some Pd(II) co-ordination chemistry. The various complexes are described in Part B.

Part A: Synthesis and characterisation of bipodal *N'*-acyl and *N'*-benzoylthioureas

6.1 Introduction

In chapter 1, the bipodal *N'*-acyl- and *N'*-aroylthioureas were described as ligands with two -C(O)-NH-C(S)- chelating moieties linked to each other by a spacer group. They are relatively novel compounds, and only a limited number are described in the literature^{1,2}. According to the reports, these were all synthesised by the Douglass and Dains process, either, by converting a difunctional acid chloride to the isothiocyanate and then reacting it with two equivalents of secondary amine (A, figure 6.1), or alternatively, by reacting a diamine with two equivalents of a simple acyl or aroyl isothiocyanate (B, figure 6.1). The former approach results in a bipodal ligand with the donor atom sequence SO-OS on either side of the spacer group, while the latter method produces a compound with OS-SO donor atom sequence. König *et al.*² synthesised a few examples of the first type using linear diacyl chlorides and, significantly, only diethylamine or longer chain dialkylamines for the *N* substituents. They reported that the yields from these reactions ranged between 60 and 80%. Köhler *et al.*¹, on the other hand, produced examples of both types, using terephthaloyl and isophthaloyl chlorides for the SO-OS ligands, and a variety of difunctional amines for the OS-SO ligands. However, the yields reported for these reactions were consistently poor, and only ranged between 10 and 40 %. Surprisingly, the authors made no attempts to explain the reasons for these low values.

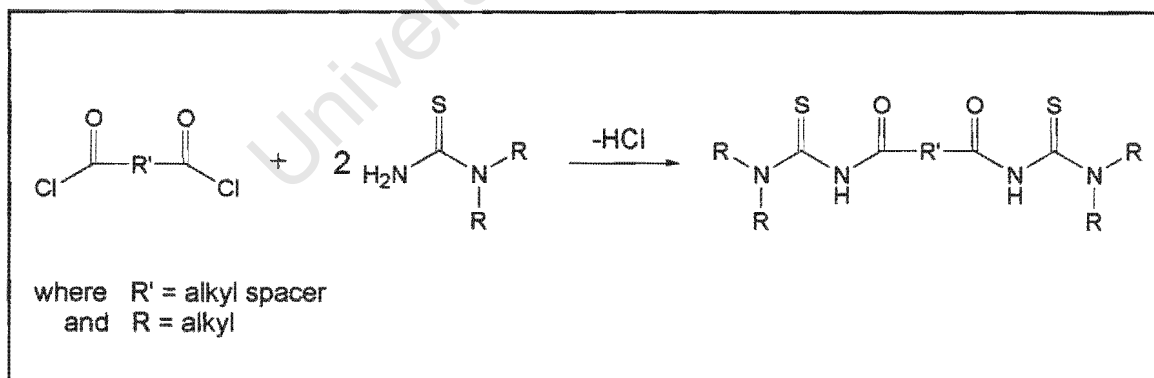
Figure 6.1 Synthesis of bipodal *N'*-acyl- and *N'*-aroylthioureas from difunctional acids (A) or from diamines (B)



Based on the results in chapters 2 and 3, it seemed reasonable to expect that Douglass and Dains type reactions with difunctional acid chlorides or diamines might yield, in addition to the targeted bipodal ligands, two possible side-products: an asymmetric compound with an acyl/aroylthiourea moiety and an amidic moiety on opposite sides of the spacer group, and a symmetric product with only amidic moieties on either end of the spacer. Furthermore, it was considered likely that the final mixture of target ligand and these side-products would depend on the same steric and electronic factors that influenced the outcome of the simple amine – acyl/aroyl isothiocyanate reactions. For these reasons, the qualitative investigations described in chapters 2 and 3 were essentially extended to include reactions with a series of difunctional acid chlorides and diamines. However, in most of these reactions the final yield of the targeted bipodal *N'*-acyl or *N'*-aroylthiourea was either very high (> 80%) or else very low (< 20%), and with the benefit of the data gathered from the simple isothiocyanate – amine reactions, it was considerably easier to recognise the link between such a result and a particular steric or electronic property of one of the reagents. It was therefore considered unnecessary to recover the symmetric and asymmetric side-products from each reaction, and accordingly, only in a limited number of cases were these byproducts isolated and characterised.

For the synthesis of bipodal *N'*-acylthioureas with dimethylamine or cyclic amines as the *N* substituents, the Douglass and Dains process proved wholly unsuitable. As a result, these compounds had to be prepared by following Dixon and Hawthorne's³ approach i.e. by adding an appropriately substituted thiourea directly to the diacyl chloride (see figure 6.2).

Figure 6.2 Synthesis of bipodal *N'*-acylthioureas by addition of *N*-substituted thiourea to a difunctional acyl chloride



6.2 Nomenclature and Collective Terminology

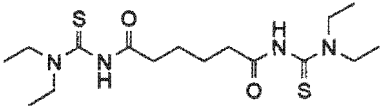
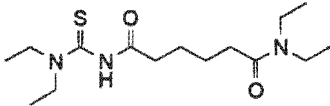
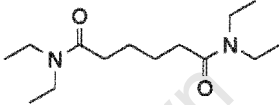
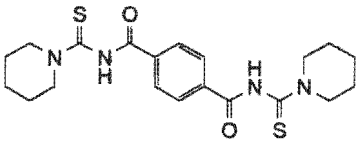
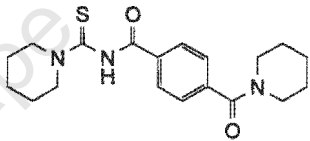
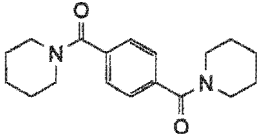
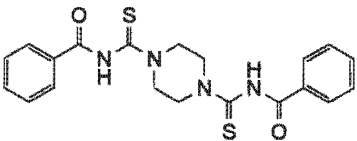
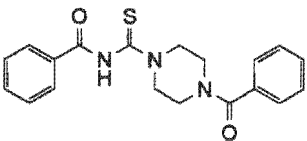
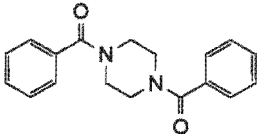
To simplify the following discussions and to avoid any confusion, it is appropriate at this stage to introduce some collective terminology and to address the issue of product nomenclature. The bipodal ligands have been divided into three subgroups: acylbis(thioureas), aroylbis(thioureas) and aminebis(thioureas). As is explained below, this subdivision is based on the spacer linking the two chelating moieties. However, where

these compounds are discussed collectively, and where it has been unnecessary to distinguish *N*-acyl'- from *N'*-aroylthiourea variants, they are simply referred to as *bipodal thioureas*. The two possible side-products, on the other hand, are distinguished as the *amidic products*, or more specifically as the *asymmetric* and *symmetric amides*.

As was the case for the simple *N*-substituted *N'*-acyl- and *N'*-aroylthioureas, the formal IUPAC nomenclature for the bipodal ligands and the amidic side-products is complicated and does not lend itself to a convergent system of classification for these compounds. The bipodal *N'*-acylthioureas, for example, are named, either as thioureas, amides, or as derivatised dioic acids, depending on their *N* substituents and their spacer groups (see table A8.2, appendix 8 for examples). A more uniform naming system that is appropriate in the context of a group discussion of *N'*-acyl- and *N'*-aroylthioureas, was applied by König *et al.*², and is illustrated by examples in table 6.1. They classified their SO-OS type bipodal *N'*-acylthioureas (i.e. those with alkyl chain spacers) as *acylbis(thioureas)*, and retained the trivial name of the diacid from which a particular compound was derived. For example, the bipodal *N'*-acylthiourea derived from adipoyl chloride, was given the name adipoylbis(thiourea). However, the common practice of distinguishing the two thiourea nitrogens on either side of the thiocarbonyl carbon as *N* and *N'* presents a complication, since each bipodal compound contains two such sets of nitrogens. König *et al.*² resolved this problem by reverting to the system where the acyl substituted nitrogen (i.e. the amidic *N'* nitrogen) is assigned the position 1, while the alkyl substituted nitrogen (*N*) is assigned the position 3. To distinguish between the analogous sets of nitrogens on either side of the linking spacer, they used the notation 1,1' and 3,3'. Thus, the adipoylbis(thiourea) derived by reacting adipoyl isothiocyanate with two equivalents of diethylamine was named as 3,3,3',3'-tetraethyl-1,1'-adipoylbis(thiourea) (**1a**, table 6.1). This system of nomenclature is convenient, and can also be consistently applied to the SO-OS bipodal *N'*-aroylthioureas that are derived from reagents like terephthallic or isophthallic acid (see **2a**, table 6.1). In the text below, these compounds are collectively distinguished as the *aroylbis(thioureas)*.

The trivial names of the parent diacids can also be used for the two side-products formed in these reactions. Furthermore, since both the asymmetric and symmetric compounds essentially retain amidic groups at each end of the spacer, they can both be classed as amides i.e. the two side-products derived from adipoyl isothiocyanate can be distinguished as the asymmetrically and symmetrically substituted adipamides. Since only two nitrogens are found in the symmetric amides, it would seem obvious to distinguish them as *N* and *N'*. However, to avoid confusion with the designation used for the simple *N*-substituted *N'*-acyl and *N'*-aroylthioureas, and because the asymmetric amides contain three nitrogens (i.e. two on the side with the thiourea moiety), the numbering system of 1 and 1' (for the amidic nitrogens on either side of the spacer) was again considered more appropriate. According to this system, the symmetric amidic side-product from the reaction of adipoyl isothiocyanate with diethylamine would be named 1,1,1',1'-tetraethyladipamide (**1c**, table 6.1). For the asymmetric compounds, where an amidic and an acylthiourea moiety are found on opposite ends of the linking spacer, the third nitrogen is designated as the *N* nitrogen. Thus, the asymmetric compound from the reaction of adipoyl isothiocyanate and diethylamine would be named as 1,1-diethyl-1'-(*N,N*-diethylthiocarbamoyl)adipamide (**1b**, table 6.1).

Table 6.1 Examples to illustrate the nomenclature used for the bipodal *N'*-acyl- and *N'*-aroylthioureas, and also the associated symmetric and asymmetric amidic side-products

Bipodal <i>N'</i> -acyl- and <i>N'</i> -aroylthioureas	Amidic side-products
 1a 3,3,3',3'-tetraethyl-1,1'-adipoylbis(thiourea)	 1b 1,1-diethyl-1'-(<i>N,N</i>-diethylthiocarbamoyl)-adipamide
	 1c 1,1,1',1'-tetraethyladipamide
 2a 3,3'-dipiperidyl-1,1'-terephthaloylbis(thiourea)	 2b 1-piperidyl-1'-(<i>N</i>-piperidylthiocarbamoyl)-terephthalamide
	 2c 1,1'-dipiperidylterephthalamide
 3a 1,4-bis(<i>N</i>-benzoylthiocarbamoyl)piperazine	 3b 1-benzoyl-4-(<i>N</i>-benzoylthiocarbamoyl)-piperazine
	 3c 1,4-dibenzoylpiperazine

According to the system applied by König *et al.*², one might have expected to classify the OS-SO type bipodal ligands derived from the difunctional amines as *aminebis(thioureas)* or, to specify the nature of the acyl/aroyl substituent, as *aminebis(acylthioureas)* and *aminebis(aroylthioureas)*. These terms are indeed used in the discussions below, but should be regarded as loosely applied collective names, adopted only to facilitate discussion. Although this system appears to be a logical application of the nomenclature applied for the SO-OS bipodal thioureas derived from the diacids, it is unfortunately flawed. The OS-SO compounds should not be called thioureas because the substituents on either side of the amine spacer are essentially thioamide groups and not complete thiourea moieties i.e. the thiourea nitrogens linked to the spacer must be considered part of the linking group since it is named as an amine. Accordingly, a more correct approach to naming these particular compounds, is to classify them as disubstituted amines. This nomenclature has been used in the following text, but only when referring to specific compounds. For example, the bipodal aroylthiourea formed by reacting piperazine with two equivalents of benzoyl isothiocyanate is named as 1,4-bis(*N*-benzoylthiocarbamoyl)piperazine (**3a**, table 6.1). Similarly, the symmetric and asymmetric side-products from this particular reaction are named as 1,4-dibenzoylpiperazine and 1-(*N*-benzoylthiocarbamoyl)-4-benzoylpiperazine respectively (**3b** and **3c**, table 6.1).

6.3 Experimental Approach

For the synthesis of the acyl- and aroylbis(thioureas) by the Douglass and Dains process, the diacid chlorides were first reacted with two equivalents of potassium thiocyanate. This was followed by the addition of two equivalents of secondary amine. In the case of the *aminebis(thioureas)*, two equivalents of an acyl or benzoyl isothiocyanate were prepared in the normal manner, before one equivalent of the diamine spacer was added to the reaction mixture. The acylbis(thioureas) synthesised using Dixon and Hawthorne's process³, were prepared by reacting two equivalents of *N*-substituted thiourea with a diacyl chloride in the presence of triethylamine base.

Most of the acylbis(thioureas) were derived from adipoyl chloride. Apart from the failed Douglass and Dains reactions with piperidine and pyrrolidine, the isothiocyanate derivative of this diacyl chloride was used in reactions with morpholine, diethylamine and dibutylamine. The adipoyl chloride itself was also added directly to *N,N*-dimethylthiourea and *N*-piperidylthiourea to produce the dimethyl and piperidyl substituted ligands in appreciable yields. The other diacyl chlorides that were used, were suberoyl and succinyl chloride. The former has a six carbon chain spacer and was used in a Douglass and Dains reaction with dibutylamine. Succinyl chloride has a two carbon spacer and was reacted with *N,N*-dimethylthiourea.

The aroylbis(thioureas) for this project were all derived via the Douglass and Dains process from terephthaloyl and isophthaloyl chloride. The former reagent has the acid chloride moieties in *para* positions on the phenyl ring spacer, while the latter has them in meta positions relative to each other. The amines added to the isothiocyanate intermediates were diethylamine, dibutylamine and piperidine.

The diamines chosen as spacers for the synthesis of the aminebis(thioureas) were piperazine and 1,4-dimethylethylenediamine. Each of these reagents was reacted with butanoyl isothiocyanate and with benzoyl isothiocyanate.

All bipodal thiourea products were found to be solids at room temperature, and most of them readily precipitated after the respective reaction mixtures in acetone were poured into water. In the majority of cases the compounds were recovered by filtration, and then subsequently purified by recrystallisation from acetone – water or ethanol – water mixtures. However, in those instances where yields were low, or where the proportions of amidic side-products were also of interest, the product mixtures were extracted into chloroform. They were then separated into their individual components by column chromatography using silica gel columns, and acetone in chloroform solutions as eluents.

6.4 Results and Discussion

The acylbis(thiourea) ligands (ligands H_2L^{30} to H_2L^{36})*, aroylbis(thiourea) ligands (H_2L^{37} - H_2L^{40}) and aminebis(thiourea) ligands (H_2L^{41} to H_2L^{44}) that were synthesised are listed in tables 6.1a, 6.1b and 6.1c respectively, along with their melting points and the yields in which they were obtained. The complete set of characterisation data for each compound can be found in the experimental section (section 6.9). (Yields and characterisation data of any amidic side-products that were recovered and characterised are also given in the experimental section.)

All the products were submitted, as usual, for C, H, N, and S elemental microanalysis, and for ^1H and ^{13}C NMR spectroscopy. However, with some of the bipodal thioureas, samples were also prepared for IR spectroscopy. Although this technique is not often employed in the characterisation of *N,N*-dialkyl-*N'*-acyl- and *N'*-aroylthioureas, it is useful for verifying the presence of NH and C=O groups[†]. These groups have prominent absorption bands near 3200 cm^{-1} and 1700 cm^{-1} respectively. (Because of these prominent bands, the IR spectra of the unbound ligands are useful as reference spectra against which the IR spectra of the metal – ligand complexes can be compared i.e. ligand deprotonation and bidentate *S,O* co-ordination to metal ions like Pt(II) and Pd(II) is characterised by the absence of the NH band, and a 200 cm^{-1} bathochromic shift of the C=O band[‡].)

* In this chapter, the H_2L^n notation has been used exclusively to indicate that the bipodal ligands have two chelating moieties, each with an acidic proton. This should not be confused with the H_2L^n notation that was used for the *N*-monosubstituted *N'*-acylthioureas H_2L^{27} to H_2L^{29} in chapter 5.

† The IR spectra of these compounds are generally regarded as complicated and most of the characteristic absorption bands contained in these spectra have yet to be unambiguously assigned.

Table 6.2a List of acylbis(thiourea) ligands with yields and melting points (ligands H_2L^{30} to H_2L^{33} synthesised by Douglass and Dains process, and ligands H_2L^{34} to H_2L^{36} by acyl chloride – *N*-substituted thiourea addition³⁾)

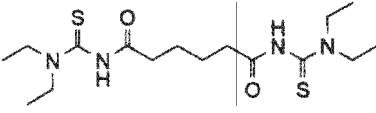
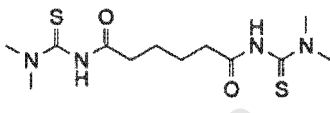
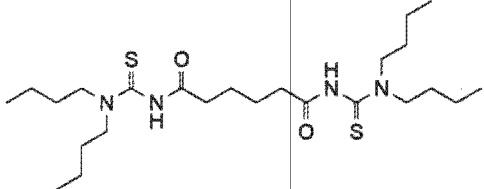
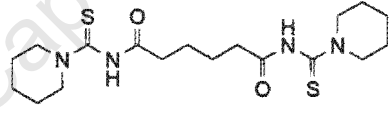
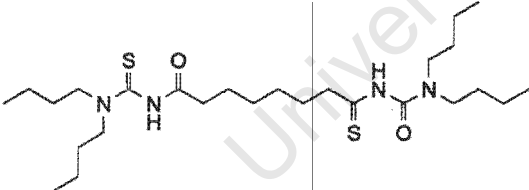
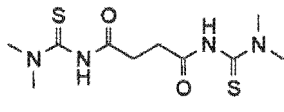
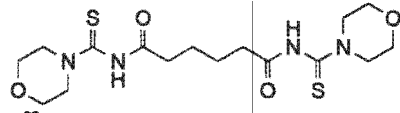
Acylbis(thioureas)	
 H_2L^{30}: 68.4%, mp: 120 – 121°C	 H_2L^{34}: 71.4%, mp: 161 – 163°C
 H_2L^{31}: 78.0%, mp: 128 – 130°C	 H_2L^{35}: 58.7%, mp: 161 – 162°C
 H_2L^{32}: 76.1%, mp: 80 – 82°C	 H_2L^{36}: 15.0%, mp: 160 – 162°C
 H_2L^{33}: 4.8%, mp: 176 – 177°C	

Table 6.2b List of aroylbis(thiourea) ligands with yields and melting points

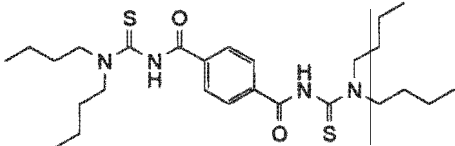
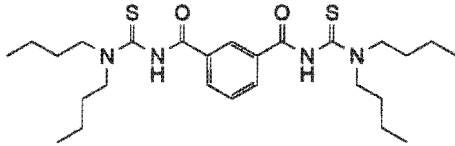
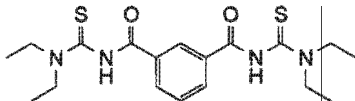
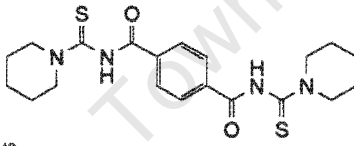
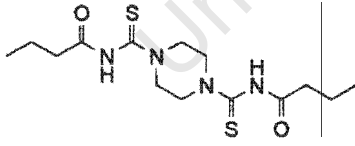
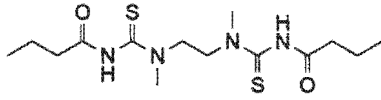
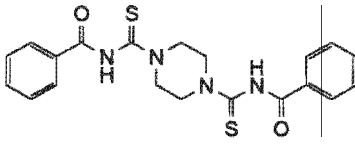
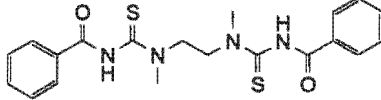
Aroylbis(thioureas)	
 H_2L^{37}: 94.0%, mp: 154 – 155°C	 H_2L^{39}: 79.3%, mp: 100 – 103°C
 H_2L^{38}: 86.7%, mp: 141 – 143°C	 H_2L^{40}: 5.3%, mp: 163 – 165°C

Table 6.2c List of aminebis(thiourea) ligands with yields and melting points

Aminebis(thioureas)	
 H_2L^{41}: 12.1%, mp: 168 – 170°C	 H_2L^{43}: 32.0%, mp: 156 – 158°C
 H_2L^{42}: 72.6%, mp: 190 – 193°C	 H_2L^{44}: 94.7%, mp: 174 – 177°C

6.4.1 The acylbis(thioureas)

The three acylbis(thioureas) synthesised by addition of diethylamine or dibutylamine to either adipoyl or suberoyl isothiocyanate, were obtained in yields that ranged between 65 and 80% (H_2L^{30} – H_2L^{32} , table 6.1a). These results were regarded as satisfactory and appeared to be in good agreement with the results reported by König *et al.*². The analogous reaction with morpholine, however, had a similar outcome to the early reactions with piperidine and pyrrolidine, in that less than 5% of the desired bipodal ligand H_2L^{33} was obtained. In view of the findings of chapter 2, the contrasting results recorded for the two groups of amines (i.e. dialkyl vs. cyclic) were to be expected. Once more, they served to confirm the important steric influence of the amine's β methyl or methylene groups on regioselectivity in an acyl isothiocyanate – amine reaction. The low yield from the morpholine reaction again underlined the tendency of the cyclic amines to form amidic products with sterically unhindered acyl isothiocyanates. (Since dimethylamine was known to behave like a cyclic amine in reactions with acyl isothiocyanates the inconvenient task of introducing this gaseous reagent to a solution of adipoyl isothiocyanate under a nitrogen atmosphere, was not attempted.)

The adipoylbis(thioureas) synthesised by adding *N,N*-dimethylthiourea and *N*-piperidylthiourea directly to adipoyl chloride, were obtained in yields of 71.4 and 58.7% respectively (H_2L^{34} and H_2L^{35}). These values were also regarded as satisfactory, and were seen to emphasize the importance of Dixon and Hawthorne's³ process as an alternative to the problematic reactions between acyl isothiocyanates and cyclic amines. The 15% yield recorded for the succinylbis(thiourea) compound (H_2L^{36}), should not detract from this, since succinyl reagents are difficult to functionalise without obtaining appreciable amounts of cyclic side-products (see section 6.4.1.1 for further discussion).

As far as the general properties of the acylbis(thiourea) group of compounds are concerned, it was of interest to note that they were all found to have significantly higher melting points than any of the simple *N*-substituted *N'*-butanoylthioureas (see section 2.6.2, chapter 2). Even the suberoylbis(thiourea) ligand (H_2L^{32}), with its six membered alkyl chain spacer and its four *n*-butyl substituents, turned out to be a crystalline material with a melting point of 80 – 82°C. The alkyl substituents on the ends of each ligand seemed to have a marked influence on solubility. The three compounds with the methyl and ethyl substituents (H_2L^{30} , H_2L^{34} , H_2L^{36}), for instance, appeared to be significantly more water soluble than any of the other acylbis(thioureas), and required an unusually long time (i.e. 10 to 15 days) to precipitate from the acetone - water mixtures used in recrystallisation. Much less soluble, not only in aqueous solvent systems, but also in organic solvents like acetone, ethanol and chloroform, were the adipoylbis(thioureas) with the morpholino and piperidyl substituents (H_2L^{33} , H_2L^{35}). The former had to be dissolved in deuterated dimethyl sulfoxide ($\text{DMSO}-d_6$) to prepare an adequately concentrated sample for ^{13}C NMR spectroscopy*.

* Although using this NMR solvent instead of CDCl_3 , appeared to have very little effect on most of the ^1H and ^{13}C resonance shifts, the characteristic NH singlet was found about 2 ppm further downfield than usual i.e. between 10 and 11 ppm. This was also observed for the aminebis(aroylthioureas), since the NMR samples of these compounds had to be dissolved in $\text{DMSO}-d_6$ as well.

Due to their symmetry, all the acylbis(thioureas) (and for that matter, the other types of bipodal thioureas) produced relatively uncomplicated ^1H and ^{13}C NMR spectra (see figures 6.10 and 6.12 in part B). The four methylene groups of the spacer in 3,3,3',3'-tetraethyl-1,1'-adipoylbis(thiourea) (H_2L^{31}), for example, only gave two sets of ^1H resonance peaks: a triplet near 2.4 ppm from the two methylene groups adjacent to the carbonyl carbons (α and α') and a multiplet near 1.7 ppm from the β and β' methylene groups making up the middle of the spacer. The two dissociable *N'* protons of this compound also produced only one broad singlet (near 8 ppm in CDCl_3). The typical effects of restricted rotation at the $\text{C}(\text{S})\text{-NR}_2$ bonds⁵ were also evident again. For example, in the ^1H spectrum of 1,1,1',1'-tetraethyl-3,3'-adipoylbis(thiourea) (H_2L^{30}), the four ethyl groups produced two sets of doublet and triplet resonance peaks.

The ^{13}C spectra of these compounds were found to be equally simple. The four carbons of the alkyl chain spacer in the adipoylbis(thiourea) ligands (H_2L^{30} , H_2L^{31} , H_2L^{33} - H_2L^{35}), for instance, produced only two ^{13}C resonance peaks, while the six carbons of the suberoylbis(thiourea)'s (H_2L^{32}) spacer produced three ^{13}C peaks. Furthermore, even though these ligands possessed two $\text{-C}(\text{O})\text{-NH-C}(\text{S})\text{-}$ chelating moieties, their ^{13}C spectra included only one carbonyl and one thiocarbonyl carbon resonance peak, and, as was seen in the ^{13}C spectra of the simple *N,N*-disubstituted *N'*-butanoyl thiourea ligands (table 5.2, chapter 5), these appeared close to 169 and 179 ppm respectively.

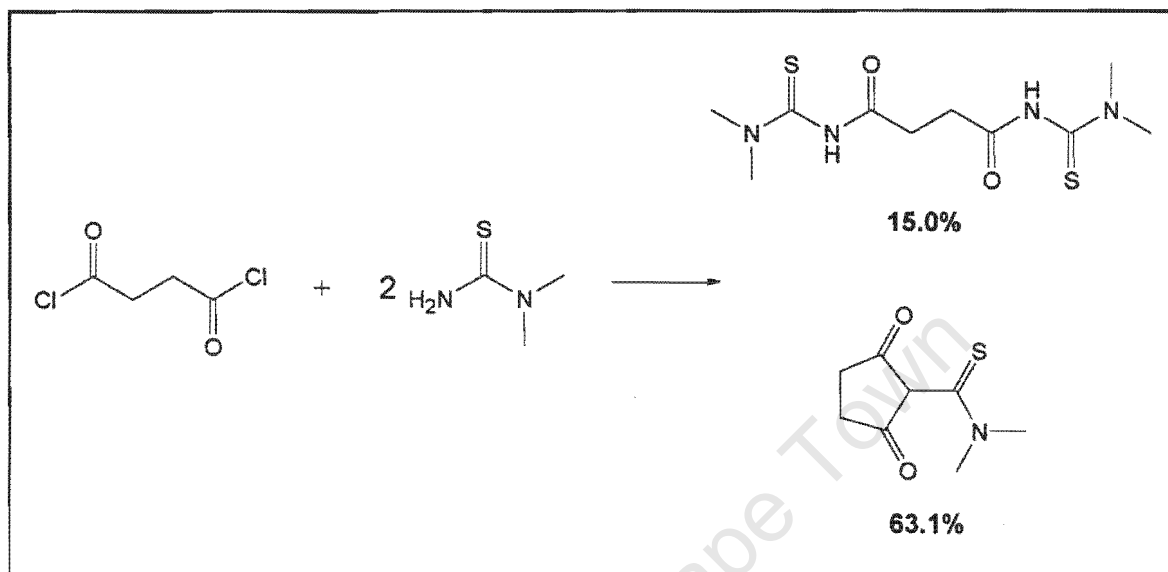
6.4.1.1 Synthesis of 3,3,3',3'-tetramethyl-1,1'-succinylbis(thiourea) H_2L^{36}

From the two reports on the subject of bipodal thioureas^{1,2}, it appeared that the shortest acylbis(thiourea) that had been prepared to date was a glutarylbis(thiourea)² (the spacer of this compound was a three carbon *n*-alkyl chain). Bearing this in mind, a number of attempts were made to produce a ligand using succinyl chloride, a diacyl chloride with a two carbon spacer. This proved difficult, and all attempts using the Douglass and Dains procedure, failed at the first step i.e. when the succinyl chloride was added to two equivalents of thiocyanate. Each time, a dark brown material was formed. Using thin layer chromatography and ^1H NMR spectroscopy this material was found to be a complex mixture of unidentified components. It was only partially soluble in the acetone reaction solvent, and it consistently failed to yield either detectable amounts of the targeted ligand, or any of the anticipated amidic side-products when it was mixed with secondary amine.

In a subsequent attempt, the succinyl chloride was added to two equivalents of *N,N*-dimethylthiourea, according to Dixon and Hawthorne's process³. This approach was somewhat more successful and the desired 3,3,3',3'-tetramethyl-1,1'-succinylbis(thiourea) (H_2L^{36}) was obtained in 15.0 % yield. However, the major product from this reaction was a cyclic succinimide derivative (i.e. 1-(*N,N*-dimethylthiocarbamoyl)-succinimide – see figure 6.3) that formed when both carbonyl carbons of the succinyl chloride reacted with the unsubstituted nitrogen of the same *N,N*-dimethylthiourea molecule. Although this particular synthesis was not studied any further it is conceivable that the targeted succinylbis(thiourea) may be obtained in

higher yields by appropriately manipulating the concentrations of the reagents and the rates at which they are mixed i.e. by slow addition of acyl chloride to a more concentrated excess of *N,N*-dimethylthiourea.

Figure 6.3 Reaction scheme showing the succinylbis(thiourea) (H_2L^{36}) and succinimide derivatives from the reaction between succinyl chloride and *N,N*-dimethylthiourea



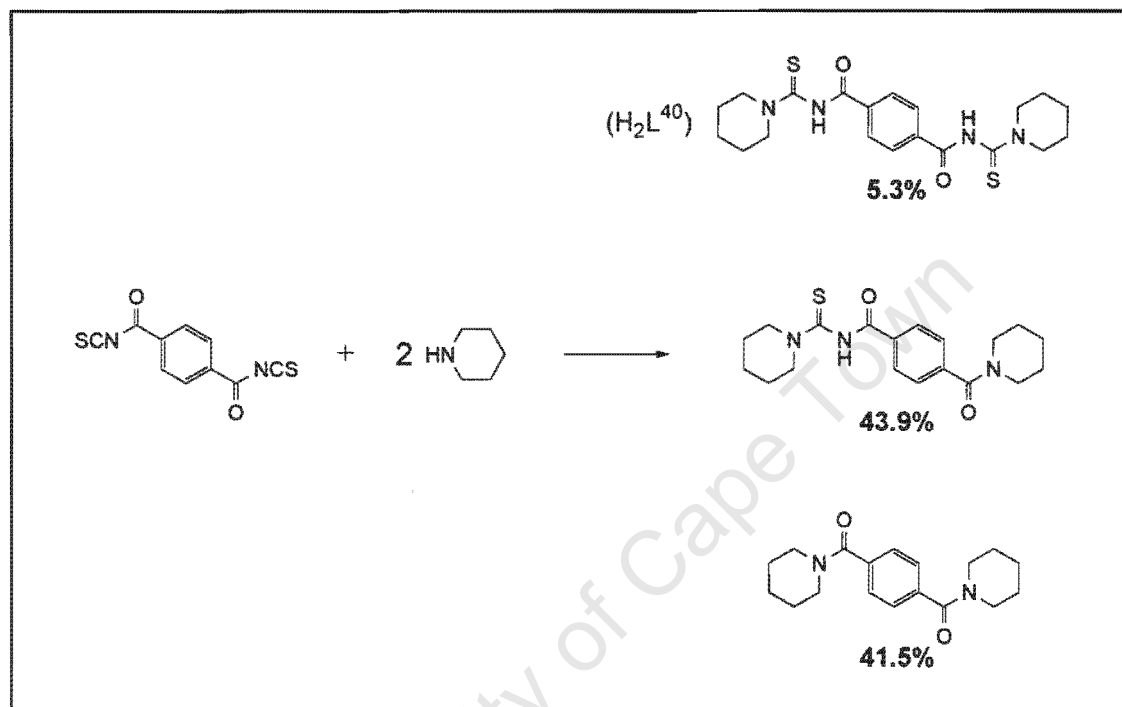
6.4.2 The aroylbis(thioureas)

The aroylbis(thioureas) (see table 6.1b) were all synthesised using the Douglass and Dains process. With diethylamine and dibutylamine, terephthaloyl and isophthaloyl isothiocyanate reacted as intended, giving the bis(thioureas) in high yields ($H_2L^{37} - H_2L^{39}$). This was not unexpected, and even in crude form, these particular compounds were obtained as reasonably pure, crystalline materials. Assignments of ^1H and ^{13}C NMR resonances was also straightforward, and in this respect, all three compounds exhibited the characteristics typical of their simple *N,N*-dialkyl-*N'*-benzoylthiourea counterparts.

From the reaction of piperidine with terephthaloyl isothiocyanate, the yield of 3,3'-dipiperidyl-1,1'-terephthaloylbis(thiourea) target (H_2L^{40}) was only 5.3%. In this instance, the crude products formed a semi-crystalline paste when the reaction mixture was poured into water at the end of the synthesis. This material was extracted into chloroform and then separated into its individual components using a silica gel column with chloroform as eluent. Under these conditions, the small fraction of terephthaloylbis(thiourea) was eluted first. This was followed by two more substantial product fractions, the first being the asymmetric amide with amidic and thiourea moieties on opposite ends of the spacer (43.9%), and the second, the symmetrical piperidyl substituted terephthalamide (41.5%) (see figure 6.4). Special care was taken to confirm the identity of the asymmetric amide and to ensure that this fraction was not just a mixture of the terephthaloylbis(thiourea) and the symmetrical terephthalamide. (Most useful in this regard were the ^1H

NMR spectra and the resonance peaks of the four phenyl ring protons. In the spectra of the two symmetrical compounds, the four protons produced, as expected, a single sharp peak - at 7.40 ppm for the terephthalamide and at 7.93 ppm for the terephthaloylbis(thiourea). In the spectrum of the asymmetric amide, however, these protons produced two sets of well resolved doublets (7.46 and 7.85 ppm)).

Figure 6.4 Product distribution from the reaction between terephthaloyl isothiocyanate and piperidine



The product distribution from the terephthaloyl isothiocyanate - piperidine reaction is of particular interest because it reflects on the role of the carbonyl-isothiocyanate moiety ($-C(O)NCS$) as a *para*-substituent* i.e. the influence that this group has on the carbonyl carbon reactivity of its counterpart on the opposite side of the phenyl ring. Based on a simple summation, the total number of amide and the total number of benzoylthiourea moieties from all three product fractions give an overall amide : benzoylthiourea product ratio, P_r , of 2.33. The value lies between the P_r value of 1.07 determined from the benzoyl isothiocyanate - piperidine reaction, and the value of 4.09 found from the *p*-nitrobenzoyl isothiocyanate - piperidine reaction (see table 3.2, chapter 3). Not surprisingly, this indicates that, compared to a proton (or *p*-chloro and *p*-methoxy groups), a *para* $-C(O)NCS$ group is electron withdrawing and therefore has an activating

* The direct comparison of the $-C(O)NCS$ group to other *para*-substituents in benzoyl isothiocyanate - amine reactions is somewhat simplistic, because it does not account for the fact that this group itself can react with an amine. Especially in the latter stages of reaction, there will be amidic and thiourea moieties that fulfill the role of *para*-substituent and hence exert an influence on the final product distribution. However, since the carbonyl group is also retained in both these moieties, the overall effects of the change are probably small.

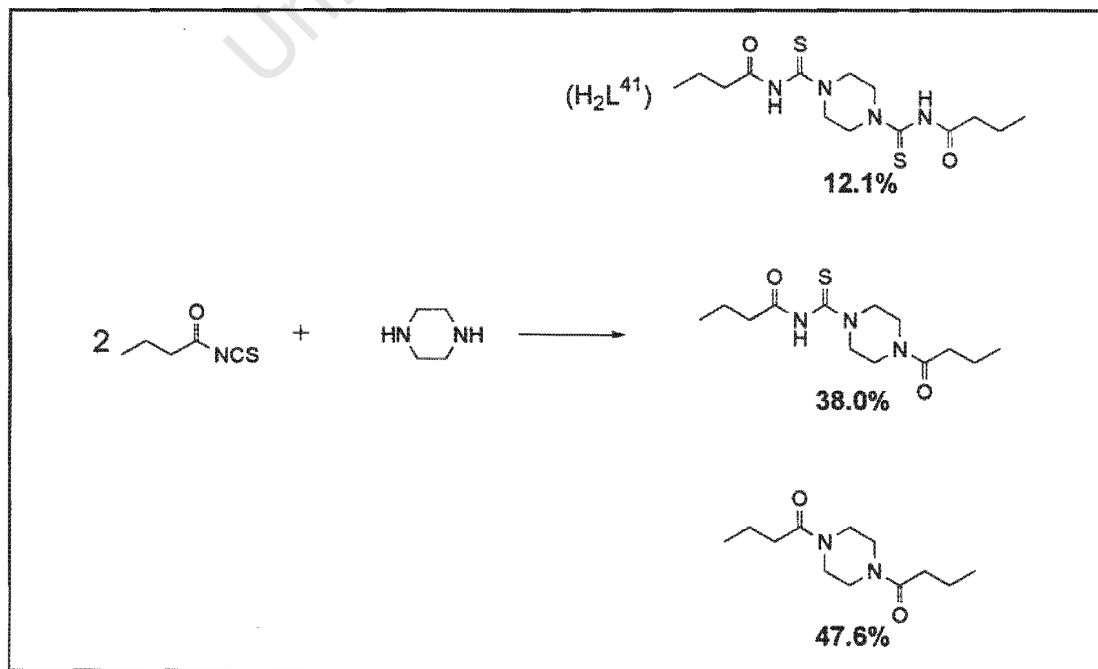
effect on the carbonyl carbon of its opposite counterpart in terephthaloyl isothiocyanate. The $-C(O)NCS$ group is, however, significantly less electron withdrawing and activating than a *p*-nitro group. This intermediate strength electron withdrawing effect seems to be typical of carbonyl group *para*-substituents⁶.

6.4.3 The aminebis(thioureas)

The four amine-linked thioureas ($H_2L^{41} - H_2L^{44}$, table 6.2c) were all found to have high melting points ($>150^\circ\text{C}$), and were noticeably less soluble than the acyl- and aroylbis(thioureas). The aminebis(aroylthioureas) in particular (H_2L^{42} , H_2L^{44}), only readily dissolved in DMSO and DMF, and samples had to be dissolved in $\text{DMSO-}d_6$ for NMR spectroscopy. As with the other types of bipodal thioureas, however, the NMR spectra were relatively simple and the characteristic acyl- and aroylthiourea resonance peaks easy to identify.

Considering the pronounced effects of amine geometry on the outcome of amine – acyl isothiocyanate reactions (see section 2.4.2), it was initially assumed that piperazine would react similarly to its monofunctional analogue, piperidine. At first glance, it was thus not surprising to find that the 1,4-bis-(*N*-butanoylthiocarbamoyl)piperazine (H_2L^{41}) was only formed in 12.1 % yield, and that the bulk of the product mixture from this synthesis was made up of the asymmetric and symmetric amides (38.0 % and 47.6 % respectively – see figure 6.5). However, with the acylthiourea moieties of the asymmetric amide also taken into consideration, the overall yield of acylthiourea units came to 31%. This value was well above the 8.5 % yield of butanoylthiourea recorded from the analogous piperidine – butanoyl isothiocyanate reaction (see table 2.1, chapter 2), and thus considerably higher than originally anticipated.

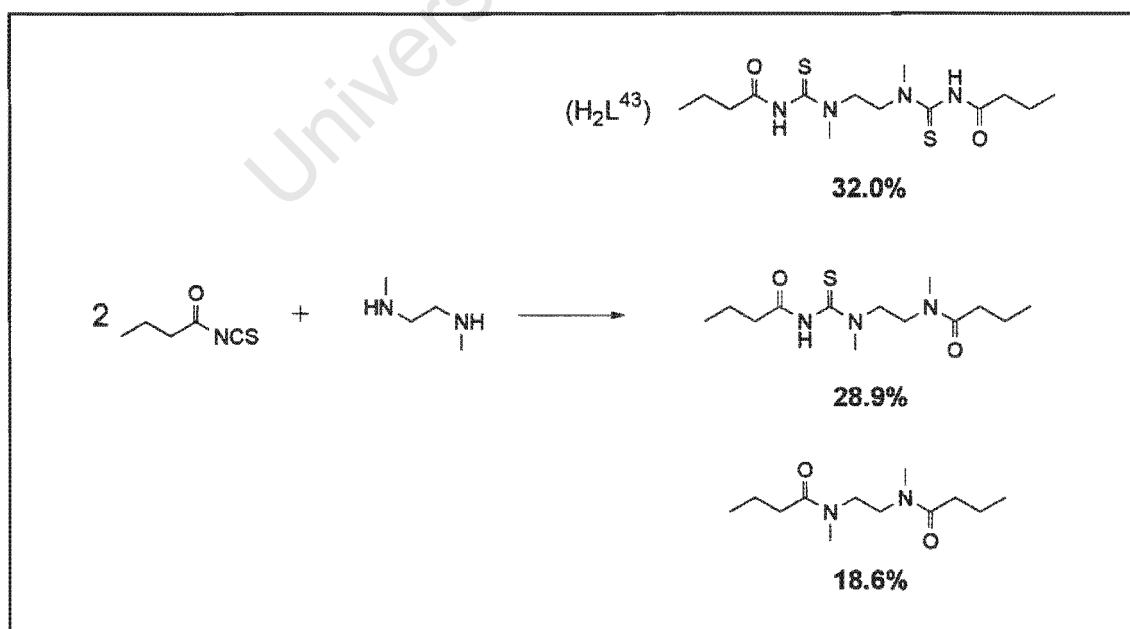
Figure 6.5 Product distribution from the reaction between butanoyl isothiocyanate and piperazine



A surprisingly high yield was also recorded for the piperazine-linked benzoylthiourea (H_2L^{42}). This bipodal thiourea was obtained in 72.6 % yield, again a much higher value than the 41.8 % of benzoylthiourea product from the related piperidine - benzoyl isothiocyanate reaction (see table 3.2, chapter 3). It is possible that the differences may be related to the fact that piperazine ($pK_a = 9.82$) is a noticeably less basic amine than piperidine ($pK_a = 11.12$)⁷. As was illustrated in chapter 3, the less basic amines (i.e. the weaker nucleophiles in hard – hard type reactions) are expected to produce higher yields of the thiourea products when added to acyl or benzoyl isothiocyanates. The lower pK_a of piperazine may be attributed to the mutual electron withdrawing effects that the two nitrogen atoms of this compound exert on each other. It is thus conceivable that once one of these nitrogens is linked to a carbonyl carbon in an amidic bond, or the thiocarbonyl carbon of an acyl or aroyl isothiocyanate, that the electron withdrawing effect on the remaining unreacted nitrogen may even be increased. This would further lower its basicity (i.e. its nucleophilicity) and enhance the tendency of it reacting to form an acyl- or aroylthiourea moiety.

As a spacer for the synthesis of aminebis(thioureas), 1,4-dimethylethylenediamine proved to be even more suitable than piperazine. In the reaction with butanoyl isothiocyanate, the bipodal thiourea (H_2L^{43}) and the asymmetric amide were formed in yields of 32.0 % and 28.9 % respectively (figure 6.6), while the reaction with benzoyl isothiocyanate produced 94.7% of bipodal thiourea (H_2L^{44}). Although this ethylenediamine is estimated to be a stronger base than piperazine ($pK_a = \pm 10.3$)*, its suitability as a spacer is probably attributable to its structure. It is essentially a secondary amine with a methyl and an ethylene substituent on each nitrogen, and the latter group should afford each nitrogen with some degree of F strain steric shielding.

Figure 6.6 Product distribution from the reaction between butanoyl isothiocyanate and 1,4-dimethylethylenediamine



* This pK_a was estimated using the empirical methods proposed by Perrin *et al.*⁷ for pK_a prediction.

6.4.3.1 Crystal and molecular structure of 1,4-bis(*N*-benzoylthiocarbamoyl)piperazine (H_2L^{42})

A crystal of 1,4-bis(*N*-benzoylthiocarbamoyl)piperazine (H_2L^{42}) was submitted for analysis by single crystal X-ray diffraction. The primary intention was to compare the molecular structure of this compound with that of 3,3,3',3'-tetraethyl-1,1'-terephthaloylbis(thiourea), an aroylbis(thiourea) for which the crystal and molecular structure has also recently been determined⁸. Apart from having their donor atoms in opposite sequence (i.e. OS-SO compared to SO-OS), these two bipodal ligands have substantially different melting points and solubilities. Furthermore, the properties of the complexes that they form with the d^8 metal ions also appear to differ significantly (see Part B).

A suitable crystal of the 1,4-bis(*N*-benzoylthiocarbamoyl)piperazine (H_2L^{42}), was obtained by dissolving the compound in a minimum amount of warm DMSO, and then leaving this solution to stand exposed to the atmosphere for several weeks (the formation of crystals suitable for crystallographic analysis may have resulted from the slow hygroscopic absorption of atmospheric moisture by the DMSO mother liquor, rather than by a process of evaporative concentration). The compound crystallises in the space group $P2_1$ with 2 molecules per unit cell. The structure was solved and refined using SHELXS-97 and SHELXL-97^{9,10}. The full sets of data solution and refinement parameters are given in Appendix 4, along with fractional atomic co-ordinates, bond lengths and bond angles, bonded torsion angles, anisotropic temperature factors and hydrogen bonding parameters. For comparison, the bond lengths associated with the chelating moieties in the molecule have been listed in table 6.3, along with the analogous values from the terephthaloylbis(thiourea)⁸. The averaged set of bond lengths compiled for chapter 5 (table 5.5) from reported structures of simple *N,N*-dialkyl-*N'*-aroylthioureas, is also included in this table.

In figure 6.7a, it can be seen that the overall shape of the molecule is approximately linear, with the benzoylthiourea sidearms extended away from the central piperazine ring. The ring itself is in the chair conformation, and starting with the thiocarbonyl groups, the sidearms are in an *anti* relationship to each other. The structure is however, not quite centrosymmetric because the two sides of the molecule are not identical to each other. Both -C(S)-NH-C(O)- chelating moieties are in the non-chelating *E,Z'* form. This is the conformation in which the sulphur and oxygen donor atoms of the moiety are pointed almost in opposite directions, and that is reported to be typical of unco-ordinated *N,N*-dialkyl-*N*-benzoylthiourea ligands⁴ (the bonded torsion angles for C3A-N2A-C1A-S1A and C1A-N2A-C3A-O3A are $-123.6(3)^\circ$ and $-12.2(4)^\circ$, and for C3B-N2B-C1B-S1B and C1B-N2B-C3B-O3B are $127.6(2)^\circ$ and $7.5(4)^\circ$ respectively).

Although none of these structural aspects appear to be particularly remarkable, it is worth noting that the overall structure of the bipodal terephthaloylbis(thiourea) (figure 6.7b) is similar, and that it can essentially be described in the same terms. For instance, the overall shape of the aroylbis(thiourea) is also approximately linear, with the two sidearms extended away from the phenyl ring spacer and in an *anti* orientation relative to each other. Furthermore, as in the 1,4-bis(*N*-benzoylthiocarbamoyl)piperazine structure, the donor atoms of each chelating moiety are found in the non-chelating *E,Z'* conformation.

Figure 6.7a The molecular structure of 1,4-bis(*N*-benzoylthiocarbamoyl)piperazine (H_2L^{42}), showing the atom numbering scheme for the non-hydrogen atoms. Hydrogen atoms are omitted for clarity

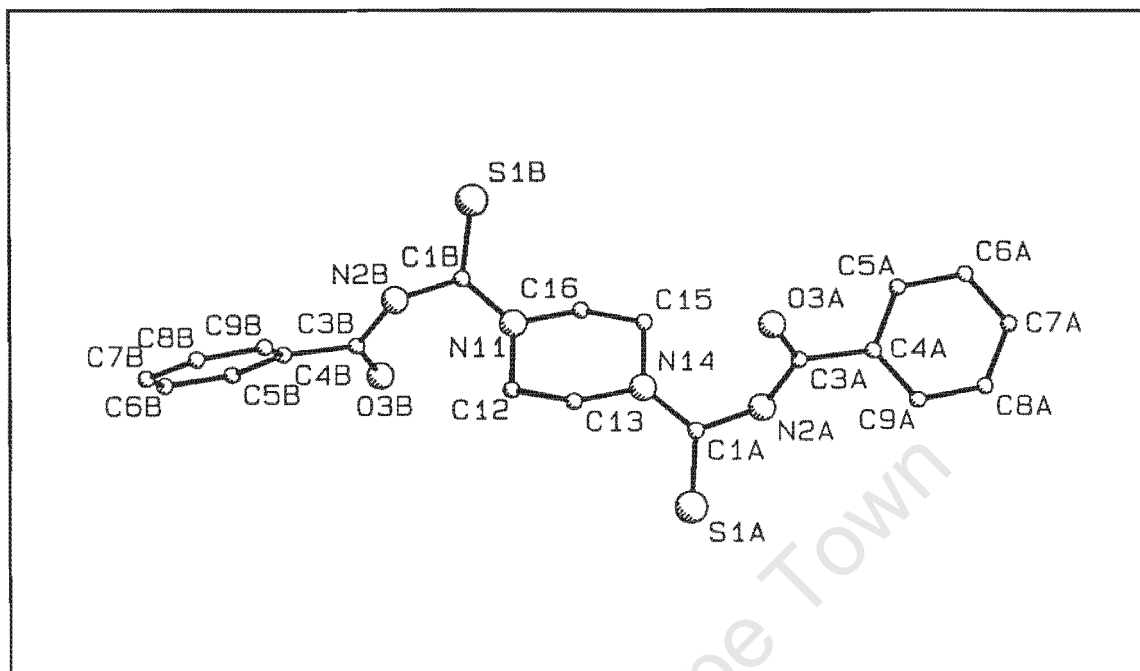


Figure 6.7b For comparison, the molecular structure of the 3,3,3',3'-tetraethyl-1,1'-terephthaloyl-bis(thiourea) ligand⁸. Hydrogen atoms are omitted for clarity

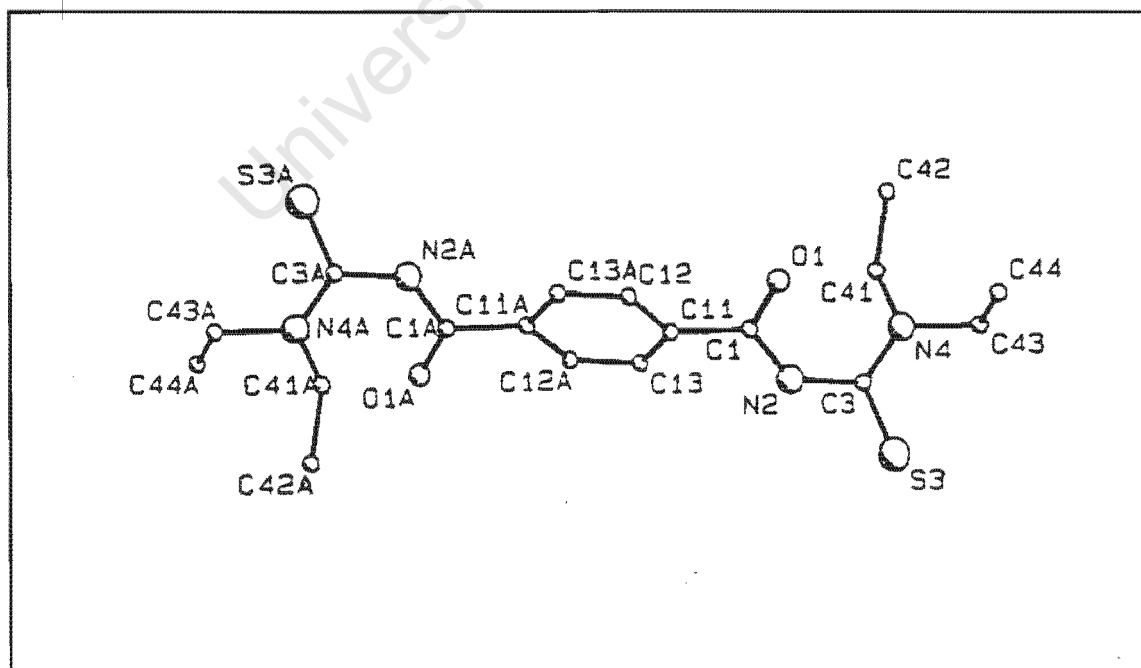
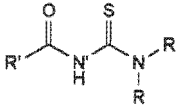


Table 6.3 Average bond lengths associated with the chelating moieties in 1,4-bis(*N*-benzoylthiocarbamoyl)piperazine (H_2L^{42}) and 3,3,3',3'-tetraethyl-1,1'-terephthaloylbis(thiourea)⁸. Included for comparison are average bond lengths from various *N,N*-disubstituted *N'*-aroylthiourea ligands¹¹⁻¹⁴ (standard deviations* appear in parentheses)

Bond 	Bond Lengths (Å)		
	H_2L^{42}	Terephthaloyl- bis(thiourea) ⁸	HL average
R'—C(O)	1.449 (± 0.004)	1.491 (± 0.003)	1.498 (± 0.002)
C=O	1.217 (± 0.003)	1.215 (± 0.003)	1.213 (± 0.004)
(O)C—N'	1.362 (± 0.003)	1.365 (± 0.003)	1.374 (± 0.011)
N'—C(S)	1.366 (± 0.003)	1.418 (± 0.003)	1.409 (± 0.016)
C=S	1.495 (± 0.003)	1.664 (± 0.003)	1.666 (± 0.006)
(S)C—NR ₂	1.309 (± 0.003)	1.321 (± 0.003)	1.327 (± 0.006)

* the standard deviations listed for the H_2L^{42} ligand and the aroylbis(thiourea)⁸ are experimental deviations recorded for the measurements from the crystallographic data collection

In both crystal structures, each bipodal ligand was found to be intermolecularly hydrogen bonded at four points. With the piperazine-linked H_2L^{42} compound, the hydrogen bonding occurred between the oxygen atoms (i.e. the outer donor atoms in the sequence OS-SO) and the *N'* hydrogens of adjacent molecules. The packing diagram in figure 6.8a shows that individual H_2L^{42} molecules were arranged side-by-side, and were joined to each neighbouring molecule via two hydrogen bonds, one from each sidearm. In this way the molecules were linked into a continuous stack-like arrangement. With the terephthaloylbis(thiourea) ligand (figure 6.8b), the hydrogen bonding was found to occur between the sulphur atoms (i.e. also the outer donor atoms in the sequence SO-OS) and the *N'* hydrogens. In the crystal structure of this compound each side-arm of a particular molecule was linked (via two hydrogen bonds) to a different neighbour. This meant that the individual molecules were effectively linked end-to-end in a more linear chain-like arrangement (see packing diagram in figure 6.8b).

Since none of the structural features depicted in the diagrams of either bipodal ligand appeared to be particularly unusual, it was quite astonishing to notice from a comparison of bond lengths (see table 6.3), that at least four pairs of bonds in the piperazine-linked ligand (H_2L^{42}) were significantly shorter than expected. By far the most unusual were the two C=S bonds (C1A-S1A, C1B-S1B). At 1.484(3) Å and 1.506(3) Å, these were more than 0.15 Å shorter than any other type of thiocarbonyl double bond (bond length range of 1.66 Å to 1.72 Å¹⁵), let alone the average C=S bond in *N,N*-dialkyl-*N'*-aroylthioureas (average bond length of 1.666 Å). Surprisingly, the other bonds from the thiocarbonyl carbons were also noticeably shorter than the *N,N*-dialkyl-*N'*-aroylthiourea average; those to the amidic nitrogens (C1A-N2A and C1B-N2B, or N-C(S) in table 6.3) by about 0.05 Å, and those to the piperazine nitrogens (C1A-N14 and C1B-N11, or (S)C-NR₂ in table 6.3) by 0.02 Å. It is significant that the latter difference is the smallest, since this indicates that the bond order of these bonds (i.e. the (S)C-NR₂ partial double bonds) was only marginally affected. The fourth set of shortened bonds in the H_2L^{42} compound, were the phenyl ring to carbonyl carbon bonds (C3A-C4A, C3B-C4B, or R¹-C(O) in table 6.3). At 1.452(4) Å and 1.446(4) Å these were approximately 0.05 Å shorter than the average for the *N'*-aroylthioureas (1.498 Å). The difference is substantial, since typical carbonyl carbon to aromatic carbon bonds usually only vary from 1.48 Å to 1.50 Å¹⁵. In this respect, it was also surprising to find that the torsion angles O3A-C3A-C4A-C5A and O3B-C3B-C4B-C5B in this ligand were -27.9(4)° and -25.2(4)°. These angles indicate that the carbonyl groups and their phenyl ring substituents were not quite coplanar with each other, and accordingly, the degree of resonance interaction between them would have been reduced. This should have resulted in a bond length increase, not a decrease as observed.

Unfortunately, the reasons for the unusual bond lengths in the H_2L^{42} ligand are not understood at this stage. No such anomalies have been recorded from other related structures. Despite the similar configurational aspects, the analogous bonds of the terephthaloylbis(thiourea), for instance, all conformed to the average bond distances for *N,N*-dialkyl-*N'*-aroylthioureas. Even in aroylthioureas with unusual *N* and *N'* substituents like aza-crown ethers¹⁴ or calix(4)arene¹⁶, and in the monosubstituted *N*-alkyl-*N'*-benzoylthioureas with their oxygen donor locked into an intramolecular hydrogen bond^{12,14,17}, the bonds associated with the chelating moieties do not vary significantly from the averages listed in table 6.3.

Figure 6.8a Packing diagram of the 1,4-bis(*N*-benzoylthiocarbamoyl)piperazine (H_2L^{42}) crystal unit cell (viewed down *b* axis) showing the intermolecular hydrogen bonds between oxygen atoms and *N'* hydrogens of adjacent molecules

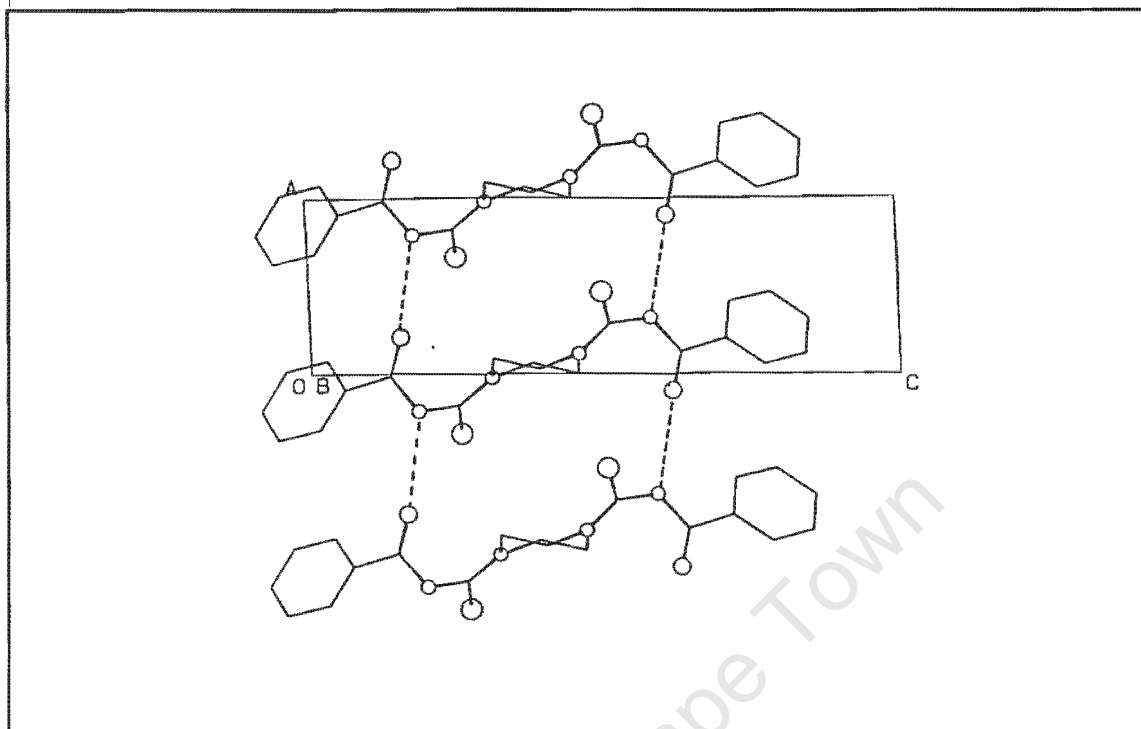
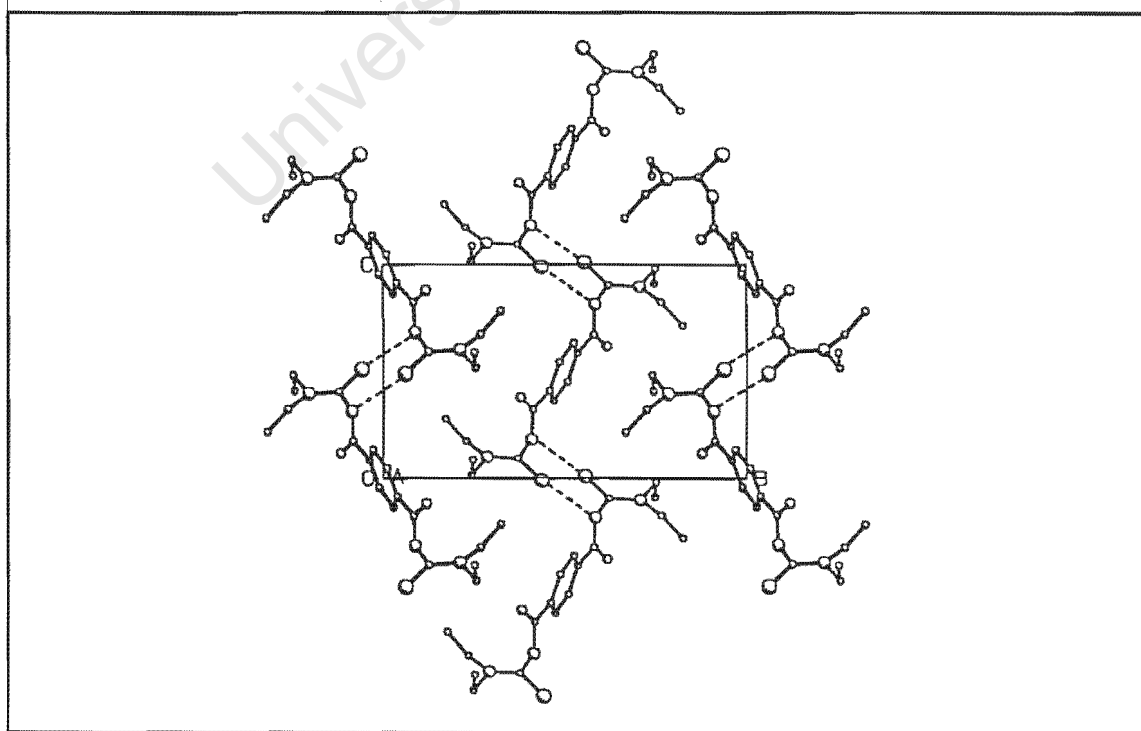


Figure 6.8b For comparison, packing diagram of the 3,3,3',3'-tetraethyl-1,1'-terephthaloylbis(thiourea)⁸ crystal unit cell (viewed down *a* axis) showing the intermolecular hydrogen bonds between sulphur atoms and *N'* hydrogens of adjacent molecules



6.5 Summarising Remarks

The results discussed above have shown that the problem of amide side-product formation was prevalent in the Douglass and Dains synthesis of the bipodal thioureas as well. Thus, in selecting a set of amine and acyl or aroyl isothiocyanate reagents from which to synthesise such a ligand, it is again important to consider to what extent the steric and electronic properties of each reagent will inhibit the isothiocyanate substitution reaction at the carbonyl carbon. In terms of their electronic and steric properties, the difunctional acyl and aroyl isothiocyanates employed in the course of this work, were not particularly ideal reagents. Unless they were reacted with the sterically hindered amines like diethylamine and dibutylamine, they predominantly formed the symmetric and asymmetric amides.

In terms of their steric properties, the ethylenediamine and, especially, the piperazine that were used to synthesise the aminebis(thioureas) could also not be considered ideal. However, with the short chain spacers between the mutually electron withdrawing amino groups of these diamines, they were moderately rather than strongly basic nucleophiles⁷. As was observed in the simple aroyl isothiocyanate – amine reactions (see section 3.4.5, chapter 3), this factor contributed significantly to the improving yields of the targeted ligands.

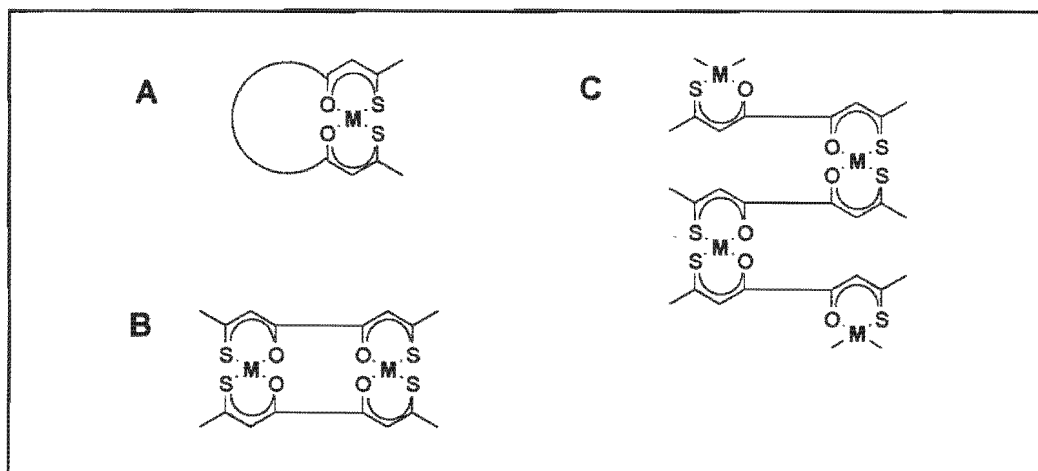
With the synthesis of the dimethyl and piperidyl substituted acylbis(thioureas), it was demonstrated that Dixon and Hawthorne's³ process of directly adding an *N,N*-substituted thiourea to an acyl halide can also be successfully applied to the preparation of the bipodal thioureas. Again this alternative should prove useful when a difunctional acyl halide starting material and the amine reactant with which the acyl isothiocyanate intermediate is to be derivatised, possess the steric and electronic attributes required for a successful Douglass and Dains synthesis.

Part B: The Pt(II) and Pd(II) co-ordination chemistry of bipodal *N'*-acyl- and *N'*-benzoylthioureas

6.6 Introduction

Although the bipodal thioureas are relatively novel forms of *N'*-acyl and *N'*-aroylthiourea ligands, they have already been shown to form neutral complexes with divalent d^8 metal ions^{1,2}. They co-ordinate to these metals in the same bidentate fashion as the simple *N,N*-dialkyl-*N'*-acyl- and *N'*-aroylthioureas do, after the $-C(O)-NH-C(S)-$ chelating moieties have been deprotonated. However, because each bipodal ligand possesses two chelating moieties, the metal to ligand stoichiometry with divalent metal ions is expected to be 1:1 (complexes of this type are thus denoted as $[M(L-S,O)]$ and not $[M(L-S,O)_2]$). Although the donor atoms are expected to adopt a *cis* square planar orientation around ions like Pt(II) and Pd(II), the overall geometry and constitution of the complexes may vary considerably. The simplest possible compound will be formed if both chelating moieties of a ligand molecule react with the same metal ion (A, figure 6.9). The formation of this mononuclear cyclic product would clearly require a long and flexible spacer group in the ligand. With short or rigid spacers, it is more likely that the two chelating moieties of a ligand molecule are co-ordinated to different metal centres. This mode of co-ordination can give rise, either to polymeric complexes (i.e. linear co-ordination polymers of the type $[M(L-S,O)]_x$ ¹⁸, or to metallamacrocycles made up of two or more metal – ligand pairs i.e. $[M(L-S,O)]_{2,3,\dots}$ (see B and C in figure 6.9). (Köhler *et al.*¹ suggested that metallamacrocycles would be formed if the donor atoms adopted the *cis* configuration around the metal centre, while *trans* co-ordination would have resulted in the formation of linear polymer chains. However, it is also possible to accommodate the *cis* conformation in a polymer chain, if the chelating moieties of each ligand are in an *anti* type orientation as shown in C of figure 6.9).

Figure 6.9 Schematic representation showing some of the *cis*- $[M(L-S,O)]$ type complexes that can result from co-ordination reactions between the bipodal ligands (H_2L^n) and square planar metal ions like Pt(II) and Pd(II). (Although only SO-OS ligands are shown in the illustration, similar structures could be drawn for their OS-SO counterparts)



König *et al.*² prepared Pt(II), Pd(II), and Ni(II) complexes with 3,3,3',3'-tetraethyl-1,1'-adipoylbis(thiourea) as the bipodal ligand. Using vapour phase osmometry to determine molar masses, they concluded that the Pd(II) and Ni(II) complexes were trimetallamacrocycles consisting of three metal – ligand pairs (i.e. $[M(L-S,O)]_3$ or 3:3 complexes). Surprisingly, the Pt(II) complex they found was of the form $[Pt(H_2L)Cl_2]$, thus indicating that the chelating moieties of the ligand were not deprotonated and that only the sulphur atoms of each moiety were co-ordinated to the metal centre. Köhler *et al.*¹ produced Pd(II) and Ni(II) complexes using a variety of tere- and isophthaloylbis(thioureas), and also aminebis(thioureas). They were able to determine the crystal and molecular structure of a Ni(II) – 3,3,3',3'-tetraethyl-1,1'-terephthaloyl-bis(thiourea) complex and thereby establish with certainty that it had formed a trimetallamacrocycle ($[Ni(L-S,O)]_3$). The complexes of all the aminebis(thioureas), on the other hand, were found to be completely insoluble, and Köhler *et al.*¹ deduced that they had formed metal co-ordination polymers of the type $[M(L-S,O)]_x$.

The Pt(II) and Pd(II) co-ordination chemistry of the three groups of bipodal thioureas was also studied in the course of this project. The metal – ligand complexes were prepared and characterised in much the same way that the mononuclear Pt(II) - *N'*-acyl- and *N'*-aroylthiourea complexes were prepared for chapter 5. The decision to include a study of Pd(II) complexes, was partly based on the desire to obtain more square planar compounds that were adequately crystalline for single crystal x-ray diffractometry. The intention was to expand on the data reported by Köhler *et al.*¹ and König *et al.*², and to obtain more conclusive structural evidence about the metallamacrocyclic or polymeric nature of individual complexes.

6.7 Experimental Approach

The preparation of both Pt(II) and Pd(II) complexes with the bipodal thioureas was essentially based on the procedure described in chapter 5 (section 5.6.1). To start with, the ligand was dissolved along with 2.2 equivalents of sodium acetate base (at least 2 equivalents were required to ensure that both chelating moieties of the ligand were deprotonated). This was then followed by the dropwise addition of a solution containing the metal ion. One equivalent of the latter was required to satisfy the overall 1:1 metal – ligand stoichiometry. The metal ion solutions were prepared using potassium tetrachloroplatinate and potassium tetrachloropalladate salts. Whenever possible, the reactions were carried out in a solvent mixture of water and acetonitrile. However, due to the poor solubilities of some of the bipodal ligands and complexes, a number of reactions were carried out in mixtures of water and dimethyl formamide instead. The reaction products were always recovered by centrifugation, and if soluble, purified by recrystallisation.

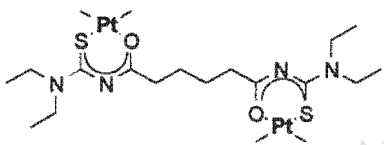
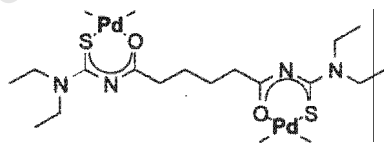
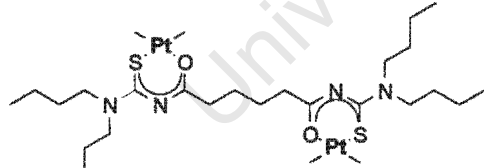
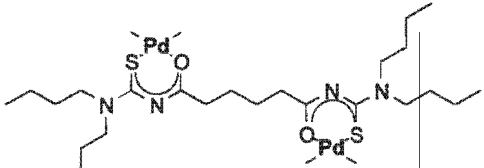
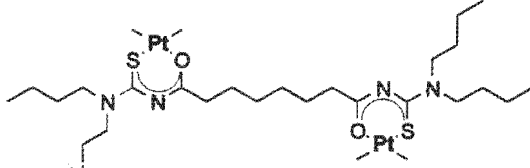
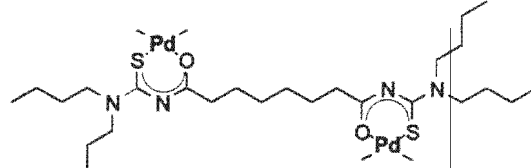
Complexes were prepared with ligands from each of the three groups of bipodal thioureas. From the acylbis(thioureas), the ethyl, butyl and piperidine substituted adipoylbis(thioureas) (H_2L^{30} , H_2L^{31} , H_2L^{35}) and the butyl substituted suberoylbis(thiourea) (H_2L^{32}) were used to produce both Pt(II) and Pd(II) complexes. Complexes of both metal ions were also prepared with the butyl substituted iso- and terephthaloylbis(thioureas) (H_2L^{37} , $H_2L^{39}H_2$), while the ethyl substituted isophthaloylthiourea (H_2L^{38}) was

only used for co-ordination to Pt(II). From the aminebis(thioureas), only the piperazine and ethylenediamine-linked aminebis(aroylthioureas) were used as ligands (H_2L^{42} , H_2L^{44}), the former in a reaction with Pd(II) and the latter for co-ordination to Pt(II).

6.8 Results and Discussion

Lists of the Pt(II) and Pd(II) complexes of the acylbis(thiourea), aroylbis(thiourea) and aminebis(aroylthiourea) ligands appear in tables 6.4a, 6.4b and 6.4c respectively, along with their melting temperatures and the yields in which they were obtained. ^1H , ^{13}C and ^{195}Pt NMR and C, H, N, S elemental analysis data for each compound can be found in the experimental section (section 6.9.4).

Table 6.4a List of the $[Pt(L-S,O)]_x$ and $[Pd(L-S,O)]_x^*$ type complexes prepared with acylbis(thiourea) ligands, with corresponding yields and melting points

Pt(II) and Pd(II) - acylbis(thiourea) complexes	
 $[Pt(L^{30}-S,O)]_x$: 84.0%, mp: 120 – 140°C	 $[Pd(L^{30}-S,O)]_x$: 85.6%, mp: 90 – 100°C
 $[Pt(L^{31}-S,O)]_x$: 78.0%, mp: 55 – 65°C	 $[Pd(L^{31}-S,O)]_x$: 91.0%, mp: 50 – 60°C
 $[Pt(L^{32}-S,O)]_x$: 82.4%, mp: 45 – 55°C	 $[Pd(L^{32}-S,O)]_x$: 93.0%, mp: 60 – 70°C

* In the $[M(L-S,O)]_x$ notation the subscript 'x' serves to indicate uncertainty about the macrocyclic or polymeric nature of the complex. For the aroylbis(thiourea) complexes where the macrocyclic structures were determined by X-ray crystallography, the 'x' is replaced by the appropriate integer – see table 6.4b.

Table 6.4b List of the $[\text{Pt}(\text{L}-\text{S},\text{O})]_x$ and $[\text{Pd}(\text{L}-\text{S},\text{O})]_x$ type complexes prepared with aroylbis(thiourea) ligands, with corresponding yields and melting points

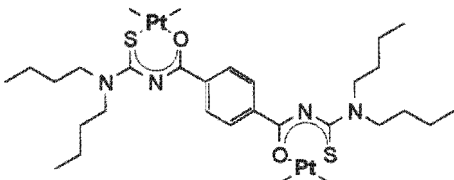
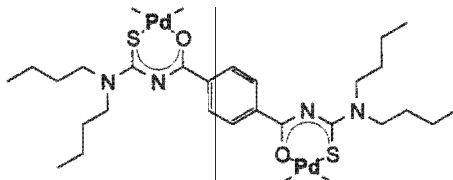
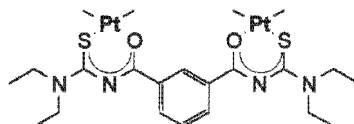
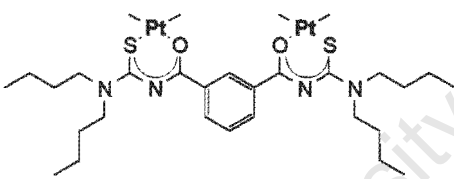
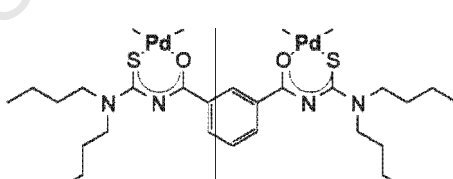
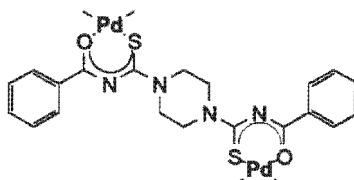
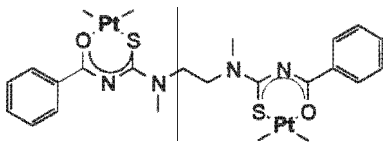
Pt(II) and Pd(II) - aroylbis(thiourea) complexes	
 $[\text{Pt}(\text{L}^{37}-\text{S},\text{O})]_3$: 95.4%, mp: 295 – 296°C	 $[\text{Pd}(\text{L}^{37}-\text{S},\text{O})]_x$: 90.9%, mp: 275 – 277°C
 $[\text{Pt}(\text{L}^{38}-\text{S},\text{O})]_2$: 89.6%, decomposition (> 300°C)	
 $[\text{Pt}(\text{L}^{39}-\text{S},\text{O})]_x$: 93.3%, mp: 255 – 257°C	 $[\text{Pd}(\text{L}^{39}-\text{S},\text{O})]_2$: 94.7%, mp: 251 – 255°C

Table 6.4c The $[\text{Pt}(\text{L}-\text{S},\text{O})]_x$ and $[\text{Pd}(\text{L}-\text{S},\text{O})]_x$ type complexes prepared with aminebis(thiourea) ligands, with corresponding yields and melting points

Pt(II) and Pd(II) - aminebis(thiourea) complexes	
 $[\text{Pd}(\text{L}^{42}-\text{S},\text{O})]_x$: 94%, decomposition (> 250°C)	 $[\text{Pt}(\text{L}^{44}-\text{S},\text{O})]_x$: 92%, decomposition (> 300°C)

6.8.1 Pt(II) and Pd(II) co-ordination chemistry of the acylbis(thioureas) (H_2L^{30} - H_2L^{32} , H_2L^{35})

6.8.1.1 General Observations

The suberoylbis(thiourea) (H_2L^{32}), and the ethyl and butyl substituted adipoylbis(thioureas) (H_2L^{30} , H_2L^{31}), appeared to behave fairly uniformly in the reactions with Pt(II) and Pd(II), and all three ligands gave high yields of neutral *S,O* co-ordinated $[M(L-S,O)]_x$ complex with both metal ions. The common features of these reactions and their products are described below and in the following two sections (6.8.1.2 and 6.8.1.3). The reactions with the piperidyl substituted adipoylbis(thiourea) (H_2L^{35}) are discussed separately (in section 6.8.1.4), since this ligand seemed to produce a more complex mixture of co-ordination products with both Pt(II) and Pd(II).

From the set of reactions that produced only the neutral $[M(L-S,O)]_x$ complexes ($[Pt(L^{30}-S,O)]_x$ to $[Pt(L^{32}-S,O)]_x$, and $[Pd(L^{30}-S,O)]_x$ to $[Pd(L^{32}-S,O)]_x$), it was generally found that very fine yellow $[Pt(L-S,O)]_x$, or orange $[Pd(L-S,O)]_x$ suspensions formed after the ligand and metal solutions were mixed. With the Pt(II) reactions, 10 to 20 minutes would elapse before the reaction solution took on the typical yellow colouration of Pt(II) – thiourea complexes. This was followed by gradual clouding as the fine $[Pt(L-S,O)]_x$ suspension began to appear. The Pd(II) reactions were noticeably faster, with an orange colour emerging the moment a few drops of metal solution were added to the ligand solution. Appearance of $[Pd(L-S,O)]_x$ suspension also began well before all the metal solution had been added. The observed differences in reaction kinetics for the two metal ions were not unexpected since it is well known that the chloride ligands of the $PdCl_4^{2-}$ anion are more labile to substitution than the chlorides of the $PtCl_4^{2-}$ ion¹⁹. (Effects of this difference were also observed in the Pt(II) and Pd(II) co-ordination reactions of the aroylbis(thiourea) and aminebis(thiourea) ligands).

All the precipitated $[Pt(L-S,O)]_x$ and $[Pd(L-S,O)]_x$ complexes of the acylbis(thioureas) were so fine that they had to be recovered by centrifugation at high speed over a period of 15 minutes or more. Despite several concerted attempts at recrystallisation, these materials were never obtained in crystalline form, let alone as crystals suitable for X-ray crystallography. The normal process of dissolution in chloroform – ethanol mixtures, followed by slow evaporation of the solvent, always left the product as a solidified glass-like material. Although these glass-like materials moved as single spots on aluminium oxide TLC plates, and had the C,H,N,S elemental contents expected for the respective $[M(L-S,O)]_x$ products, they did not exhibit sharply defined melting behaviour. Instead, the transition from solid phase to a melt typically occurred over a 10 to 20°C temperature range with a clear softening of the product before it reached the molten phase. Although the $[Pt(L-S,O)]_x$ and $[Pd(L-S,O)]_x$ complexes were all soluble in chloroform and methylene chloride, their dissolution was noticeably slower than that of the mononuclear $[Pt(L-S,O)_2]$ complexes of simple *N'*-acylthioureas. On addition of solvent, the glassy materials (even if finely ground) took on a gel-like consistency, and then steadily disintegrated into fine thread-like fragments that were eventually taken up in the solution.

TLC separations, when conducted on silica gel plates, were beset by the same problem of sample streaking that had complicated separations of the mononuclear $[\text{Pt}(\text{L-S,O})_2]$ *N'*-acylthiourea complexes (see section 5.4.1.1 in chapter 5). Interestingly, the streaking of the $[\text{Pd}(\text{L-S,O})]_x$ products was somewhat less pronounced than the streaking observed with the $[\text{Pt}(\text{L-S,O})]_x$ complexes. Again, the problem was best avoided by using aluminium oxide plates. Although TLC separations on this stationary phase were tested with a number of different solvent combinations as mobile phases, it was never possible to obtain more than a single, well defined spot from any of the $[\text{Pt}(\text{L-S,O})]_x$ and $[\text{Pd}(\text{L-S,O})]_x$ samples.

It would be naive to deduce, just from the single spots on the TLC plates, that the $[\text{Pt}(\text{L-S,O})]_x$ and $[\text{Pd}(\text{L-S,O})]_x$ samples each consisted of only one metallacyclic isomer, rather than a mixture of different sized cyclic and polymeric complexes (it is quite probable that for a particular $[\text{Pt}(\text{L-S,O})]_x$ or $[\text{Pd}(\text{L-S,O})]_x$ complex, these isomeric species would all have very similar R_f values). Such a deduction would be inconsistent with the gradual melting observed for all six samples, as this type of melting behaviour is usually associated with impure or mixtures of compounds, or with polymeric materials. Nicholson²⁰ and Young²¹, for example, have pointed out that it is not possible to define a single melting temperature for polymers, as melting generally takes place over a range of temperature. This is because polymers are effectively mixtures, comprising molecular chains with a range of molar masses. With linear amorphous polymers it is also common to observe a glass transition on heating. This is when the bulk material ceases to be brittle and glassy in character, and becomes less rigid and more rubber-like. The dissolution behaviour observed for the $[\text{Pt}(\text{L-S,O})]_x$ and $[\text{Pd}(\text{L-S,O})]_x$ complexes also appears to be consistent with the possibility that these compounds were of polymeric form. According to the literature^{20,21}, the dissolution of polymer materials is a slow process, often with two discernible stages. First, the solvent diffuses into the polymer to give a swollen gel. This gel then gradually breaks up as molecules of solvated polymer are carried into solution.

It may be argued that the acylbis(thiourea) $[\text{Pt}(\text{L-S,O})]_x$ and $[\text{Pd}(\text{L-S,O})]_x$ complexes were not likely to have been of polymeric form, since linear metal co-ordination polymers are usually brittle and insoluble materials^{22,23}. However, it has been pointed out that the properties of brittleness and poor solubility are only associated with co-ordination polymers because these materials have traditionally been produced by using rigid and planar, conjugated bipodal ligands to couple the metal centres^{18,22}. According to reports, far more soluble polymers are obtained when using bipodal ligands with flexible spacers instead. Rather appropriately, this was first demonstrated with linear bipodal β -diketones that were structurally very similar to the adipoylbis(thioureas) i.e. these ligands consisted of two $-\text{C}(\text{O})-\text{CH}_2-\text{C}(\text{O})-$ bidentate chelating moieties linked by alkyl chain spacers^{18,22}.

Although the melting and dissolution behaviour is also inadequate evidence from which to conclude that the $[\text{Pt}(\text{L-S,O})]_x$ and $[\text{Pd}(\text{L-S,O})]_x$ acylbis(thiourea) complexes were truly of polymeric form, it is very difficult to reconcile the above mentioned properties with any suggestion that the complexes were isomerically pure compounds. A number of isomerically pure 3:3 and 2:2 (metal to ligand) metallacyclic complexes (i.e. $[\text{M}(\text{L-S,O})]_3$ and $[\text{M}(\text{L-S,O})]_2$) were synthesised in the course of this project using the aroylbis(thioureas).

These particular complexes were crystalline compounds that melted at well defined temperatures, and unlike the acylbis(thiourea) complexes, did not exhibit any unusual dissolution characteristics. König *et al.*² deduced from vapour phase osmometric measurements that the 3,3,3',3'-tetraethyl-1,1'-adipoylbis(thiourea) (ligand H_2L^{30}) had formed 3:3 metallamacrocycles with Pd(II) and Ni(II). Unfortunately, however, they did not list melting points for these complexes or discuss their melting properties. It is therefore not possible to deduce whether the complexes they described, were isomerically pure compounds.

6.8.1.2 IR, ^1H and ^{13}C NMR spectroscopy

The IR spectra of the individual $[Pt(L-S,O)]_x$ and $[Pd(L-S,O)]_x$ acylbis(thiourea) complexes were compared with the spectra of their parent ligands, primarily to confirm that the chelating moieties were deprotonated in the complexes and that the oxygen donor of each moiety was also bound to a metal centre. In all cases, the strong NH bands, originally observed near 3200 cm^{-1} in the spectra of the unbound ligands, were completely absent. The C=O bands, which were prominent near 1700 cm^{-1} in the spectra of the unbound ligands were always shifted closer to 1500 cm^{-1} . This shift is typical after bidentate co-ordination to divalent d^8 metal ions like Pt(II), Pd(II) and Ni(II)^{4,24}. (Due to the presence of a number of strong overlapping bands in the 1500 cm^{-1} region, the C=O band is not particularly conspicuous in the spectra of the complexes and therefore more difficult to assign accurately.)

As was observed for the mononuclear Pt(II) – *N'*-acyl and *N'*-aroylthiourea complexes, the ^1H and ^{13}C NMR spectra of the acylbis(thiourea) $[Pt(L-S,O)]_x$ and $[Pd(L-S,O)]_x$ complexes typically consisted of a single set of ligand resonance peaks and closely resembled the spectra of the parent ligands (see figures 6.10a and 6.10b). Again, the only differences between the ligand and complex spectra, were those effected by deprotonation and *S,O* bidentate co-ordination of the chelating moieties (see section 5.4.1.2, chapter 5). In the ^1H spectra, it was interesting to observe that the pair of triplet resonances assigned to the α methylenes of the ethyl or butyl substituents (peaks 3 and 3' in figure 6.10a) were again sharper and shifted closer together. This was one of the consistent changes observed in the ^1H spectra of the mononuclear $[Pt(L-S,O)_2]$ complexes, and it was ascribed to the influences of *S,O* co-ordination on the conformation and partial double bond character of the C(S)-NR₂ bonds. In this respect, the bipodal acylbis(thioureas) and the simple *N'*-acylthioureas were clearly affected to a very similar degree.

In comparing the ^{13}C spectra of the complexes and the unbound ligands, it was of particular interest to note the chemical shift changes of the carbonyl and thiocarbonyl carbon resonance peaks (see figure 6.10b and table 6.5). For the $[Pt(L-S,O)]_x$ complexes, the carbonyl peaks, which had been found close to 169.7 ppm in the spectra of the unbound ligands, were shifted downfield to around 177.4 ppm, while the thiocarbonyl peaks were shifted upfield, from 179.3 ppm to 166.4 ppm on complex formation. This crossed-over shift pattern, corresponded virtually exactly to the shift pattern recorded for the Pt(II) – *N,N*-dialkyl-*N'*-butanoylthiourea complexes (see table 5.3, chapter 5).

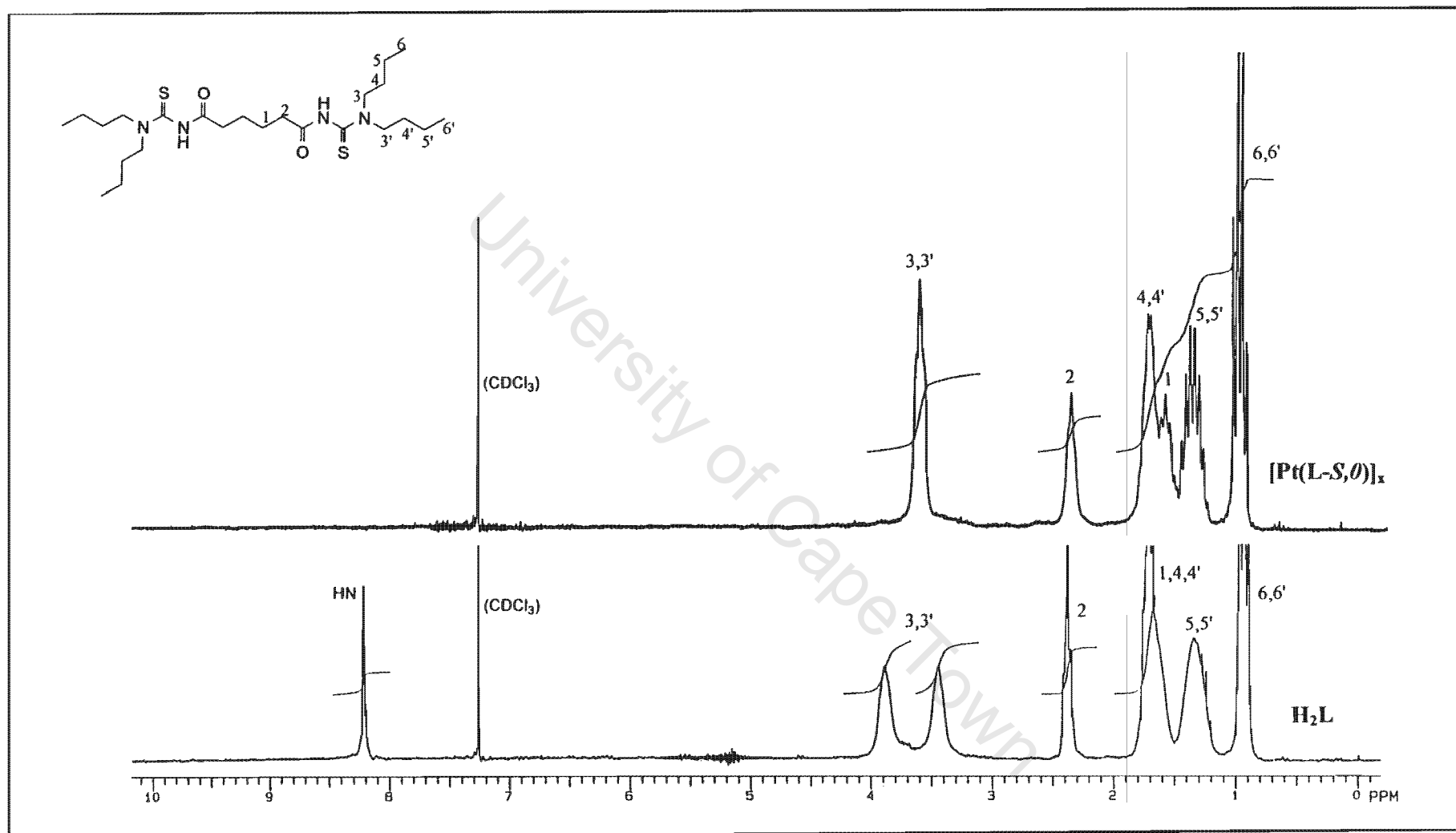


Figure 6.10a Representative ^1H NMR spectra showing the characteristic differences between the ^1H spectra of 3,3,3',3'-tetrabutyl-1,1'-adipoylbis(thiourea) (H_2L^{31}) and its $[Pt(L^{31}-S,O)]_x$ complex

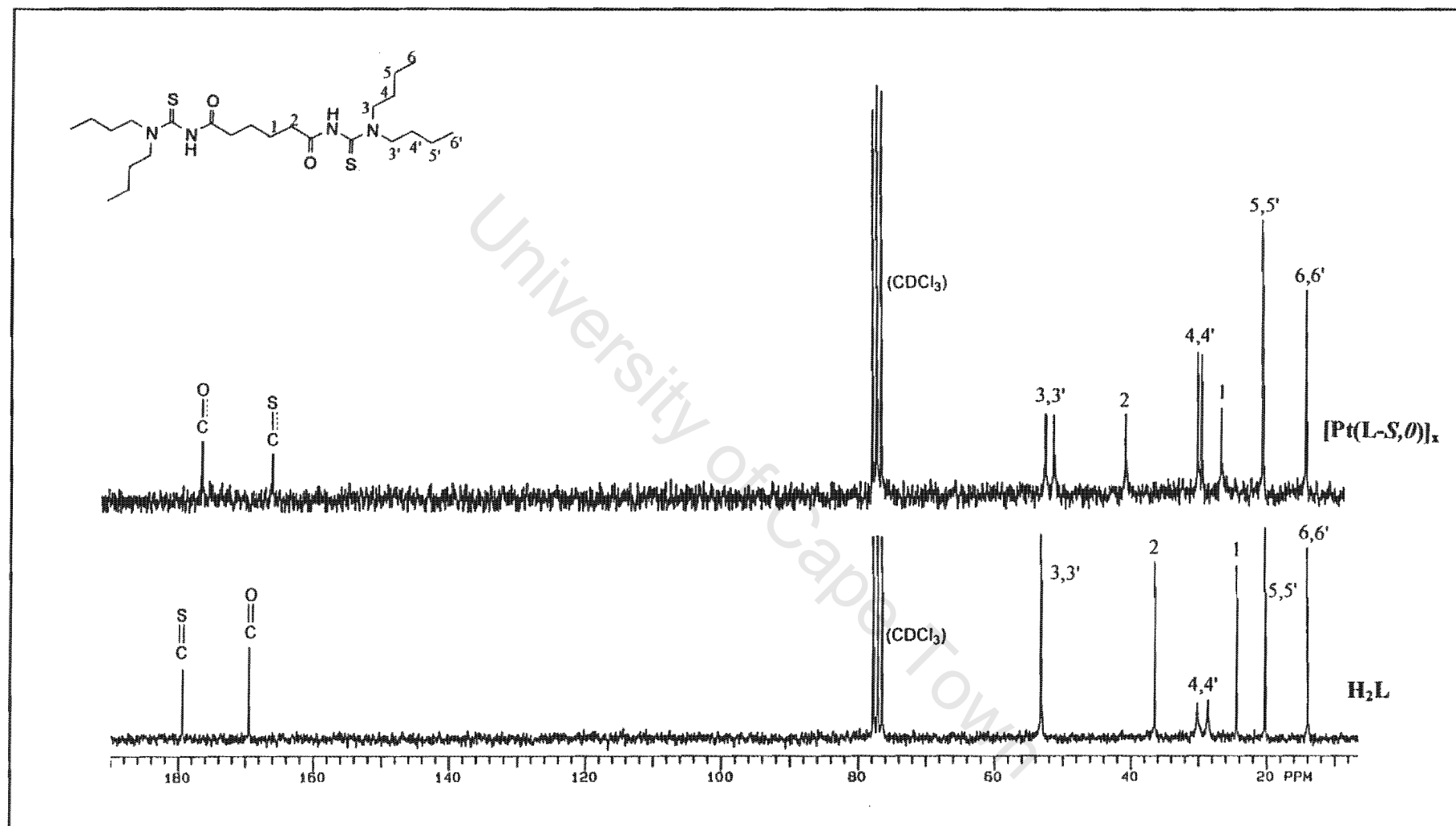


Figure 6.10b Representative ^{13}C NMR spectra showing the characteristic differences between the ^{13}C spectra of 3,3,3',3'-tetrabutyl-1,1'-adipoylbis(thiourea) (H_2L^{31}) and its $[\text{Pt}(\text{L}^{31}\text{-S,O})]_x$ complex.

Table 6.5 Average ^{13}C chemical shifts for the carbonyl and thiocarbonyl carbons of the acylbis(thiourea) ligands (H_2L^{30} – H_2L^{32}) and their Pt(II) and Pd(II) $[\text{M}(\text{L}-\text{S},\text{O})]_x$ complexes

	$\delta \text{ }^{13}\text{C}=\text{O}$ (ppm)			$\delta \text{ }^{13}\text{C}=\text{S}$ (ppm)		
	H_2L	$\rightarrow$	$[\text{M}(\text{L}-\text{S},\text{O})]_x$	H_2L	$\rightarrow$	$[\text{M}(\text{L}-\text{S},\text{O})]_x$
$[\text{Pt}(\text{L}-\text{S},\text{O})]_x$ complexes	169.7 (± 0.3)	$\rightarrow$ + 7.7	177.4 (± 0.2)	179.3 (± 0.4)	$\rightarrow$ -12.9	166.4 (± 0.3)
$[\text{Pd}(\text{L}-\text{S},\text{O})]_x$ complexes	169.7 (± 0.3)	$\rightarrow$ +10.2	179.9 (± 0.1)	179.3 (± 0.4)	$\rightarrow$ - 8.9	170.4 (± 0.3)

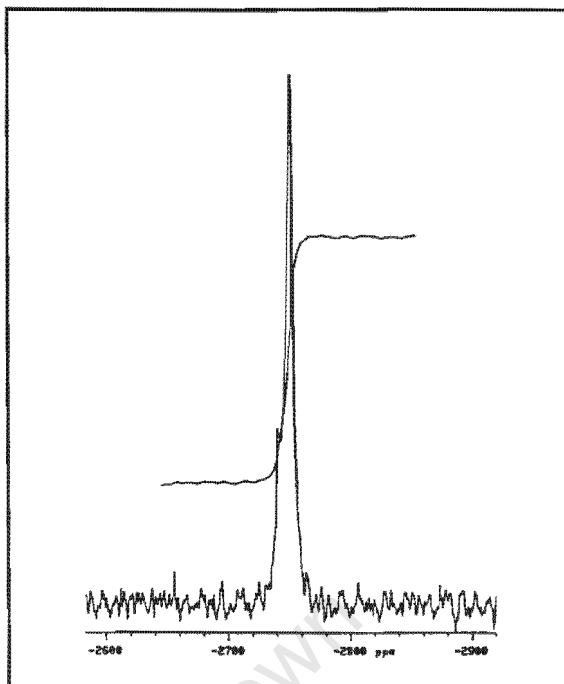
Although a similar shift pattern was observed for the $[\text{Pd}(\text{L}-\text{S},\text{O})]_x$ complexes, the co-ordination to Pd(II) appeared to have a more pronounced effect on the carbonyl carbon resonance, and a slightly diminished influence on the shift of the thiocarbonyl peak. Thus, the carbonyl peak was shifted downfield by 10.2 ppm (to 179.9 ppm), while the thiocarbonyl resonance moved upfield by 8.8 ppm. (In the ^{13}C spectra of the $[\text{Pt}(\text{L}-\text{S},\text{O})]_x$ complexes, the analogous shift differences were 7.7 and 12.9 ppm).

It has already been pointed out that the ^1H and ^{13}C NMR spectra of the $[\text{Pt}(\text{L}-\text{S},\text{O})]_x$ and $[\text{Pd}(\text{L}-\text{S},\text{O})]_x$ acylbis(thiourea) complexes only consisted of single sets of ligand resonance peaks. As such, they provided very little information to resolve the question concerning the metallacyclic or polymeric conformation of these complexes. The only feature of any significance in this regard, was a very slight peak broadening observed for the ^{13}C peaks associated with the carbons of the alkyl chain spacers. While line broadening in NMR spectroscopy may have a number of origins, it is also known to be a consequence of the restricted molecular motion experienced by polymeric molecules ²¹.

6.8.1.3 ^{195}Pt Chemical Shifts

The ^{195}Pt spectra of the three $[\text{Pt}(\text{L}-\text{S},\text{O})]_x$ complexes ($[\text{Pt}(\text{L}^{30}-\text{S},\text{O})]_x$ – $[\text{Pt}(\text{L}^{32}-\text{S},\text{O})]_x$) were each found to contain a relatively broad resonance peak, very close to -2750 ppm. Since this was the same spectral region in which the ^{195}Pt resonance lines of the mononuclear $[\text{Pt}(\text{L}-\text{S},\text{O})_2]$ complexes were found (see table 5.4, chapter 5), these shifts confirmed that co-ordination at the metal centres had occurred with *cis* conformation of the *S,O* donor atoms. However, with base widths of at least 40 ppm, these ^{195}Pt resonance signals were significantly broader than the sharply defined resonance lines found in the spectra of the simple $[\text{Pt}(\text{L}-\text{S},\text{O})_2]$ complexes (see figure 6.10).

Figure 6.10 The broad ^{195}Pt resonance peak of (*cis*-3,3,3',3'-tetrabutyl-1,1'-adipoylbis(thiourea)-platinum (II))_x ($[\text{PtL}^{31}\text{-S,O}]_x$) at -2751 ppm. (Note also the second minor peak at -2741 ppm)



At first glance, it seemed reasonable to suggest that the peak broadening was consistent with the proposal that the $[\text{Pt}(\text{L-S,O})_2]$ and $[\text{Pd}(\text{L-S,O})_2]$ acylbis(thiourea) complexes were of polymeric form. However, closer examination of the three spectra revealed that each broadened ^{195}Pt peak was actually comprised of at least two resonance signals: the major peak at -2750 ppm, and a small, virtually obscured shouldering peak at -2740 ppm. Although the latter resonance was less than half the height of the major peak, it contributed significantly to the base width of the overall peak. These results suggest that each $[\text{Pt}(\text{L-S,O})]_x$ sample consisted of at least two, closely related species. Since a mixture of two different species could also cause gradual melting behaviour, the possibility that the samples contained two types of metallacyclic complexes, or a mixture of metallacyclic and polymeric complexes could not be ruled out.

6.8.1.4 Pt(II) and Pd(II) co-ordination chemistry of 3,3'-bipiperidyl-1,1'-adipoylbis(thiourea) (H_2L^{35})

The Pt(II) and Pd(II) co-ordination reactions with the piperidyl substituted adipoylbis(thiourea) (H_2L^{35}) were carried out in a mixture of DMF and water because of the ligand's poor solubility in the acetonitrile – water solvent system. In the case of Pd(II), the reaction produced a granular, orange coloured precipitate which appeared within five minutes of mixing the metal and ligand solutions. Somewhat surprisingly, the analogous reaction with Pt(II) occurred in an equally short space of time, producing a granular, yellow precipitate.

Elemental microanalysis of both products revealed that their C, H, N and S contents were too low for them to have consisted only of $[\text{M}(\text{L-S,O})]_x$ type complexes. On the other hand, for charged complexes with two chloride ions included as ligands (i.e. complexes of the type $[\text{M}(\text{H}_2\text{L-S})\text{Cl}_2]$ where the H_2L^{35} ligand was not

deprotonated and only bound to the metal ion via its sulphur donor atoms), the C, H, N, and S contents were too high. Both materials were found to melt over a 10°C temperature range, the Pt(II) product from 165 – 175°C, and the Pd(II) product from 180 – 190°C. TLC separations indicated that both products were complex mixtures, containing components with widely varying polarities. Even on aluminium oxide plates, and with a range of solvents as mobile phases, the samples were drawn into continuous streaks without any well defined spots to indicate separated individual components. Unfortunately, the ^1H and ^{13}C NMR spectra were also too complicated to facilitate identification of any of the constituents. Peaks in the ^1H spectra were found to be broad and poorly resolved. Here, it was only of interest to note that a few small overlapping peaks did occur in the downfield region between where NH resonances were to be expected. The ^{13}C spectra were extremely complicated, containing many more peaks than the spectra of the other acylbis(thiourea) $[\text{Pt}(\text{L}-\text{S},\text{O})_2]$ and $[\text{Pd}(\text{L}-\text{S},\text{O})_2]$ complexes. Even in the downfield region between 160 and 180 ppm, it was possible to distinguish more than ten separate peaks. Furthermore, many of the ^{13}C peaks were also found to be broad and overlapping.

Although the characterisation data does not provide any conclusive evidence, it is tempting to speculate that the product mixtures arose as a result of incomplete co-ordination of the ligands. In other words, while some of the chelating moieties may have undergone the expected deprotonation and bidentate co-ordination, a substantial number remained in protonated form, and were thus only linked to metal centres via their sulphur donors. Although this problem may have arisen as a result of the unusually rapid precipitation of the reaction products (i.e. their poor solubility in the DMF – water mixture), it is also important to recall that the co-ordination reaction of Pt(II) and *N*-piperidyl-*N'*-butanoylthiourea (HL^4) also yielded two distinct product fractions after column separation: a non-polar fraction determined to be the mononuclear $\text{Pt}(\text{L}^4-\text{S},\text{O})_2$ complex, and a more substantial fraction composed of polar compounds (see section 5.4.1.1, chapter 5). Amongst the latter were thought to be the $[\text{Pt}(\text{HL}^4-\text{S})(\text{L}^4-\text{S},\text{O})\text{Cl}]$ complex, as well as the *cis* and *trans*- $[\text{Pt}(\text{HL}^4-\text{S})_2\text{Cl}_2]$ species. With a bipodal ligand like the adipoylbis(thiourea), it is quite conceivable that one chelating moiety could be bidentately co-ordinated to a metal centre, while the other was bound to another metal centre, but in the protonated, monodentate form. With these two modes of co-ordination, the composition and polarity of any metallacyclic complexes and short chain co-ordination polymers (i.e. oligomers) can be expected to vary widely.

6.8.2 Pt(II) and Pd(II) co-ordination chemistry of the aroylbis(thioureas) (H_2L^{37} – H_2L^{39})

6.8.2.1 General Observations

In contrast to the reactions with the acylbis(thiourea) ligands, the co-ordination reactions with the terephthaloyl- and isophthaloylbis(thioureas) (H_2L^{37} – H_2L^{39}) produced relatively pure crystalline Pt(II) and Pd(II) complexes in yields that always exceeded 85% (see table 6.4b). These compounds were soluble in chloroform and methylene chloride, and even on silica gel TLC plates they moved as single, well defined spots. Although the melting points of the products were also sharply defined, they were so high that sample

decomposition occurred during, or soon after melting. (For the Pt(II) - 3,3,3',3'-tetraethyl-1,1'-isophthaloylbis(thiourea) ([Pt(L³⁸-S,O)]₂) complex, decomposition began at 300°C, and without any signs of melting.) C, H, N, and S elemental microanalysis confirmed that the metal to ligand stoichiometry of the products was 1 : 1 and that they were compounds of the neutral [M(L-S,O)]_x type. Fortunately, by slow recrystallisation of the complexes from chloroform or chloroform – ethanol mixtures, it was usually possible to obtain single crystals suitable for X-ray crystallographic analysis. It was thus established that the Pt(II) and Pd(II) complexes of these bipodal ligands were in the form of metallamacrocycles and not linear co-ordination polymers (see sections 6.8.2.4 – 6.8.2.6 below).

6.8.2.2 ¹H and ¹³C NMR spectroscopy

The ¹H and ¹³C NMR spectra of the [Pt(L-S,O)]_x and [Pd(L-S,O)]₂ aroylbis(thiourea) complexes all consisted of a single set of ligand resonances, with only the recognised effects of ligand deprotonation and S,O bidentate co-ordination (see section 5.4.1.2, chapter 5) to distinguish them from the spectra of the unbound ligands. The ¹H NMR peaks were well resolved, while in the ¹³C spectra, none of the resonance lines showed any signs of broadening (see figures 6.12a and 6.12b for examples). As was observed for the [M(L-S,O)]_x complexes of the acylbis(thioureas), changing from a Pt(II) to a Pd(II) metal centre only had a significant effect on the ¹³C resonances of the carbonyl and thiocarbonyl carbons. For the [Pd(L-S,O)]_x complexes the two resonance lines of these carbons appeared close to 170 ppm. This was downfield of the analogous [Pt(L-S,O)]_x resonance lines, which in turn were found close to 167 ppm. (With respect to the latter, it was of interest to recall that the thiocarbonyl and carbonyl carbon resonance lines of the mononuclear Pt(II) – *N'*-benzoylthiourea complexes ([Pt(L-S,O)]₂) were also found in this region i.e. near 168 ppm).

6.8.2.3 ¹⁹⁵Pt NMR spectroscopy

The ¹⁹⁵Pt spectrum of a recrystallised sample of the Pt(II) - 3,3,3',3'-tetrabutyl-1,1'-terephthaloylbis(thiourea) ([Pt(L³⁷-S,O)]₃) was found to contain a single resonance peak at -2719 ppm. This indicated that the donor atoms of the chelating moieties were co-ordinated in *cis* bidentate fashion, as a resonance line close to -2720 ppm is characteristic for *cis*-[Pt(L-S,O)]₂ type complexes of the *N'*-aroylthioureas^{12,14,25}. The ¹⁹⁵Pt resonance signal of this aroylbis(thiourea) complex was also found to be much sharper than any of the peaks recorded from the Pt(II) – acylbis(thiourea) complexes. This provided an indication that the aroylbis(thiourea) sample consisted of just one metallacyclic isomer. Attempts were also made to acquire a ¹⁹⁵Pt spectrum for the Pt(II) - 3,3,3',3'-tetraethyl-1,1'-isophthaloylbis(thiourea) complex ([Pt(L³⁸-S,O)]₂). However this particular compound was not soluble enough in CDCl₃ to allow preparation of an adequately concentrated sample.

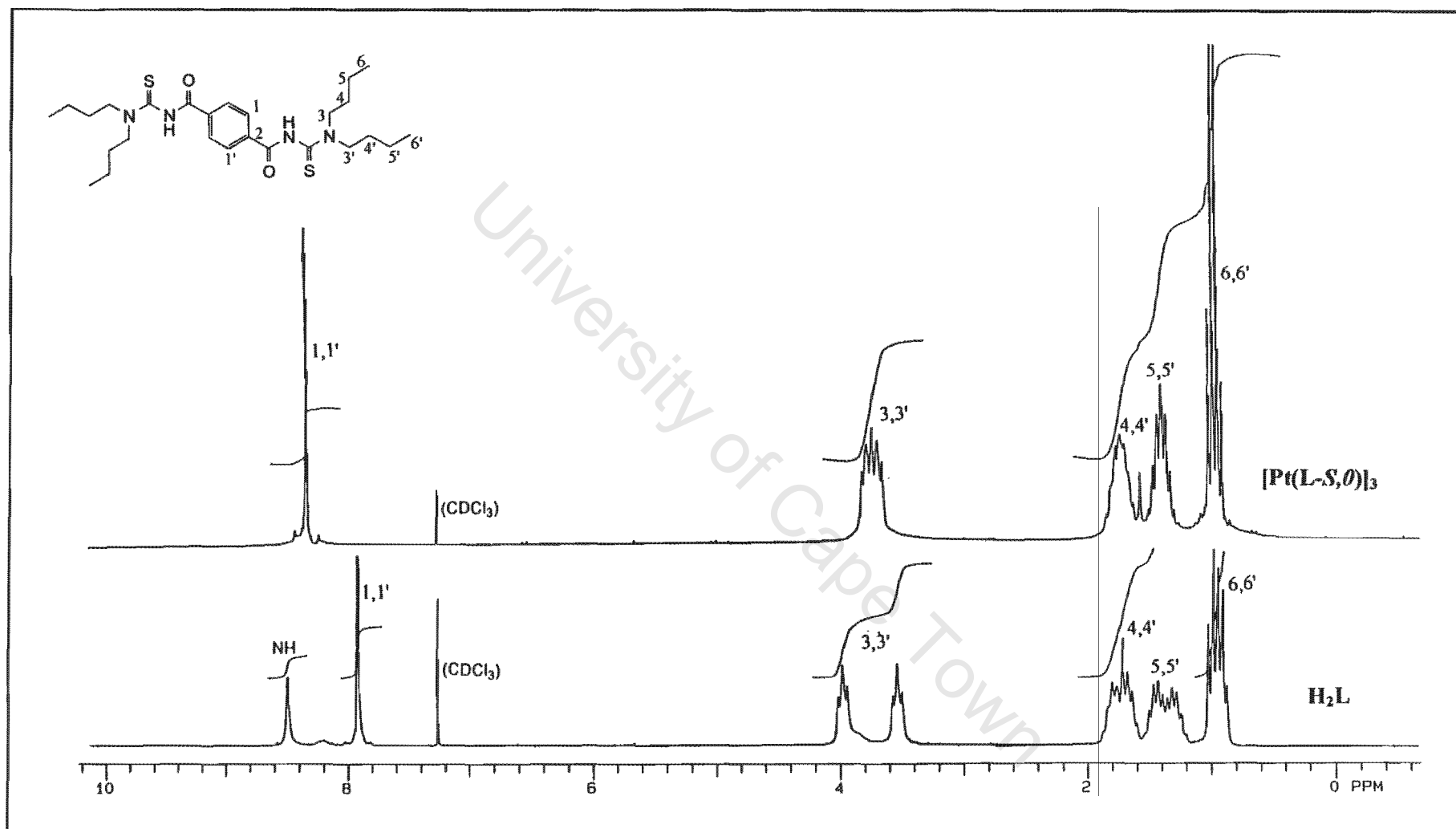


Figure 6.12a Representative ^1H NMR spectra showing the characteristic differences between the ^1H spectra of 3,3,3',3'-tetrabutyl-1,1'-terephthaloylbis(thiourea) ligand (H_2L^{37}) and its $[\text{Pt}(\text{L}^{37}\text{-S},\text{O})]_3$ complex

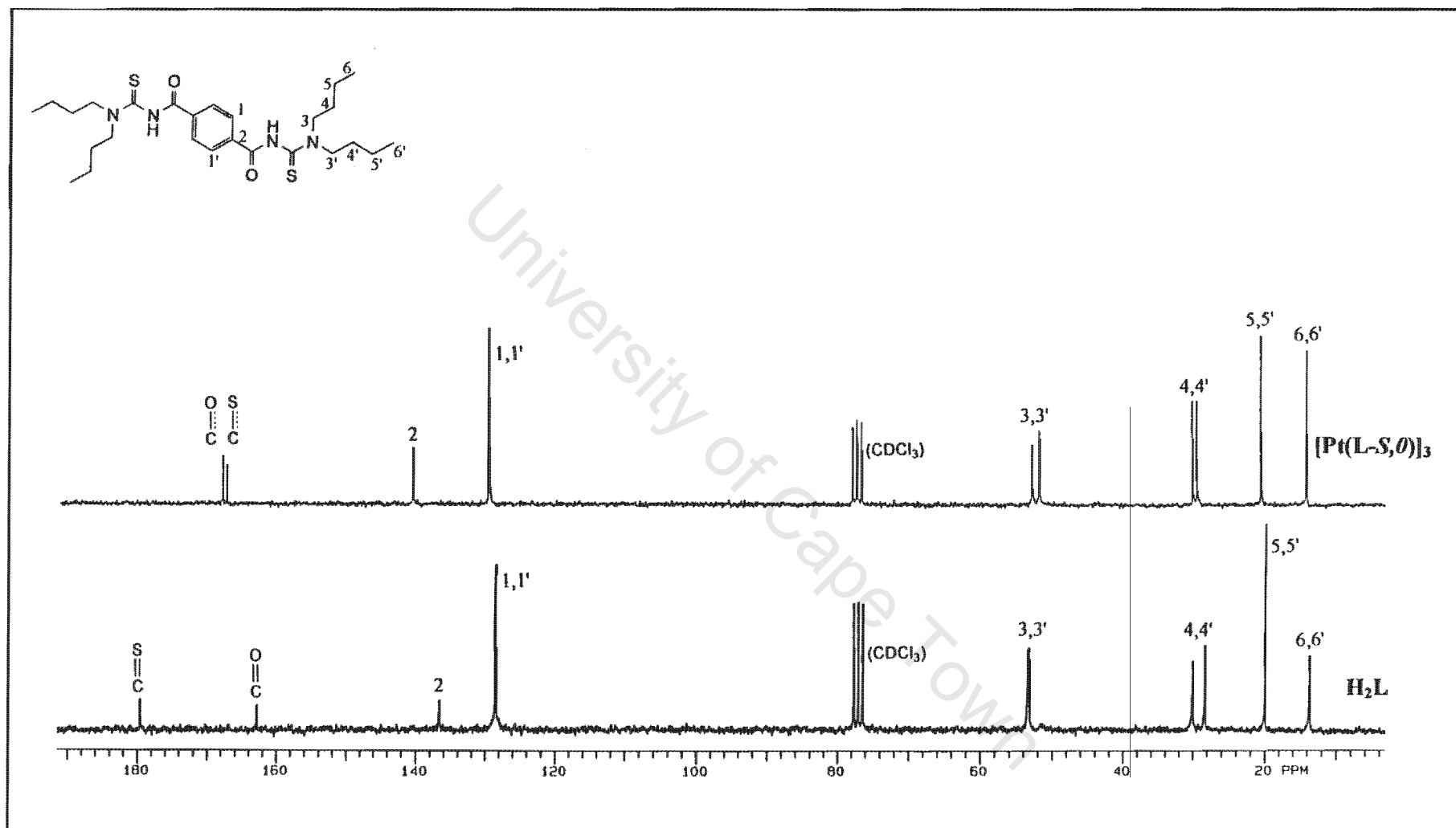


Figure 6.12b Representative ^{13}C NMR spectra showing the characteristic differences between the ^{13}C spectra of 3,3,3',3'-tetrabutyl-1,1'-terephthaloylbis(thiourea) ligand (H_2L) and its $[Pt(L-S,O)_3]$ complex

6.8.2.4 Crystal and molecular structure of a 3:3 *cis*-Pt(II) -3,3,3',3'-tetrabutyl-1,1'-terephthaloyl-bis(thiourea) metallamacrocyclic [Pt(L³⁷-S,O)]₃

This Pt(II) – terephthaloylbis(thiourea) complex was recrystallised from a 3 : 1 mixture of chloroform and ethanol. Although the crystals obtained were of suitable dimensions for crystallographic analysis, they were found to be extremely unstable once removed from the mother liquor. They disintegrated, not as a result of molecular decomposition, but because solvent guest molecules in the crystal lattice rapidly evaporated. (Drying the crystals in air for 24 hours, left a yellow, friable material that was found to be the analytically pure [Pt(L³⁷-S,O)]₃ complex.) To overcome the problem, a single crystal was drawn, with mother liquor, into a tapered Lindemann capillary. This was sealed with polyethylene plugs and cooled to –100°C for the crystallographic data collection.

The complex was found to crystallise in the monoclinic space group P2₁/c with 4 molecules per unit cell. The structure was solved using SHELXS-97 and refined by least squares methods using SHELXL-97^{10,26}. The non-hydrogen atoms of the Pt(II) – terephthaloylbis(thiourea) complex itself were modeled anisotropically. Hydrogen atoms were placed in geometrically calculated positions, and refined with temperature factors 1.2 times those of the parent atoms. The solvent guests in the lattice displayed high thermal motion and were modeled isotropically. The full sets of experimental and refinement parameters, fractional co-ordinates, bond lengths, bond angles, and torsion angles are reported in Appendix 5. The average bond lengths and bond angles associated with the metal – ligand chelate rings of the structure are summarised in table 6.6. Once again, the analogous measurements reported for the mononuclear [M(L-S,O)₂] type complexes of other *N'*-aroylthioureas are listed for comparison, as well as the values determined by Köhler *et al.*¹ from the 3:3 metallamacrocyclic Ni(II) – 3,3,3',3'-tetraethyl-1,1'-terephthaloylbis(thiourea) complex.

The molecular structure represented in figure 6.13a, shows that co-ordination occurred in *cis* bidentate fashion, but in such a way that three ligand molecules and three metal centres were assembled into a 3:3 metallamacrocyclic (hence the subscript '3' in the notation [Pt(L³⁷-S,O)]₃). In this structure, the macrocyclic ring is almost planar since the aromatic rings of the terephthaloyl moieties are virtually coplanar with the co-ordination planes of the three metal centres. Nevertheless, a small degree of buckling from perfect planarity can be seen when the macrocycle is viewed side-on (figure 6.13b). (The distortion is also evident from the non-bonded torsion angles through the oxygen atoms i.e. the torsion angles O2A-O11A-O2C-O11C, O2C-O11C-O2B-O11B and O2B-O11B-O2A-O11A, which are –16.1(5), 8.6(5) and 22.7(5)° respectively.) However, despite these signs of strain in the macrocycle, no unusual deformation is manifest at any of the metal centres. While this is difficult to judge from figure 6.13a, it is much more obvious from the values listed for the bond angles O-Pt-O', S'-Pt-O, S-Pt-O' and S-Pt-S' in table 6.6. Although these indicate that the arrangement of each set of four donor atoms at a metal centre, is slightly distorted from an ideal square, this distortion corresponds very closely to the distortion observed in the mononuclear [Pt(L-S,O)₂] complexes of the *N'*-aroylthioureas and also the Pt(II) -*N'*-acylthiourea complex [Pt(L¹⁰-S,O)₂] (see table 5.5, chapter 5).

Figure 6.13a The molecular structure of the 3:3 *cis*-[3,3,3',3'-tetrabutyl-1,1'-terephthaloylbis(thioureato)-platinum(II)]₃ metallamacrocyclic ([Pt(L³⁷-S,O)]₃) with chloroform, water and ethanol solvent guests. (Hydrogen atoms have been omitted for clarity)

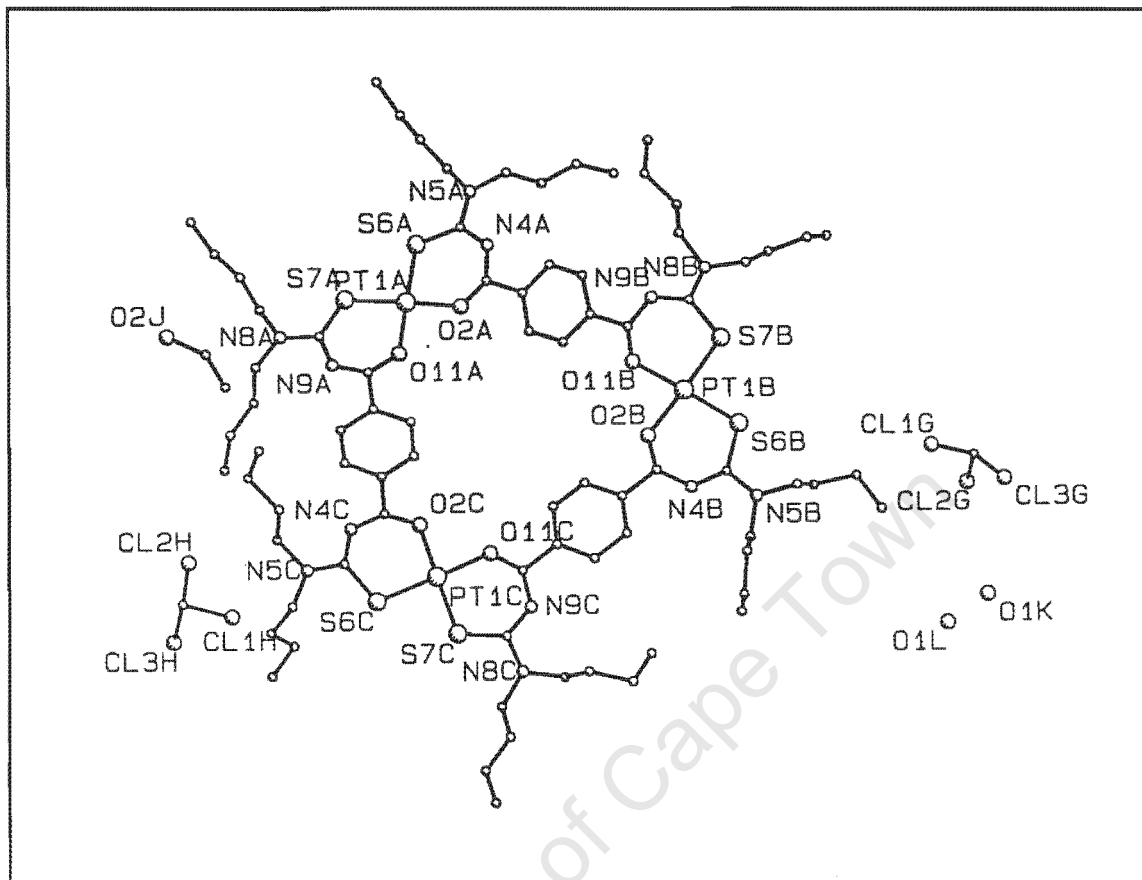


Figure 6.13b Side view of *cis*-[3,3,3',3'-tetrabutyl-1,1'-terephthaloylbis(thioureato)-platinum(II)]₃ complex showing the buckling of the overall metallamacrocyclic. (Hydrogen atoms and butyl groups have been omitted for clarity)

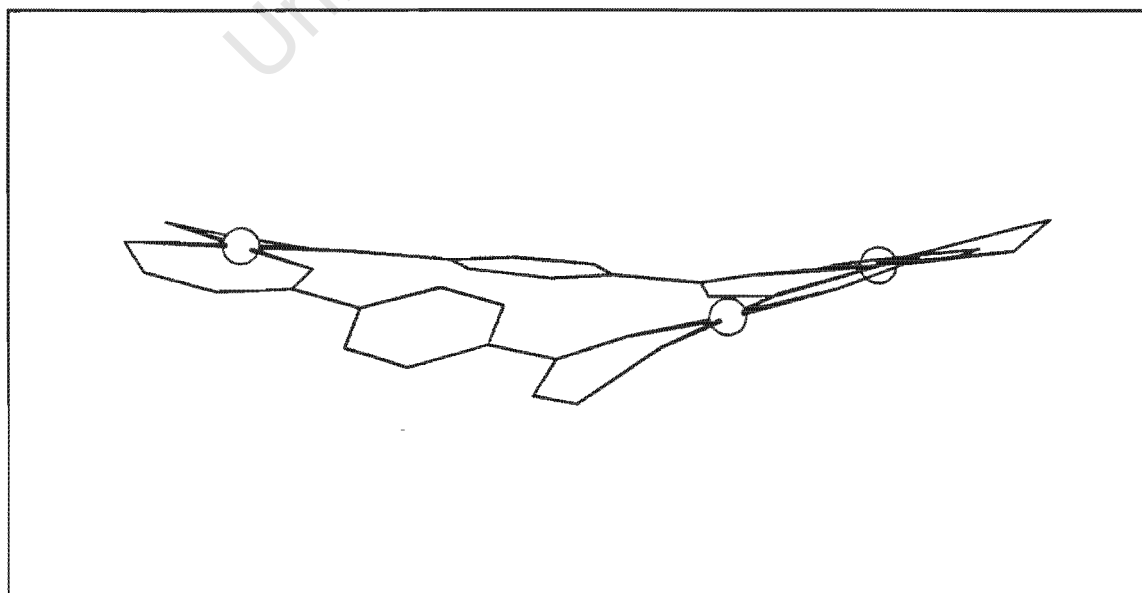
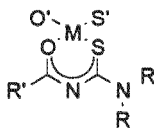


Table 6.6 Average bond lengths and bond angles associated with the chelating moieties around the three Pt(II) centers of the 3:3 *cis*-[3,3,3',3'-tetrabutyl-1,1'-terephthaloylbis(thioureato)-platinum(II)]₃ metallamacrocycle ([Pt(L³⁷-S,O)]₃). Included for comparison are the analogous bond lengths reported for the 3:3 *cis*-[3,3,3',3'-tetraethyl-1,1'-terephthaloylbis(thioureato)-nickel(II)]₃ metallamacrocycle¹ and the average bond lengths and angles for the mononuclear, square planar [M(L-S,O)₂] complexes^{13,14,27-30}

Bond / Angle	Bond Lengths (Å) / Angles (°)		
	[Pt(L ³⁷ -S,O)] ₃	[Ni(L-S,O)] ₃ ¹	[M(L-S,O) ₂] average
R'—C(O)	1.500 (± 0.012)	1.52	1.487 (± 0.015)
C=O	1.263 (± 0.014)	1.26	1.261 (± 0.009)
(O)C≡N'	1.323 (± 0.011)	1.34	1.318 (± 0.011)
N'≡C(S)	1.340 (± 0.012)	1.36	1.342 (± 0.006)
C≡S	1.726 (± 0.014)	1.73	1.724 (± 0.010)
(S)C—NR ₂	1.342 (± 0.012)	1.35	1.341 (± 0.010)
O—M	2.031 (± 0.009)	1.83	2.016 (± 0.008)*
S—M	2.234 (± 0.005)	2.13	2.226 (± 0.006)*
O—M—O'	82.8 (± 0.3)	-	82.6 (± 0.6)*
S—M—S'	87.0 (± 0.8)	-	88.4 (± 0.2)*
O—M—S/O'—M—S'	95.1 (± 0.3)	-	94.5 (± 0.3)*

* average values of bond lengths and angles involving the metal centres were calculated using values reported for [Pt(L-S,O)₂] structures only i.e. from references 14 and 30

Equally clear from table 6.6 is that the bond lengths associated with the Pt(II) centres, and the rest of the chelating moieties in the macrocycle are also all very similar to those found in $[\text{Pt}(\text{L-S},\text{O})_2]$ and the other square planar $[\text{M}(\text{L-S},\text{O})_2]$ complexes.

The 3:3 metallamacrocycles of the $[\text{Pt}(\text{L}^{37}\text{-S},\text{O})_3]$ complex were found to pack in layers parallel to $[011]$, along with a number of solvent molecules as guests in the crystal lattice. Despite the high thermal motion of these guests, it was possible to identify and locate at least two molecules of chloroform, one molecule of ethanol and two molecules of water (per macrocycle) in the structure. None of these were found within any of the macrocyclic rings, but instead, were trapped in pockets closer to the flexible *n*-butyl side-chains. The packing of the structure appeared to be stabilised by hydrogen bonds between the oxygen atoms of the ethanol and water molecules - $\text{O}(2\text{J})_{\text{ethanol}} \cdots \text{O}(1\text{L})_{\text{water}}$ is 2.548 Å (via $1 + x, 1 + y, z$), $\text{O}(2\text{J})_{\text{ethanol}} \cdots \text{O}(1\text{K})_{\text{water}}$ is 3.081 Å (via $1 + x, 1 + y, z$) and $\text{O}(1\text{K})_{\text{water}} \cdots \text{O}(1\text{L})_{\text{water}}$ is 2.668 Å.

According to the literature, there have been a few cases where chloroform guest molecules have been detected in crystalline metal – ligand complexes of the *N,N*-dialkyl-*N'*-benzoylthioureas. After recrystallisation from pure chloroform or chloroform – methanol mixtures, Beyer *et al.*³¹, identified, amongst others, $[\text{Ni}(\text{L-S},\text{O})_2]$ and $[\text{Pd}(\text{L-S},\text{O})_2]$ complexes of *N*-pyrrolidyl-*N'*-benzoylthiourea, each with one chloroform guest per molecule of complex. In these instances, the identity of the solvent guest and the ratio of host to guest molecules was established by elemental analysis, thermogravimetry and IR spectroscopy. Although it is known that the $[\text{Ni}(\text{L-S},\text{O})_2]$ complexes will also form adducts with pyridine³¹, the 3:3 $[\text{Pt}(\text{L}^{37}\text{-S},\text{O})_3]$ metallamacrocycle appears to be the first metal – *N'*-aroylthiourea type complex found to include ethanol and water as guests as well, and for which the crystal structure with its solvent guests has been determined by X-ray diffraction. Unfortunately, the crystals of this complex were found to be too unstable for thermogravimetric analysis and it was therefore not possible to determine whether any more solvent molecules were present in the crystal lattice. Nevertheless, the inclusion of the solvent guests was independently confirmed by ¹H NMR spectroscopy. For this purpose, a number of large solvated crystals (with dimensions > 1 mm³) were removed from the mother liquor and rapidly rinsed with two portions of deuterated methylene chloride. They were then immediately dissolved in a fresh aliquot of this solvent for acquisition of the spectrum. Apart from the ¹H resonances due to the terephthaloyl and butyl groups of the complex, the spectrum also showed characteristic resonances of chloroform (s, 7.34 ppm), ethanol (t, 1.21 ppm, q, 3.67 ppm) and water (br s, 1.56 ppm). From resonance integrals, the ratio of chloroform to ethanol in the sample was found to be 2:1.

The process of assembly required for the high yield formation of the 3:3 $[\text{Pt}(\text{L}^{37}\text{-S},\text{O})_3]$ metallamacrocycle is remarkable if one considers the molecular structure of the tetraethyl substituted terephthaloylbis(thiourea) ligand shown earlier in figure 6.7b (this was the same ligand which Köhler *et al.*¹ used to produce the 3:3 $[\text{Ni}(\text{L-S},\text{O})_3]$ metallamacrocycle). In this structure, the two chelating moieties of the ligand are essentially found in an *anti* orientation. Although this in itself is not surprising, the conformation, especially for a ligand with a relatively rigid spacer, seems ideally suited to the formation of a linear co-ordination polymer (see diagram C in figure 6.9). To be accommodated in a 3:3 macrocycle, the chelating moieties of the

ligands are required to be in the *syn* orientation. Judging by the high yield of the crystalline 3:3 [Ni(L-*S,O*)]₃ complex reported by Köhler *et al.*¹ (90%), and by the high yield of the [Pt(L³⁷-*S,O*)]₃ complex obtained in this work (95.4%), the ligands appear to adopt the necessary conformation with almost resolute uniformity during the process of co-ordination.

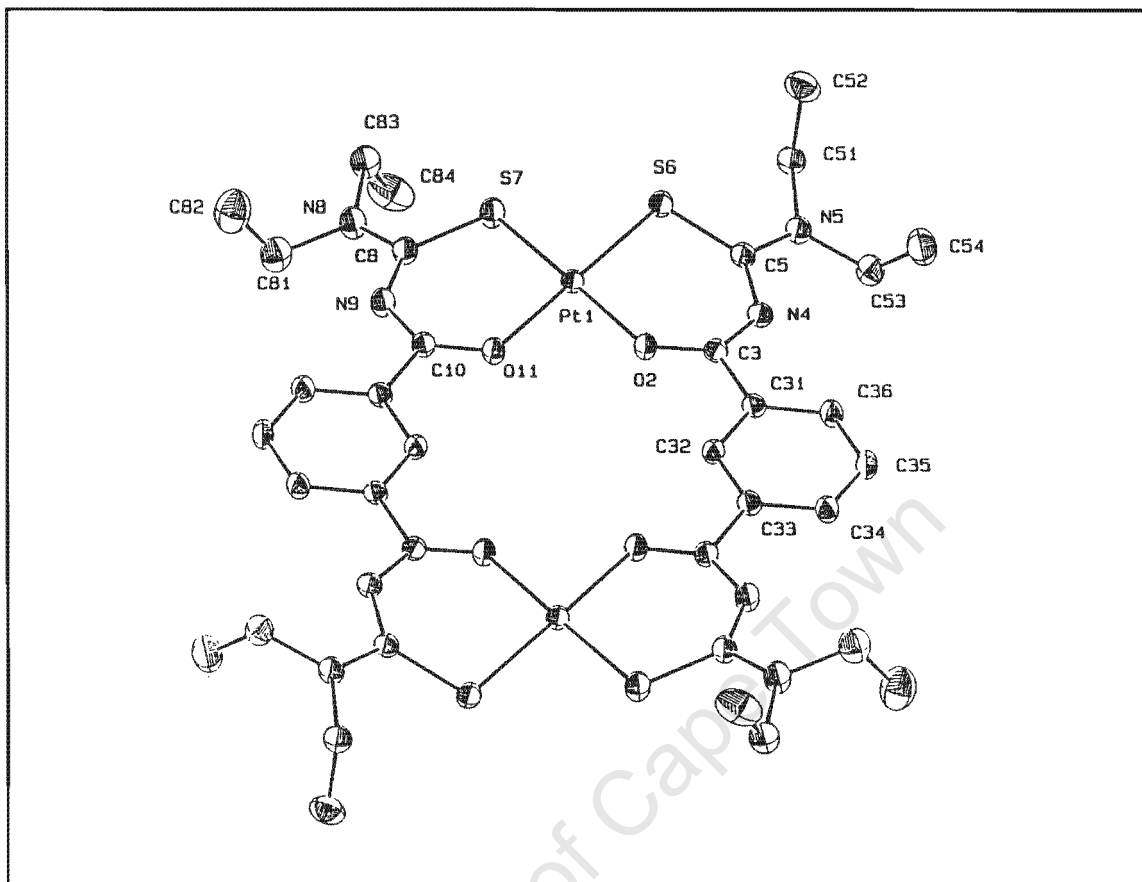
6.8.2.5 Crystal and molecular structure of a 2:2 *cis*-Pt(II) -3,3,3',3'-tetraethyl-1,1'-isophthaloylbis-(thiourea) metallamacrocyclic [Pt(L³⁸-*S,O*)]₂

This complex was sparingly soluble in chloroform, and for dissolution the sample had to be finely ground, and the solvent heated. Crystallisation occurred after cooling, and did not require the addition of ethanol. Unlike the 3:3 [Pt(L³⁷-*S,O*)]₃ compound, this complex did not crystallise with solvent guests in the crystal lattice, and accordingly, the crystals were found to be quite stable once removed from the mother liquor.

The crystal submitted for X-ray crystallography was found to be of the triclinic space group $P\bar{1}$ with one molecule per unit cell (half the molecule in the asymmetric unit). The structure was solved using SHELXS-97 and refined by least squares methods using SHELXL-97^{9,10}. All non-hydrogen atoms were modeled anisotropically, while hydrogen atoms were placed in geometrically calculated positions, and refined with temperature factors 1.2 times those of their parent atoms. The full sets of experimental and refinement parameters, fractional co-ordinates, bond lengths, bond angles, and torsion angles are reported in the tables of Appendix 6. The average bond lengths and bond angles associated with the metal – ligand chelate rings of the structure are also summarised in table 6.7 where they can again be compared to analogous data from the mononuclear square planar [M(L-*S,O*)]₂ type complexes. Bond data recorded for the closely related 2:2 Pd(II) - 3,3,3',3'-tetrabutyl-1,1'-isophthaloylbis(thiourea) metallamacrocyclic ([Pd(L³⁹-*S,O*)]₂ - see section 6.8.2.6) is also listed in these tables.

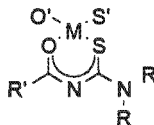
The molecular structure represented in figure 6.14 shows the [Pt(L³⁸-*S,O*)]₂ metallamacrocyclic comprised of two ligands with their chelating moieties bidentately co-ordinated to two Pt(II) centres. As was expected, the four donor atoms around each metal centre are co-ordinated in the *cis* configuration. In each asymmetric unit, the phenyl ring is almost coplanar with the co-ordination plane of the metal (i.e. the plane of the phenyl ring is tilted at 7° to the co-ordination plane). The overall macrocycle is planar, and unlike the 3:3 [Pt(L³⁷-*S,O*)]₃ complex shows no signs of twisting or buckling. With values of 84.3°, 86.3° and 94.7° for the angles O-Pt-O', S-Pt-S' and O-Pt-S respectively (table 6.7), the arrangement of donor atoms around the metal centre is distorted from an ideal square. However, this is not substantially different from the distortion observed in the mononuclear [Pt(L-*S,O*)]₂ complexes, where the angles O-Pt-O', S-Pt-S' and O-Pt-S have average values of 82.6°, 88.4° and 94.5° respectively (see table 6.6). From the bond lengths listed in table 6.7, it is also evident that the bonds associated with the chelating moieties in the [Pt(L³⁸-*S,O*)]₂ complex are all typical for square planar Pt(II) - *N'*-aroylthiourea complexes. Presumably due to their planarity, the molecules were found to pack quite closely in layers parallel to [110]. However, there was no evidence of any strong intermolecular contacts.

Figure 6.14 The molecular structure of the 2:2 *cis*-[3,3,3',3'-tetraethyl-1,1'-terephthaloylbis(thioureato)-platinum(II)]₂ metallamacrocycle ([Pt(L³⁸-S,O)₂]). (Hydrogen atoms have been omitted for clarity)



This Pt(II) – isophthaloylbis(thiourea) complex and the [Pd(L³⁹-S,O)]₂ complex described in the following section (6.8.2.6) appear to be the first [M(L-S,O)]_x type complexes (of the bipodal thioureas) for which the 2:2 metallamacrocyclic structure has been conclusively established. The results are important since it is generally difficult to obtain precise data about the macrocyclic or polymeric structures of these compounds by any other methods of characterisation. In this respect, it is interesting to note that Köhler *et al.*¹ also prepared Ni(II) complexes with isophthaloylbis(thioureas). The products that they obtained were violet powders that melted above 300°C, and they concluded that these complexes were in the form of coordination polymers. However, in very recent work³², the 3,3,3',3'-tetraethyl-1,1'-isophthaloylbis(thiourea) ligand was used to prepare a Ni(II) complex. Although the product obtained from this reaction was also in the form of a violet powder, it was subsequently recrystallised as a green pyridine adduct from a solution of pyridine and acetone. Single crystal diffractometry revealed the compound to be a 2:2 Ni(II) – ligand metallamacrocycle with two axial pyridine ligands weakly bound to each Ni(II) centre (i.e. [Ni(L-S,O)(Py)₂]₂). Pyridine guests were also included in the crystal lattice of this compound. On standing in air, both the axially co-ordinated pyridines, and the pyridine guests were lost, and the green crystals readily reverted back to a friable violet solid.

Table 6.7 Average bond lengths and bond angles associated with the chelating moieties around the Pt(II) centers of the 2:2 *cis*-[3,3,3',3'-tetraethyl-1,1'-isophthaloylbis(thioureato)platinum(II)]₂ metallamacrocycle ([Pt(L³⁸-S,O)]₂) and the 2:2 *cis*-[3,3,3',3'-tetrabutyl-1,1'-isophthaloylbis(thioureato)palladium(II)]₂ metallamacrocycle ([Pd(L³⁹-S,O)]₂) (see section 6.8.2.6). Average bond lengths and angles for the mononuclear, square planar [M(L-S,O)]₂ complexes^{13,14,27-30} are again included for comparison

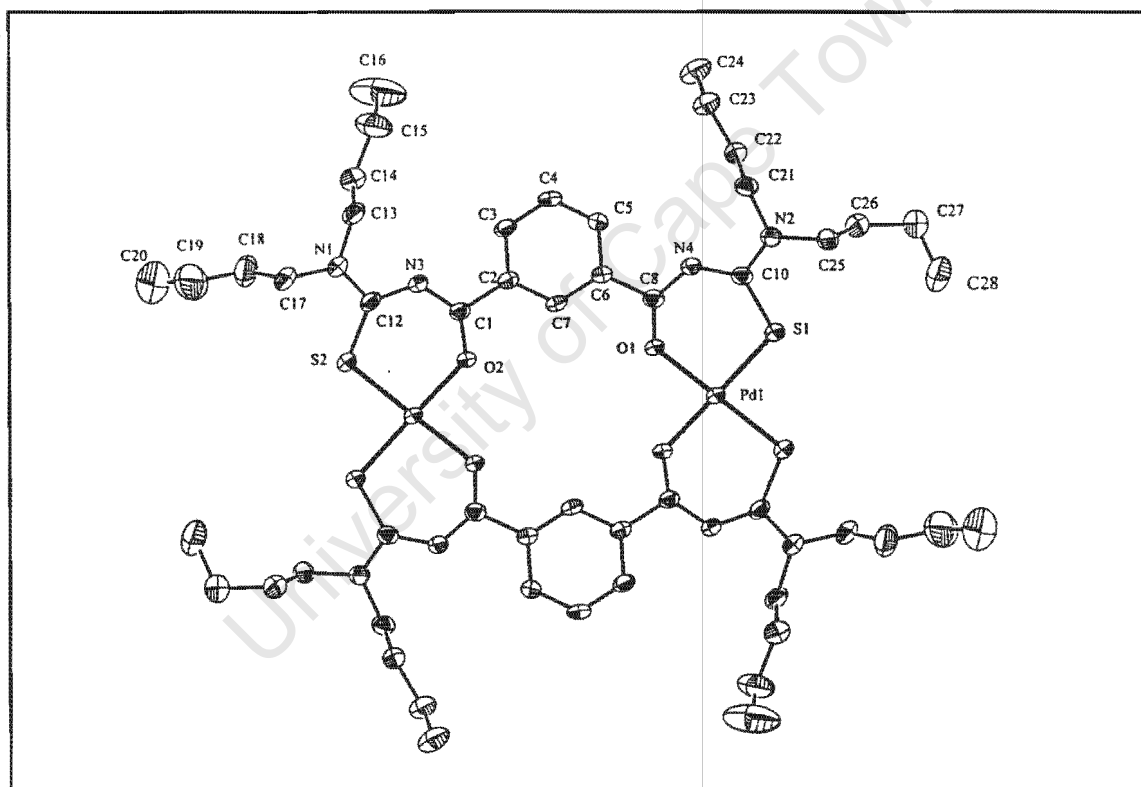
Bond / Angle	Bond Lengths (Å) / Angles (°)		
	[Pt(L ³⁸ -S,O)] ₂	[Pd(L ³⁹ -S,O)] ₂	[M(L-S,O)] average
R—C(O)	1.491	1.492	1.487 (± 0.015)
C=O	1.271	1.272	1.261 (± 0.009)
(O)C≡N'	1.315	1.332	1.318 (±0.011)
N'≡C(S)	1.340	1.341	1.342 (±0.006)
C≡S	1.722	1.740	1.724 (± 0.010)
(S)C—NR ₂	1.340	1.343	1.341 (± 0.010)
O—M	2.035	2.027	2.03 (± 0.05)*
S—M	2.230	2.242	2.248 (± 0.042)*
O—M—O'	84.3	84.7	85.1 (± 0.1)*
S—M—S'	86.3	86.4	87.5 (± 0.7)*
O—M—S/O'—M—S'	94.7	94.5	93.7 (± 0.2)*

* average values of bond lengths and angles involving the metal centres were calculated using values reported for [Pd(L-S,O)]₂ structures only i.e. references 28 and 29. Analogous values for [Pt(L-S,O)]₂ structures are listed in table 6.6

6.8.2.6 Crystal and molecular structure of a 2:2 *cis*-Pd(II) - 3,3,3',3'-tetrabutyl-1,1'-isophthaloylbis-(thiourea) metallamacrocycle [Pd(L³⁹-S,O)₂]

In almost every respect, this Pd(II) complex closely resembled the 2:2 [Pt(L³⁸-S,O)]₂ metallamacrocycle described above. It also crystallised from pure chloroform, in the triclinic space group $P\bar{1}$ with one molecule per unit cell. No solvent molecules were included in the crystal lattice. The structure was solved and refined as described for the [Pt(L³⁸-S,O)]₂ complex (however, to reduce thermal disorder of the butyl chains, the crystallographic data collection was carried out at -60°C)³³. The experimental and refinement parameters, and the full set of structural data can be found in Appendix 7. The average bond lengths and angles associated with the metal centres and chelating moieties of this complex are also listed in table 6.7.

Figure 6.15 The molecular structure of the 2:2 *cis*-[3,3,3',3'-tetrabutyl-1,1'-terephthaloylbis(thioureaato)-palladium(II)]₂ metallamacrocycle ([Pd(L³⁹-S,O)]₂). (Hydrogen atoms have been omitted for clarity)



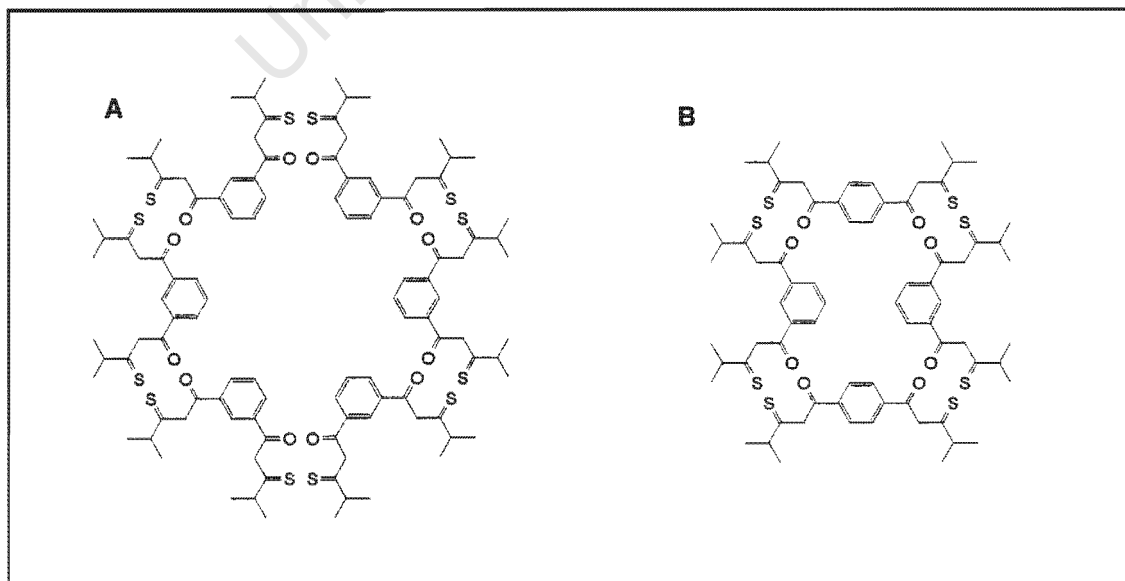
The molecular structure of the [Pt(L³⁹-S,O)]₂ complex (figure 6.15) shows a *cis* co-ordinated 2:2 metal – ligand complex with no significant conformational differences from the structure of the 2:2 [Pt(L³⁸-S,O)]₂ metallamacrocycle. The marked similarities between the two complexes are also evident from the bond lengths and angles listed in table 6.7. It may appear somewhat surprising that the Pt – donor atom and Pd – donor atom bond lengths are so similar for the two complexes. However, in the mononuclear [Pt(L-S,O)] and [Pd(L-S,O)] type complexes of *N*-aroylthioureas, the metal – donor atom bonds are also very similar to each other (compare values in tables 6.6 and 6.7).

6.8.2.7 Larger Pt(II) and Pd(II) metallamacrocycles with iso- and terephthaloylbis(thioureas) ?

For the 2:2 macrocyclisation with Pd(II) and Pt(II), the isophthaloylbis(thiourea) ligands were required to adopt a geometry in which the phenyl ring spacer was essentially in an *anti* orientation relative to the chelating moieties of its sidearms i.e. the donor atoms of the chelating moieties and the phenyl ring were on opposite sides of the ligand's long axis. Had the sidearms with their chelating moieties rotated through 180° at any stage during co-ordination and assembly, the ligands would have been 'V' shaped, with the phenyl ring at the apex of the V, and the donor atoms projecting outward from the sidearms. A simple model, as depicted by diagram A of figure 6.16, suggests that this conformation would have been ideally suited to the assembly of a 6:6 metallamacrocyclic complex (i.e. $[M(L-S,O)]_6$). Unfortunately, with the overwhelming tendency of the isophthaloylbis(thioureas) to form the 2:2 complexes, this form of complex was never detected in the course of this work.

However, in considering the prospects for producing other large macrocyclic $[M(L-S,O)]_x$ complexes, it also became apparent that a 4:4 metallamacrocyclic complex might be obtained by combining equimolar amounts of iso- and terephthaloylbis(thiourea) ligands for co-ordination with Pt(II) or Pd(II). Diagram B in figure 6.16 illustrates how such a mixed ligand complex might be assembled. It shows that the macrocyclic complex would be comprised of four metal centres alternately linked by isophthaloyl- and terephthaloylbis(thiourea) ligands. (Note, that in both structures A and B, *cis* co-ordination of donor atoms would be maintained at each metal centre.)

Figure 6.16 Schematic diagram showing how a 6:6 metallamacrocyclic complex (A) might be formed with isophthaloylbis(thiourea) ligands, and how a 4:4 metallamacrocyclic complex (B) could be produced using an equimolar mixture of tere- and isophthaloylbis(thiourea) for co-ordination with Pt(II) or Pd(II). (For clarity only the ligands and the donor atoms are shown)



The possibility of synthesising a mixed ligand 4:4 complex, was first investigated using the tetrabutyl substituted iso- and terephthaloylbis(thiourea) ligands (H_2L^{37} and H_2L^{39}). 2.5 mmol of each ligand was dissolved in an acetonitrile – water mixture, along with 10 mmol of sodium acetate base (i.e. a sufficient amount to deprotonate all the chelating moieties). This was followed by the addition of Pt(II) (5.0 mmol), also dissolved in an acetonitrile – water solution. The reaction produced a fine yellow precipitate, as anticipated. Unfortunately, however, this product was found to be a two component mixture, consisting of only the 2:2 Pt(II) – isophthaloylbis(thiourea) and the 3:3 Pt(II) – terephthaloylbis(thiourea) complexes ($[Pt(L^{37}-S,O)]_3$ and $[Pd(L^{39}-S,O)]_2$). NMR spectroscopy and TLC separations of crude samples failed to provide any sign of the desired 4:4 complex. On recrystallisation, the 3:3 and 2:2 complexes could be readily separated into their respective crystalline forms.

Although it may seem counterintuitive not to have obtained any mixed ligand complexes with such a closely related pair of ligands, it must be pointed out that effectively the same result was recorded when the reaction was repeated with Pd(II), and when the tetraethyl substituted isophthaloylbis(thiourea) ligand (H_2L^{38}) was used in combination with the tetrabutyl substituted terephthaloylbis(thiourea) (H_2L^{37}) for co-ordination to Pt(II) and Pd(II).

6.8.3 Pt(II) and Pd(II) co-ordination chemistry of the aminebis(aroylthioureas) (H_2L^{42} , H_2L^{44})

Due to poor ligand solubility, the co-ordination reactions with the aminebis(aroylthioureas) were carried out in warmed (60°C), 4 : 1 mixtures of DMF and water (see experimental procedures, section 6.9.3). Under these conditions, the reaction between Pd(II) and the 1,4-bis(*N*-benzoylthiocarbamoyl)piperazine ligand ($L^{42}H_2$) produced an orange coloured, amorphous powder in a crude yield of 94% (calculated against the yield expected for the $[Pd(L^{42}-S,O)]_n$ product). Even in its crude form, this material was found to have a C, H, N, and S content that closely matched the values calculated for the desired $[Pd(L^{42}-S,O)]_n$ complex. IR spectroscopy also provided the typical signs that the ligand had been deprotonated, and that the carbonyl groups were involved in co-ordination to the Pd(II) centres. The product decomposed above 250°C, and without any signs of melting. The reaction between Pt(II) and the ethylenediamine-linked aminebis(aroylthiourea) ligand (H_2L^{44}) produced a yellow amorphous powder. This product was also found to have the C, H, N and S elemental content required for the expected $[Pt(L^{44}-S,O)]_n$ complex. It was recovered in 92% yield (i.e. calculated against the yield expected for the $[Pt(L^{44}-S,O)]_n$ complex) and was found to decompose above 300°C.

Both products were found to be completely insoluble in a range of organic solvents (including hot DMF and hot DMSO) and it was therefore not possible to recrystallise the materials or to prepare solutions for NMR spectroscopy. As with the complexes of the acylbis(thioureas), the question concerning the polymeric or macrocyclic structure of these particular compounds therefore remains unresolved. Köhler *et al.*¹ synthesised Ni(II) and Cu(II) complexes using aminebis(thiourea) ligands. They also found the reaction products to be insoluble in commonly used organic solvents, and regarded this as an indication that the

complexes were in the form of metal co-ordination polymers. However, considering the poor solubilities of the aminebis(thiourea) ligands themselves, it is not inconceivable, that any 2:2 or 3:3 macrocycles would also prove to be quite insoluble.

6.8 Concluding Remarks

To a large extent, the above investigation shows that the bipodal thiourea ligands behave much like their simple *N,N*-dialkyl-*N'*-acyl- and *N'*-aroylthiourea counterparts, and in many respects, the study serves to confirm results reported by Köhler *et al.*¹ and by König *et al.*². However, since the crystal structures and the ¹⁹⁵Pt NMR spectra indicated that donor atoms of the bipodal ligands were also always co-ordinated in *cis* fashion, the formation of any *trans* co-ordinated metal – ligand polymers, as proposed by Köhler *et al.*¹, seems unlikely. Although it was disappointing not to have gained much further insight into the structures of the acylbis(thiourea) complexes and the complexes of the aminebis(thioureas), the iso- and terephthaloylbis(thioureas) were undoubtedly identified as a group of ligands ideally suited to the formation of macrocyclic complexes with the square planar metal ions. With these ligands the possibility of synthesising larger-ring metallamacrocycles (than the 2:2 and 3:3 complexes produced in this work), remains a tantalizing prospect.

For the co-ordination reactions with acylbis(thioureas), it may in future prove useful to employ a higher resolution separation such as high performance liquid chromatography. Such a technique could help to establish with more certainty whether the reaction products are polymeric in nature, or whether they are mixtures of separable macrocyclic complexes. For a more thorough characterisation of the aminebis(thiourea) complexes, it will be necessary to identify and synthesise more soluble ligands and complexes.

6.9 Experimental Procedures and Characterisation

6.9.1 Synthesising the bipodal thioureas

When synthesising the bipodal thioureas using the Douglass and Dains method, a procedure very similar to that described in section 2.6.1 (chapter 2) was followed. For the acyl- and aroylbis(thioureas), the diacid chloride (0.02 mol) was dissolved in anhydrous acetone (75 ml) and added dropwise to a solution of potassium thiocyanate (0.04 mol) in anhydrous acetone (75 ml). This mixture was heated to reflux for 45 minutes and then allowed to cool to room temperature. Secondary amine (0.04 mol), also dissolved in anhydrous acetone (75 ml), was then added at a dropwise rate. After a 10 minute period of stirring, the mixture was heated to reflux for an hour. Essentially the same procedure was used to produce the aminebis(thioureas). The only differences were that 0.04 moles of (monofunctional) acid chloride were reacted with 0.04 moles of potassium thiocyanate. This was then followed by the addition of 0.02 moles of difunctional amine.

For synthesis of the acylbis(thioureas) by Dixon and Hawthorne's method³, *N*-substituted thiourea (0.04 mol) was dissolved in anhydrous acetone (150 ml), along with triethylamine base (0.044 mol). The difunctional acyl chloride (0.02 mol), also in anhydrous acetone (75 ml) was added to the thiourea solution at a dropwise rate. The reaction mixture was then heated to reflux for an hour.

Recrystallisation of bipodal thiourea products was carried out in acetone – water or ethanol – water mixtures, unless the amidic side-products were also of interest. In these instances, the crude product mixtures were separated on Silica Gel 60 columns with 0 – 10% acetone in chloroform solutions as eluents.

6.9.2 Characterisation of the bipodal thioureas and some of the associated amidic side-products

Melting points, elemental microanalyses, and NMR spectra were determined or recorded using the instrumentation and conditions described in section 2.6.2 of chapter 2. For IR spectroscopy samples were pressed into KBr pellets and the spectra recorded on a Perkin Elmer 983 Infrared Spectrophotometer.

3,3,3',3'-tetraethyl-1,1'-adipoylbis(thiourea) (H_2L^{30} – table 6.2a): 68.4% yield, mp 120 – 121°C (lit.²: 122°C), Calculated for $C_{16}H_{30}N_4O_2S_2$: C, 51.30; H, 8.07; N, 14.96; S, 17.14, Found: C, 51.40; H, 8.23; N, 15.05; S, 16.97, NMR $\delta(^1H)$: 1.29 (t, 12H, $-N(CH_2CH_3)_2$), 1.73 (m, 4H, $-(O)CCH_2CH_2CH_2CH_2C(O)-$), 2.41 (t, 4H, $-(O)CCH_2CH_2CH_2CH_2C(O)-$), 3.55 + 3.94 (unres q + unres q, 4H + 4H, $-N(CH_2CH_3)_2$), 8.30 (s, 2H, $>N^H$), $\delta(^{13}C)$: 11.67, 12.97, 24.22, 36.28, 47.66, 169.71, 178.92, IR: $\nu_{CO} = 1662\text{ cm}^{-1}$, $\nu_{NH} = 3276\text{ cm}^{-1}$.

3,3',3'-tetrabutyl-1,1'-adipoylbis(thiourea) (H_2L^{31} – table 6.2a): 78.0% yield, mp 128 – 130°C (lit.²: 128°C), Calculated for $C_{24}H_{46}N_4O_2S_2$: C, 59.20; H, 9.54; N, 11.51; S, 13.17, Found: C, 59.23; H, 9.57; N, 11.62; S, 13.04, NMR $\delta(^1H)$: 0.93 (t, 12H, $-N(CH_2CH_2CH_2CH_3)_2$), 1.33 (br unres m, 8H, $-N(CH_2CH_2CH_2CH_3)_2$), 1.68 (unres m, 4H + 8H, $-(O)CCH_2CH_2CH_2CH_2C(O)-$, $-N(CH_2CH_2CH_2CH_3)_2$), 2.37 (t, 4H, $-(O)CCH_2CH_2CH_2CH_2C(O)-$), 3.45 + 3.90 (br t + br t, 4H + 4H, $-N(CH_2CH_2CH_2CH_3)_2$), 8.21 (s, 2H, $>N'H$), $\delta(^{13}C)$: 13.75, 20.03, 24.20, 28.44, 30.03, 36.30, 53.03, 169.37, 179.30, IR: $\nu_{CO} = 1647\text{ cm}^{-1}$, $\nu_{NH} = 3239\text{ cm}^{-1}$.

3,3',3'-tetrabutyl-1,1'-suberoylbis(thiourea) (H_2L^{32} – table 6.2a): 76.1% yield, mp 80 – 82°C (lit.²: 76°C), Calculated for $C_{26}H_{50}N_4O_2S_2$: C, 60.64; H, 9.81; N, 10.88; S, 12.45, Found: C, 60.75; H, 10.00; N, 11.01; S, 12.22, NMR $\delta(^1H)$: 0.92 (t, 12H, $-N(CH_2CH_2CH_2CH_3)_2$), 1.34 (unres m, 8H + 4H, $-N(CH_2CH_2CH_2CH_3)_2$, $-(O)CCH_2CH_2CH_2CH_2CH_2CH_2C(O)-$), 1.67 (unres m, 8H + 4H, $-N(CH_2CH_2CH_2CH_3)_2$, $-(O)CCH_2CH_2CH_2CH_2CH_2CH_2C(O)-$), 2.34 (t, 4H, $-(O)CCH_2CH_2CH_2CH_2CH_2CH_2C(O)-$), 3.42 + 3.93 (br t + br t, 4H + 4H, $-N(CH_2CH_2CH_2CH_3)_2$), 8.74 (s, 2H, $>N'H$), $\delta(^{13}C)$: 13.73, 20.03, 24.81, 27.99, 28.41, 30.06, 36.10, 53.03, 169.91, 179.55, IR: $\nu_{CO} = 1653\text{ cm}^{-1}$, $\nu_{NH} = 3233\text{ cm}^{-1}$.

3,3'-dimorpholino-1,1'-adipoylbis(thiourea) (H_2L^{33} – table 6.2a): 4.8% yield, mp 176 – 177°C, Calculated for $C_{16}H_{26}N_4O_4S_2$: C, 47.73; H, 6.52; N, 13.92; S, 15.93, Found: C, 47.48; H, 6.58; N, 13.85; S, 16.25, NMR (DMSO- d_6) $\delta(^1H)$: 1.51 (unres m, 4H, $-(O)CCH_2CH_2CH_2CH_2C(O)-$), 2.32 (unres t, 4H, $-(O)CCH_2CH_2CH_2CH_2C(O)-$), 3.45 + 4.10 (br unres t + br unres t, 4H + 4H, $-N<(CH_2CH_2)_2>O$), 3.64 (unres t, 8H, $-N<(CH_2CH_2)_2>O$), 10.24 (s, 2H, $>N'H$), $\delta(^{13}C)$: 24.15, 35.06, 50.93, 65.57, 169.36, 179.11, IR: $\nu_{CO} = 1670\text{ cm}^{-1}$, $\nu_{NH} = 3260\text{ cm}^{-1}$.

3,3',3'-tetramethyl-1,1'-adipoylbis(thiourea) (H_2L^{34} – table 6.2a): 71.4% yield, mp 161 – 163°C, Calculated for $C_{12}H_{22}N_4O_2S_2$: C, 45.25; H, 6.98; N, 17.59; S, 20.14, Found: C, 45.40; H, 7.07; N, 17.56; S, 20.32, NMR $\delta(^1H)$: 1.72 (m, 4H, $-(O)CCH_2CH_2CH_2CH_2C(O)-$), 2.38 (t, 4H, $-(O)CCH_2CH_2CH_2CH_2C(O)-$), 3.18 + 3.43 (s + s, 6H + 6H, $-N(CH_3)_2$), 8.56 (s, 2H, $>N'H$), $\delta(^{13}C)$: 24.22, 36.20, 43.18, 44.06, 169.00, 179.74.

3,3'-dipiperidyl-1,1'-adipoylbis(thiourea) (H_2L^{35} – table 6.2a): 58.7% yield, mp 161 – 162°C, Calculated for $C_{18}H_{30}N_4O_2S_2$: C, 54.23; H, 7.60; N, 14.06; S, 16.09, Found: C, 54.40; H, 7.92; N, 14.00; S, 15.85, NMR $\delta(^1H)$: 1.68 (unres m, 4H + 12H, $-(O)CCH_2CH_2CH_2CH_2C(O)-$, $-N<(CH_2CH_2)_2>CH_2$), 2.35 (unres t, 4H, $-(O)CCH_2CH_2CH_2CH_2C(O)-$), 3.50 + 4.05 (br unres t + br unres t, 4H + 4H, $-N<(CH_2CH_2)_2>CH_2$), 8.80 (s, 2H, $>N'H$), $\delta(^{13}C)$: 23.82, 24.28, 25.64, 36.22, 52.77, 168.94, 177.87.

3,3',3'-tetramethyl-1,1'-succinylbis(thiourea) (H_2L^{36} – table 6.2a): 15.0% yield, mp 160 – 162°C, Calculated for $C_{10}H_{18}N_4O_2S_2$: C, 41.35; H, 6.26; N, 19.29; S, 22.08, Found: C, 41.46; H, 6.46; N, 19.45; S,

21.98, NMR (DMSO-*d*₆) $\delta(^1\text{H})$: 2.55 (s, 4H, $-(\text{O})\text{CCH}_2\text{CH}_2\text{C}(\text{O})-$), 3.04 + 3.31 (s + s, 6H + 6H, $-\text{N}(\text{CH}_3)_2$), 10.45 (s, 2H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 29.97, 42.00, 43.03, 168.57, 179.96.

1-(*N,N*-dimethylthiocarbamoyl)succinimide (see figure 6.3): 63.1% yield, mp 143 – 145°C, Calculated for $\text{C}_7\text{H}_{10}\text{N}_2\text{O}_2\text{S}$: C, 45.14; H, 5.42; N, 15.04; S, 17.23, Found: C, 45.13; H, 5.67; N, 15.44; S, 17.38, NMR $\delta(^1\text{H})$: 2.84 (s, 4H, $-(\text{O})\text{CCH}_2\text{CH}_2\text{C}(\text{O})-$), 3.14 + 3.49 (s + s, 3H + 3H, $-\text{N}(\text{CH}_3)_2$), $\delta(^{13}\text{C})$: 28.79, 41.62, 43.85, 172.97, 175.01.

3,3,3',3'-tetrabutyl-1,1'-terephthaloylbis(thiourea) (H_2L^{37} – table 6.2b): 94.0% yield, mp 154 – 155°C, Calculated for $\text{C}_{26}\text{H}_{42}\text{N}_4\text{O}_2\text{S}_2$: C, 61.61; H, 8.37; N, 11.06; S, 12.65, Found: C, 61.82; H, 8.47; N, 11.23; S, 12.68, NMR $\delta(^1\text{H})$: 0.90 + 0.98 (t + t, 6H + 6H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.31 + 1.42 (m + m, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.67 + 1.79 (m + m, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 3.51 + 3.96 (t + t, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 7.91 (s, 4H, $\emptyset$), 8.47 (br s, 2H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 13.71, 13.82, 20.03, 28.41, 30.14, 53.13, 53.32, 128.28, 136.36, 162.49, 179.18.

3,3,3',3'-tetraethyl-1,1'-isophthaloylbis(thiourea) (H_2L^{38} – table 6.2b): 86.7% yield, mp 141 – 143°C, Calculated for $\text{C}_{18}\text{H}_{26}\text{N}_4\text{O}_2\text{S}_2$: C, 54.78; H, 6.65; N, 14.20; S, 16.25, Found: C, 54.93; H, 6.76; N, 14.40; S, 16.44, NMR $\delta(^1\text{H})$: 1.29 + 1.33 (t + t, 6H + 6H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.58 + 4.00 (q + q, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 7.50 (t, 1H, $\emptyset$), 7.95 (d, 2H, $\emptyset$), 8.26 (s, 1H, $\emptyset$), 9.29 (br s, 2H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 11.59, 13.44, 47.64, 47.91, 126.60, 129.38, 132.52, 132.89, 163.23, 179.12.

3,3,3',3'-tetrabutyl-1,1'-isophthaloylbis(thiourea) (H_2L^{39} – table 6.2b): 79.3% yield, mp 100 – 103°C, Calculated for $\text{C}_{26}\text{H}_{42}\text{N}_4\text{O}_2\text{S}_2$: C, 61.61; H, 8.37; N, 11.06; S, 12.65, Found: C, 61.50; H, 8.46; N, 11.13; S, 12.55, NMR $\delta(^1\text{H})$: 0.88 + 0.97 (t + t, 6H + 6H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.27 + 1.42 (m + m, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.66 + 1.76 (m + m, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 3.50 + 3.95 (t + t, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 7.53 (t, 1H, $\emptyset$), 7.98 (d, 2H, $\emptyset$), 8.23 (s, 1H, $\emptyset$), 9.03 (br s, 2H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 13.70, 13.82, 20.08, 28.35, 30.16, 52.99, 53.33, 126.58, 129.52, 132.30, 133.13, 162.89, 179.44.

3,3'-dipiperidyl-1,1'-terephthaloylbis(thiourea) (H_2L^{40} – table 6.2b): 5.3% yield, mp 163 – 165°C, Calculated for $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_2\text{S}_2$: C, 57.38; H, 6.27; N, 13.39; S, 15.32, Found: C, 57.06; H, 6.44; N, 13.21; S, 15.24, NMR $\delta(^1\text{H})$: 1.74 (unres m, 12H, $-\text{N}(\text{CH}_2\text{CH}_2)_2>\text{CH}_2$), 3.61 + 4.17 (unres t + unres t, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2)_2>\text{CH}_2$), 7.93 (s, 4H, $\emptyset$), 8.50 (br s, 2H, $>\text{N}'\text{H}$), $\delta(^{13}\text{C})$: 23.81, 25.25, 26.05, 52.89, 128.31, 136.36, 161.96, 177.61.

1-piperidyl-1'-(*N*-piperidylthiocarbamoyl)terephthalamide (see figure 6.4): 43.9% yield, mp 139 – 142°C, Calculated for $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_2\text{S}$: C, 63.46; H, 7.02; N, 11.60; S, 8.92, Found: C, 63.17; H, 7.19; N, 11.41; S, 8.69, NMR $\delta(^1\text{H})$: 1.61 (unres m, 6H + 6H, $(\text{O})\text{C}-\text{N}(\text{CH}_2\text{CH}_2)_2>\text{CH}_2$, $(\text{S})\text{C}-\text{N}(\text{CH}_2\text{CH}_2)_2>\text{CH}_2$), 3.26 + 3.70 (unres t + unres t, 2H + 2H, $(\text{O})\text{C}-\text{N}(\text{CH}_2\text{CH}_2)_2>\text{CH}_2$), 3.59 + 4.15 (unres t + unres t, 2H + 2H,

(S)C-N<(CH₂CH₂)₂>CH_{2\delta(^{13}\text{C}): 23.82, 24.4, 25.24, 25.54, 25.98, 26.47, 127.16, 128.03, 133.23, 140.79, 162.51, 168.84, 178.01.}

1,1'-dipiperidylterephthalamide (see figure 6.4): 41.5% yield, mp 193 – 196°C, Calculated for C₁₈H₂₄N₂O₂: C, 71.95; H, 8.07; N, 9.33, Found: C, 71.47; H, 8.04; N, 9.02, NMR $\delta(^1\text{H})$: 1.50 (unres m, 4H, -N<(CH₂CH₂)₂>CH₂), 1.66 (unres m, 8H, -N<(CH₂CH₂)₂>CH₂), 3.31 + 3.69 (unres t + unres t, 4H + 4H, -N<(CH₂CH₂)₂>CH₂), 7.40 (s, 4H, Ø), $\delta(^{13}\text{C})$: 24.48, 25.64, 26.43, 43.10, 48.69, 126.84, 137.50, 169.53.

1,4-bis(*N*-butanoylthiocarbamoyl)piperazine (H₂L⁴¹ – table 6.2c): 12.1% yield, mp 168 – 170°C, Calculated for C₁₄H₂₄N₄O₂S₂: C, 48.80; H, 7.04; N, 16.26; S, 18.62, Found: C, 48.92; H, 7.19; N, 16.22; S, 18.15, NMR $\delta(^1\text{H})$: 0.98 (t, 6H, (O)CCH₂CH₂CH₃), 1.69 (m, 4H, (O)CCH₂CH₂CH₃), 2.32 (t, 4H, (O)CCH₂CH₂CH₃), 3.6 – 4.3 (v br s, 8H, -N<(CH₂CH₂)₂>N-), 8.02 (s, 2H, >N'H), $\delta(^{13}\text{C})$: 13.64, 18.48, 38.97, 50.25, 169.06, 179.41, IR: ν_{CO} = 1676 cm⁻¹, ν_{NH} = 3258 cm⁻¹.

1-(*N*-butanoylthiocarbamoyl)-4-butanoylpiperazine (see figure 6.5): 38.0% yield, oil, Calculated for C₁₃H₂₃N₃O₂S: C, 54.69; H, 8.14; N, 14.72; S, 11.23, Found: C, 54.34; H, 8.31; N, 14.85; S, 11.52, NMR $\delta(^1\text{H})$: 0.97 (t, 6H, (O)CCH₂CH₂CH₃), 1.65 (m, 4H, (O)CCH₂CH₂CH₃), 2.32 (t, 4H, (O)CCH₂CH₂CH₃), 3.6 – 4.3 (v br unres, 4H, -(S)CN<(CH₂CH₂)₂>NC(O)-), 3.65 + 3.77 (t + t, 2H + 2H, -(S)CN<(CH₂CH₂)₂>NC(O)-), 8.26 + 8.29 (s + s, 1H, >N'H), $\delta(^{13}\text{C})$: 13.63, 13.91, 18.47, 18.57, 35.16, 38.88, 40.68, 44.44, 50.18, 51.32, 169.19, 171.82, 179.43.

1,4-dibutanoylpiperazine (see figure 6.5): 47.6% yield, oil, Calculated for C₁₂H₂₂N₂O₂: C, 63.67; H, 9.82; N, 12.38, Found: C, 63.04; H, 9.98; N, 12.41, NMR $\delta(^1\text{H})$: 0.95 (t, 6H, (O)CCH₂CH₂CH₃), 1.64 (m, 4H, (O)CCH₂CH₂CH₃), 2.30 (t, 4H, (O)CCH₂CH₂CH₃), 3.46 + 3.59 (t + t, 4H + 4H, -N<(CH₂CH₂)₂>N-), $\delta(^{13}\text{C})$: 13.88, 18.58, 35.13, 41.48, 45.29, 171.87.

1,4-bis(*N*-benzoylthiocarbamoyl)piperazine (H₂L⁴² – table 6.2c): 72.6% yield, mp 190 – 193°C (lit¹: 184 – 186°C), Calculated for C₂₀H₂₀N₄O₂S₂: C, 58.22; H, 4.90; N, 13.58; S, 15.55, Found: C, 58.07; H, 4.91; N, 13.60; S, 15.43, NMR (DMSO-*d*₆) $\delta(^1\text{H})$: 3.7 – 4.3 (v br d, 8H, -N<(CH₂CH₂)₂>N-), 7.54 (m, 6H, Ø), 7.95 (d, 4H, Ø), 10.90 (s, 2H, >N'H), $\delta(^{13}\text{C})$: 48.35, 128.25, 132.41, 164.06, 180.26, IR: ν_{CO} = 1680 cm⁻¹, ν_{NH} = 3304 cm⁻¹.

1,4-dimethyl-1,4-bis(*N*-butanoylthiocarbamoyl)ethylenediamine (H₂L⁴³ – table 6.2c): 32.0% yield, mp 156 – 158°C, Calculated for C₁₄H₂₆N₄O₂S₂: C, 48.51; H, 7.58; N, 16.17; S, 18.51, Found: C, 48.36; H, 7.96; N, 15.77; S, 18.32, NMR $\delta(^1\text{H})$: 0.98 (t, 6H, (O)CCH₂CH₂CH₃), 1.70 (m, 4H, (O)CCH₂CH₂CH₃), 2.31 (t, 4H, (O)CCH₂CH₂CH₃), 3.28 (s, 6H, -N(CH₃)CH₂CH₂(CH₃)N-), 4.20 (br s, 4H, -N(CH₃)CH₂CH₂(CH₃)N-), 7.88 (s, 2H, >N'H), $\delta(^{13}\text{C})$: 13.64, 8.53, 38.85, 42.22, 51.75, 169.42, 180.71.

1-methyl-1-(*N*-butanoylthiocarbamoyl)-4-methyl-4-butanylethylenediamine (see figure 6.6)*: 28.9% yield, oil, Calculated for $C_{13}H_{25}N_3O_2S$: C, 54.31; H, 8.78; N, 14.62; S, 11.15, Found: C, 54.25; H, 9.06; N, 14.75; S, 11.02, NMR $\delta(^1H)$: 0.98 (t, 6H, (O)CCH₂CH₂CH₃), 1.63 (m, 4H, (O)CCH₂CH₂CH₃), 2.27 (m, 4H, (O)CCH₂CH₂CH₃), 2.97 + 3.07 + 3.16 + 3.17 (s + s + s + s, 6H, -(S)CN(CH₃)CH₂CH₂(CH₃)NC(O)-), 3.69 + 4.02 (m + m, 4H, -(S)CN(CH₃)CH₂CH₂(CH₃)NC(O)-), 8.37 + 8.52 (s + s, H, >N'H), $\delta(^{13}C)$: 13.62, 13.91, 18.27, 18.53, 18.85, 33.78, 34.80, 35.38, 36.54, 38.75, 41.73, 42.15, 44.30, 45.51, 53.22, 53.93, 169.54, 173.65, 180.43.

1,4-dimethyl-1,4-dibutanylethylenediamine (see figure 6.6)*: 18.6% yield, oil, Calculated for $C_{12}H_{24}N_2O_2 \cdot H_2O$: C, 58.49; H, 10.66; N, 11.37, Found: C, 58.88; H, 11.07; N, 11.90, NMR $\delta(^1H)$: 0.89 (t, 6H, (O)CCH₂CH₂CH₃), 1.57 (m, 4H, (O)CCH₂CH₂CH₃), 2.20 (m, 4H, (O)CCH₂CH₂CH₃), 2.92 + 2.98 (s + s, 6H, -N(CH₃)CH₂CH₂(CH₃)N-), 3.43 + 3.48 (s + s, 4H, -N(CH₃)CH₂CH₂(CH₃)N-), $\delta(^{13}C)$: 13.89, 18.32, 18.77, 33.61, 35.37, 35.63, 36.87, 44.58, 46.96, 47.27, 173.36.

1,4-dimethyl-1,4-bis(*N*-benzoylthiocarbamoyl)ethylenediamine (H_2L^{44} – table 6.2c)*: 94.7% yield, mp 174 – 177°C, Calculated for $C_{20}H_{22}N_4O_2S_2$: C, 57.94; H, 5.36; N, 13.52; S, 15.47, Found: C, 57.71; H, 5.44; N, 13.20; S, 15.10, NMR (DMSO-*d*₆) $\delta(^1H)$: 3.12 + 3.26 + 3.49 (s + s + s, 6H, -N(CH₃)CH₂CH₂(CH₃)N-), 3.96 + 4.17 + 4.29 (t + t + s, 4H, -N(CH₃)CH₂CH₂(CH₃)N-), 7.53 (m, 6H, $\emptyset$), 7.93 (d, 4H, $\emptyset$), 10.78 (s, 2H, >N'H), $\delta(^{13}C)$ †: 41.91, 49.40, 50.82, 52.44, 128.33, 132.43, 164.02, 181.85, IR: ν_{CO} = 1680 cm⁻¹, ν_{NH} = 3197 cm⁻¹.

* ¹H and ¹³C NMR spectra complicated since compounds exist in more than one isomeric form.

† ¹³C peaks near 40 ppm obscured by resonance signals of the DMSO-*d*₆ solvent

6.9.3 Synthesising the [Pd(L-S,O)]_x and [Pt(L-S,O)]_x complexes

For the co-ordination reactions carried out in acetonitrile – water mixtures, the following procedure was used: bipodal thiourea ligand (0.5 mmol) was dissolved in acetonitrile (20 ml). Sodium acetate (1.1 mmol) was dissolved in water (10 ml) and added to the ligand solution. Potassium tetrachloropalladate or potassium tetrachloropalladite (0.5 mmol) was dissolved in water (15 ml) and diluted with an equivalent volume (15 ml) of acetonitrile. The metal solution was then added at a dropwise rate to the ligand solution, after which the mixture was left to stir for 12 hours. It was then diluted with water (60 ml), and left to stand in at 4°C for a further 12 hours. Products were recovered by centrifugation and where possible recrystallised from ethanol – chloroform solutions or from pure chloroform.

The reactions with the poorly soluble ligands were carried out in DMF – water mixtures. To begin with, the ligand was dissolved in 50 ml of warm (50 – 60°C) DMF. This was followed by the addition of the 10 ml aliquot of water containing the sodium acetate base. The metal salts were dissolved in 10 ml of water and diluted with 10 ml DMF before being added at a slow dropwise rate to the ligand solution. The entire

mixture was left to stir for a further 24 hours, with the temperature maintained between 50 and 60°C. After this period, the mixture was diluted with an equivalent volume of water (80 ml) and left to stand at 4°C for a further 24 hours. The products, usually in the form of insoluble powders, were recovered by centrifugation and washed with warm ethanol.

6.9.4 Characterising the $[\text{Pd}(\text{L}-\text{S},\text{O})]_x$ and $[\text{Pt}(\text{L}-\text{S},\text{O})]_x$ complexes

Melting points, elemental microanalyses, and ^1H and ^{13}C NMR spectra were determined or recorded using the instrumentation and conditions described in section 2.6.2 of chapter 2. ^{195}Pt spectra were once again recorded using a Varian UNITY-400 spectrometer, operating under the condition described in chapter 5 (section 5.6.2). IR spectra were recorded as explained in section 6.9.2 above, but only to confirm that ν_{NH} bands were absent and that ν_{CO} bands were characteristically shifted (thus, no IR data is listed below).

cis-[(3,3,3',3'-tetraethyl-1,1'-adipoylbis(thioureato))platinum(II)] $_x$ ($[\text{Pt}(\text{L}^{30}-\text{S},\text{O})]_x$ – table 6.4a): 84.0% yield, mp 120 – 140°C, Calculated for $\text{C}_{16}\text{H}_{28}\text{N}_4\text{O}_2\text{PtS}_2$: C, 33.85; H, 4.98; N, 9.87; S, 11.20, Found: C, 33.41; H, 4.94; N, 9.57; S, 10.91, NMR $\delta(^1\text{H})$: 1.14 + 1.26 (t + t, 6H + 6H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.68 (m, 4H, $-(\text{O})\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 2.32 (t, 4H, $-(\text{O})\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 3.65 (unres q, 8H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), $\delta(^{13}\text{C})$: 12.42, 12.97, 26.23, 40.35, 45.51, 46.56, 166.13, 177.48, $\delta(^{195}\text{Pt})$: -2750, -2741.

[(3,3,3',3'-tetraethyl-1,1'-adipoylbis(thioureato))palladium(II)] $_x$ ($[\text{Pd}(\text{L}^{30}-\text{S},\text{O})]_x$ – table 6.4a): 85.6% yield, mp 90 – 100°C, Calculated for $\text{C}_{16}\text{H}_{28}\text{N}_4\text{O}_2\text{PdS}_2$: C, 40.11; H, 5.90; N, 11.70; S, 13.39, Found: C, 40.54; H, 5.72; N, 11.68; S, 12.85, NMR $\delta(^1\text{H})$: 1.15 + 1.26 (t + t, 6H + 6H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.66 (m, 4H, $-(\text{O})\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 2.40 (unres t, 4H, $-(\text{O})\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 3.65 + 3.76 (q + q, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), $\delta(^{13}\text{C})$: 12.60, 12.94, 26.47, 39.89, 45.48, 46.74, 170.02, 180.00.

cis-[(3,3,3',3'-tetrabutyl-1,1'-adipoylbis(thioureato))platinum(II)] $_x$ ($[\text{Pt}(\text{L}^{31}-\text{S},\text{O})]_x$ – table 6.4a): 87.2% yield, mp 55 – 65°C, Calculated for $\text{C}_{24}\text{H}_{44}\text{N}_4\text{O}_2\text{PtS}_2$: C, 42.39; H, 6.54; N, 8.24; S, 9.43, Found: C, 42.95; H, 6.75; N, 8.53; S, 9.49, NMR $\delta(^1\text{H})$: 0.90 + 0.94 (t + t, 6H + 6H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.33 (m, 8H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.64 (unres m, 4H + 8H, $-(\text{O})\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 2.37 (unres t, 4H, $-(\text{O})\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})-$), 3.55 (unres t, 8H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), $\delta(^{13}\text{C})$: 13.82, 13.97, 20.26, 26.40, 29.26, 29.88, 40.42, 50.98, 52.19, 166.57, 177.20, $\delta(^{195}\text{Pt})$: -2751, -2741.

* In the names like *cis*-[(3,3,3',3'-tetraethyl-1,1'-adipoylbis(thioureato))platinum(II)] $_x$ the subscript 'x' serves to indicate uncertainty about the metallamacrocyclic or polymeric nature of the complexes. Also, the prefix '*cis*' is only included for complexes where *cis* configuration of the donor atoms was confirmed by ^{195}Pt NMR spectroscopy or from the crystal structures.

[(3,3,3',3'-tetrabutyl-1,1'-adipoylbis(thioureato))palladium(II)]_x ([Pd(L³¹-S,O)]_x – table 6.4a): 91.0% yield, mp 50 – 60°C, Calculated for C₂₄H₄₄N₄O₂PdS₂: C, 48.75; H, 7.52; N, 9.48; S, 10.14, Found: C, 48.95; H, 7.21; N, 9.25; S, 10.54, NMR δ(¹H): 0.90 + 0.94 (t + t, 6H + 6H, -N(CH₂CH₂CH₂CH₃)₂), 1.31 (m, 8H, -N(CH₂CH₂CH₂CH₃)₂), 1.61 (unres m, 4H + 8H, -(O)CCH₂CH₂CH₂CH₂C(O)-, -N(CH₂CH₂CH₂CH₃)₂), 2.42 (unres t, 4H, -(O)CCH₂CH₂CH₂CH₂C(O)-), 3.61 + 3.64 (t + t, 4H + 4H, -N(CH₂CH₂CH₂CH₃)₂), δ(¹³C): 13.81, 20.22, 25.91, 29.48, 29.85, 39.95, 50.90, 52.38, 170.60, 179.87.

cis-[(3,3,3',3'-tetrabutyl-1,1'-suberoylbis(thioureato))platinum(II)]_x ([Pt(L³²-S,O)]_x – table 6.4a): 82.4% yield, mp 45 – 55°C, Calculated for C₂₆H₄₈N₄O₂PtS₂: C, 44.10; H, 6.85; N, 7.92; S, 9.06, Found: C, 43.72; H, 6.87; N, 7.78; S, 8.60, NMR δ(¹H): 0.89 + 0.93 (t + t, 6H + 6H, -N(CH₂CH₂CH₂CH₃)₂), 1.31 (m, 8H, -N(CH₂CH₂CH₂CH₃)₂), 1.50 – 1.80 (unres m, 8H + 8H, -N(CH₂CH₂CH₂CH₃)₂), -(O)CCH₂CH₂CH₂CH₂CH₂C(O)-, 2.30 (t, 4H, -(O)CCH₂CH₂CH₂CH₂CH₂C(O)-), 3.58 (t, 8H, -N(CH₂CH₂CH₂CH₃)₂), δ(¹³C): 13.81, 20.22, 26.55, 29.27, 29.85, 40.53, 50.91, 52.16, 166.56, 177.52, δ(¹⁹⁵Pt): -2753.

[(3,3,3',3'-tetrabutyl-1,1'-suberoylbis(thioureato))palladium(II)]_x ([Pd(L³²-S,O)]_x – table 6.4a): 93.0% yield, mp 60 – 70°C, Calculated for C₂₆H₄₈N₄O₂PdS₂: C, 50.42; H, 7.83; N, 9.05; S, 10.36, Found: C, 50.16; H, 7.93; N, 8.79; S, 10.13, NMR δ(¹H): 0.90 + 0.93 (t + t, 6H + 6H, -N(CH₂CH₂CH₂CH₃)₂), 1.32 (m, 8H, -N(CH₂CH₂CH₂CH₃)₂), 1.45 – 1.75 (unres m, 8H + 8H, -N(CH₂CH₂CH₂CH₃)₂), -(O)CCH₂CH₂CH₂CH₂CH₂C(O)-, 2.38 (t, 4H, -(O)CCH₂CH₂CH₂CH₂CH₂C(O)-), 3.60 + 3.64 (t + t, 4H + 4H, -N(CH₂CH₂CH₂CH₃)₂), δ(¹³C): 13.84, 20.23, 26.47, 28.93, 29.51, 29.87, 40.03, 50.96, 52.38, 170.61, 179.92.

cis-[(3,3,3',3'-tetrabutyl-1,1'-terephthaloylbis(thioureato))platinum(II)]₃ ([Pt(L³⁷-S,O)]₃ – table 6.4b): 95.4% yield, mp 295 – 296°C, Calculated for (C₂₆H₄₀N₄O₂PtS₂)₃: C, 44.61; H, 5.77; N, 8.01; S, 9.16, Found: C, 44.80; H, 5.85; N, 8.10; S, 9.05, NMR δ(¹H): 0.94 + 0.98 (t + t, 6H + 6H, -N(CH₂CH₂CH₂CH₃)₂), 1.39 (m, 8H, -N(CH₂CH₂CH₂CH₃)₂), 1.73 (m, 8H, -N(CH₂CH₂CH₂CH₃)₂), 3.69 + 3.77 (t + t, 4H + 4H, -N(CH₂CH₂CH₂CH₃)₂), 8.32 (s, 4H, Ø), δ(¹³C): 13.88, 20.33, 29.26, 29.88, 51.60, 52.62, 129.14, 140.09, 167.09, 167.65, δ(¹⁹⁵Pt): -2719.

[(3,3,3',3'-tetrabutyl-1,1'-terephthaloylbis(thioureato))palladium(II)]_x ([Pd(L³⁷-S,O)]_x – table 6.4b): 90.9% yield, mp 275 – 277°C, Calculated for C₂₆H₄₀N₄O₂PdS₂: C, 51.08; H, 6.61; N, 9.17; S, 10.49, Found: C, 51.29; H, 6.81; N, 9.27; S, 10.37, NMR δ(¹H): 0.94 + 0.98 (t + t, 6H + 6H, -N(CH₂CH₂CH₂CH₃)₂), 1.40 (m, 8H, -N(CH₂CH₂CH₂CH₃)₂), 1.70 + 1.76 (m + m, 4H + 4H, -N(CH₂CH₂CH₂CH₃)₂), 3.76 + 3.81 (t + t, 4H + 4H, -N(CH₂CH₂CH₂CH₃)₂), 8.31 (s, 4H, Ø), δ(¹³C): 13.79, 20.25, 29.46, 29.89, 51.67, 52.77, 129.28, 139.70, 169.75, 171.30.

cis-[(3,3,3',3'-tetraethyl-1,1'-isophthaloylbis(thioureato))platinum(II)]₂ ([Pt(L³⁸-S,O)]₂ – table 6.4b): 89.6% yield, no melting observed, decomposes above 300°C, Calculated for (C₁₈H₂₄N₄O₂PtS₂)₂: C, 36.79;

H, 4.12; N, 9.54; S, 10.91, Found: C, 37.15; H, 4.09; N, 9.61; S, 11.16, NMR $\delta(^1\text{H})$: 1.28 + 1.35 (t + t, 6H + 6H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.77 + 3.84 (q + q, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 7.35 (t, 1H, $\emptyset$), 8.39 (d, 2H, $\emptyset$), 9.30 (s, 1H, $\emptyset$).

[(3,3,3',3'-tetrabutyl-1,1'-isophthaloylbis(thioureato))platinum(II)]_x ([Pt(L³⁹-S,O)]_x – table 6.4b): 93.3% yield, mp 255 – 257°C, Calculated for C₂₆H₄₀N₄O₂PtS₂: C, 44.61; H, 5.77; N, 8.01; S, 9.16, Found: C, 44.57; H, 5.94; N, 8.22; S, 9.06, NMR $\delta(^1\text{H})$: 0.93 + 0.98 (t + t, 6H + 6H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.39 (m, 8H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.70 (m, 8H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 3.68 + 3.77 (t + t, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 7.32 (t, 1H, $\emptyset$), 8.39 (d, 2H, $\emptyset$), 9.29 (s, 1H, $\emptyset$), $\delta(^{13}\text{C})$: 13.87, 20.33, 29.30, 29.96, 51.43, 52.55, 127.13, 130.97, 132.36, 137.81, 167.15, 167.62.

cis-[(3,3,3',3'-tetrabutyl-1,1'-isophthaloylbis(thioureato))palladium(II)]₂ ([Pd(L³⁹-S,O)]₂ – table 6.4b): 94.7% yield, mp 251 – 255°C, Calculated for (C₂₆H₄₀N₄O₂PdS₂)₂: C, 51.08; H, 6.61; N, 9.17; S, 10.49, Found: C, 50.94; H, 6.89; N, 9.21; S, 10.33, NMR $\delta(^1\text{H})$: 0.94 + 0.99 (t + t, 6H + 6H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.39 (m, 8H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.68 + 1.76 (m + m, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 3.76 + 3.80 (t + t, 4H + 4H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 7.33 (t, 1H, $\emptyset$), 8.34 (d, 2H, $\emptyset$), 9.27 (s, 1H, $\emptyset$), $\delta(^{13}\text{C})$: 13.82, 20.26, 29.46, 29.93, 51.49, 52.70, 126.81, 131.40, 132.73, 137.14, 169.68, 171.18.

[(1,4-bis(*N*-benzoylthiocarbamoyl)piperazine)palladium(II)]_x ([Pd(L⁴²-S,O)]_x – table 6.4c): 94% yield, no melting observed, decomposes above 250°C, Calculated for C₂₀H₁₈N₄O₂PdS₂: C, 46.46; H, 3.52; N, 10.84; S, 12.41, Found: C, 45.97; H, 3.68; N, 10.65; S, 12.83.

[(1,4-dimethyl-1,4-bis(*N*-benzoylthiocarbamoyl)ethylenediamine)platinum(II)]_x ([Pt(L⁴⁴-S,O)]_x – table 6.4c): 92% yield, no melting observed, decomposes above 300°C, Calculated for C₂₀H₁₈N₄O₂PtS₂: C, 39.53; H, 3.32; N, 9.22; S, 10.56, Found: C, 40.36; H, 3.31; N, 9.38; S, 10.72.

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Conclusion and further Prospects

Although some of the experimental work carried out in the course of this study was of a repetitive nature, the results consistently contributed to a better understanding of the synthesis and co-ordination chemistry of the *N*-substituted *N'*-acyl- and *N'*-aroylthioureas. On a number of occasions, the new insights resulted in exciting and rewarding breakthroughs. Inevitably, however, there were also some questions to which the experimental results did not provide adequate answers, and it became evident that a number of aspects will require further investigation.

As far as the Douglass and Dains synthesis is concerned, it was surprising to find just how prevalent the problem of amide side-product formation was, not only in the acyl isothiocyanate – amine reactions, but also in the reactions with the benzoyl isothiocyanates. It was therefore very pleasing to establish that the steric properties of the reagents played such a vital role in determining the outcome of each reaction. A distinct highlight in this regard, was recognising the astounding steric influence of β methylene groups and their hydrogens on the nucleophilic reactivity of the dialkylamines. The cyclic amines are very rarely distinguished from the other secondary amines on the basis of this steric property, and one cannot help wondering how many failed organic reactions might have succeeded had it been for the selection of an amine nucleophile with the appropriate geometry.

The benzoyl isothiocyanate – amine reactions also provided an insight into the important role of electronic effects in the Douglass and Dains synthesis. For one, it has been established that *N'*-benzoylthiourea yields can be significantly improved by using moderately, rather than strongly basic amines as the nucleophiles. On a more fundamental level, and certainly contrary to a previous proposal, it was shown that the outcome of the synthesis, in the absence of any steric hindrances, is to a large extent dictated by the variable reactivity of the benzoyl isothiocyanate's carbonyl carbon, and not by the reactivity of the thiocarbonyl carbon (which appears to remain relatively constant). In other words, the benzoyl isothiocyanate – amine reaction could be perceived as a synthesis for substituted amides, with the *N'*-benzoylthiourea compound relegated to the status of side-product. Fortuitously, however, the latter product often dominates since the carbonyl carbon of the benzoyl isothiocyanate is usually sufficiently deactivated for the addition reaction at the thiocarbonyl carbon to prevail. (Of course, the acyl isothiocyanate – amine reactions could be regarded in the same light, although here the carbonyl carbon is so reactive that the *N'*-acylthiourea product will only dominate if steric constraints inhibit the substitution reaction). From the reactions with the series of para substituted benzoyl isothiocyanates it became evident that the reactivity of the carbonyl carbon was essentially governed by the degree of conjugation that existed between the phenyl ring and the carbonyl group. This finding was also supported by the subsequent computational investigation into the electronic properties of the acyl and benzoyl isothiocyanates. (Here it must be added, that it was gratifying to observe the close correlation between the experimental results and the computational data).

While the thiocarbamoyl chloride – amide reaction, and the reactions with the trimethylsilylated amines failed as practical alternatives and modifications to the Douglass and Dains synthesis, it was rewarding to

discover that *N'*-acylthioureas with non-bulky substituents could be synthesised in acceptable yields using Dixon and Hawthorne's acyl chloride – *N*-substituted thiourea addition. It seems that this facile reaction has the potential to compliment, if not replace the Douglass and Dains procedure, provided that a simple process, like the thermal amine thiocyanate salt conversion, can be optimised to produce high yields of the necessary *N*-substituted thiourea reagents.

In the co-ordination reactions with Pt(II), it was shown that the *N,N*-dialkyl-*N'*-acylthioureas react, like the analogous *N'*-benzoylthioureas, to form neutral, *cis*-[Pt(L-*S,O*)₂] complexes. However, it was also pointed out, that there appear to be subtle differences between the two groups of compounds that might have the potential to be exploited in their practical application as ligands. The investigation into the *trans* co-ordination of the methoxy substituted benzoyl isothiocyanates also warrants further attention as it could yield valuable information about the detailed mechanism of co-ordination. The unprecedented form of *trans N,S* chelation observed in the unique *trans*-[Pt(LH-*N,S*)₂] complex of the monosubstituted *N*-propyl-*N'*-butanoylthiourea, provided for one of the biggest surprises from the work on the co-ordination chemistry. This mode of co-ordination should also be studied further, if only to determine whether other *N'*-acyl- and *N'*-aroylthioureas can be used to extend this potentially new class of complexes with the square planar transition metal ions.

Although the investigation into the synthesis of the bipodal thioureas could be regarded as an extension of the work described in chapters 2 and 3, it was reassuring to observe that the reactions with the difunctional reagents were governed by the same factors that influenced the simple acyl and aroyl isothiocyanate – amine reactions. A similar parallel can be drawn as far as the co-ordination chemistry of these compounds is concerned. Although it was unfortunate that very little further insight was gained into the structures of the acylbis(thiourea) and amine-linked thiourea complexes, it was exciting to find how readily the iso- and terephthaloylbis(thioureas) formed 2:2 and 3:3 metallamacrocycles with Pt(II) and Pd(II). It was, however, somewhat surprising that these tendencies could not be exploited to form larger, mixed ligand metallamacrocycles, and it remains to be seen how easily even a pair of simple *N'*-acyl- or *N'*-aroylthioureas will form *mixed ligand* complexes.

While the work in this thesis is intended to answer questions on some fundamental chemistry of the *N'*-acyl and *N'*-aroylthioureas, it should also serve to demonstrate that research in this field is by no means complete. As such it may provide encouragement to those who fear that future work in this area will be limited to the synthesis of increasingly esoteric compounds, or the identification of novel practical applications.

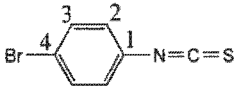
APPENDICES

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Appendix 1

Comparing calculated and crystallographic bond length and bond angle data for (*p*-bromo)phenylisothiocyanate (see chapter 3, section 3.4.1)

Table A1.1

			
Bond / (Angle)	Calculated Å / (°)	Measured Å / (°) *	Measured Å / (°) **
C ₁ -N	1.384	1.440	1.371
N=C	1.199	1.205	1.171
C=S	1.585	1.578	1.542
(C ₁ -N=C)	(148.6)	(159.1)	(154.0)
C ₁ -C ₂	1.391	1.375	1.405
C ₂ -C ₃	1.391	1.333	1.401
C ₃ -C ₄	1.400	1.399	1.405
C ₄ -Br	1.928	1.853	1.937

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Appendix 2

Crystallographic data of *cis*-[bis(*N*-piperidyl)-*N'*-(2,2-dimethylpropanoyl)thioureato)-platinum(II)]

Table A2.1 Crystal data and structure refinement

Empirical formula	C ₂₂ H ₃₈ N ₄ O ₂ PtS ₂
Formula weight	649.77
Temperature	193(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 2 ₁ /c
Unit cell dimensions	a = 9.951(1) Å α = 90° b = 15.235(1) Å β = 105.20(3)° c = 18.358(1) Å γ = 90°
Volume	2685.7(9) Å ³
Z	4
Density (calculated)	1.607 Mg/m ³
Absorption coefficient	5.404 mm ⁻¹
F(000)	1296
Crystal size	0.21 x 0.40 x 0.25 mm ³
Theta range for data collection	2.7 to 27°
Index ranges	-10 ≤ h ≤ 12, -13 ≤ k ≤ 19, -23 ≤ l ≤ 23
Reflections collected	21205
Independent reflections	5903 [R(int) = 0.0566]
Completeness to theta = 27.0°	97 %
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5903 / 0 / 281
Goodness-of-fit on F ²	1.025
Final R indices [I > 2sigma(I)]	R1 = 0.0315, wR2 = 0.0801
R indices (all data)	R1 = 0.0379, wR2 = 0.0842
Extinction coefficient	0.00282(19)
Largest diff. peak and hole	1.777 and -1.779 e.Å ⁻³

Table A2.2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pt(1)	350(1)	9853(1)	1496(1)	25(1)
S(1A)	-1485(1)	9921(1)	493(1)	31(1)
O(1)	2012(4)	9886(2)	2418(2)	42(1)
S(1)	-319(1)	8497(1)	1720(1)	37(1)
O(1A)	1062(3)	11052(2)	1332(2)	40(1)
N(1A)	-607(3)	11624(2)	299(2)	31(1)
N(2)	1097(4)	7178(3)	2480(2)	43(1)
N(2A)	-2592(4)	11122(3)	-504(2)	39(1)
C(1A)	-1509(4)	10950(3)	96(2)	28(1)
N(1)	2035(4)	8490(3)	2928(2)	37(1)
C(1)	1053(4)	8049(3)	2414(2)	33(1)
C(2A)	557(4)	11626(3)	845(2)	30(1)
C(8)	3467(5)	9633(4)	3633(3)	47(1)
C(2)	2383(4)	9318(3)	2928(2)	33(1)
C(8A)	1457(5)	12459(3)	902(2)	41(1)
C(7A)	-3709(4)	10500(3)	-829(3)	42(1)
C(3A)	-2758(5)	11965(4)	-899(3)	48(1)
C(3)	2185(6)	6721(4)	3067(3)	54(1)
C(4A)	-4133(6)	12387(4)	-876(3)	60(1)
C(6A)	-5099(5)	10885(4)	-802(3)	57(1)
C(5A)	-5344(5)	11774(5)	-1193(4)	71(2)
C(4)	3066(6)	6162(4)	2703(4)	67(2)
C(9A)	2307(8)	12609(5)	1701(3)	89(3)
C(5)	2178(8)	5497(5)	2184(4)	79(2)
C(11A)	2302(10)	12373(6)	361(5)	122(4)
C(10A)	525(9)	13270(5)	708(6)	129(4)
C(7)	167(5)	6563(3)	1978(3)	50(1)
C(6)	999(8)	5959(4)	1598(3)	69(2)
C(10)	3069(15)	9330(10)	4314(4)	217(9)
C(9)	3543(14)	10596(6)	3672(6)	193(8)
C(11)	4778(8)	9230(13)	3635(8)	247(12)

Table A2.3a Bond lengths (Å) with estimated standard deviations in parentheses

Bond	(Å)	Bond	(Å)
Pt(1)-O(1A)	2.010(3)	Pt(1)-O(1)	2.033(3)
Pt(1)-S(1A)	2.2301(14)	Pt(1)-S(1)	2.2422(11)
S(1A)-C(1A)	1.726(4)	O(1)-C(2)	1.258(5)
S(1)-C(1)	1.744(4)	O(1A)-C(2A)	1.258(5)
N(1A)-C(2A)	1.318(5)	N(1A)-C(1A)	1.350(5)
N(2)-C(1)	1.332(6)	N(2)-C(7)	1.462(6)
N(2)-C(3)	1.485(6)	N(2A)-C(1A)	1.350(5)
N(2A)-C(7A)	1.463(6)	N(2A)-C(3A)	1.463(6)
N(1)-C(2)	1.308(6)	N(1)-C(1)	1.346(5)
C(2A)-C(8A)	1.541(6)	C(8)-C(11)	1.441(10)
C(8)-C(9)	1.470(11)	C(8)-C(10)	1.480(11)
C(8)-C(2)	1.529(6)	C(8A)-C(11A)	1.466(8)
C(8A)-C(9A)	1.507(7)	C(8A)-C(10A)	1.530(9)
C(7A)-C(6A)	1.515(7)	C(3A)-C(4A)	1.522(7)
C(3)-C(4)	1.499(8)	C(4A)-C(5A)	1.514(8)
C(6A)-C(5A)	1.522(9)	C(4)-C(5)	1.508(9)
C(5)-C(6)	1.539(10)	C(7)-C(6)	1.523(8)

Table A2.3b Bond angles (°) with estimated standard deviations in parentheses

Bond angle	(°)	Bond angle	(°)
O(1A)-Pt(1)-O(1)	81.97(12)	O(1A)-Pt(1)-S(1A)	94.52(8)
O(1)-Pt(1)-S(1A)	175.89(10)	O(1A)-Pt(1)-S(1)	176.64(9)
O(1)-Pt(1)-S(1)	94.93(9)	S(1A)-Pt(1)-S(1)	88.63(4)
C(1A)-S(1A)-Pt(1)	107.94(13)	C(2)-O(1)-Pt(1)	128.2(3)
C(1)-S(1)-Pt(1)	106.33(15)	C(2A)-O(1A)-Pt(1)	130.3(3)
C(2A)-N(1A)-C(1A)	126.8(4)	C(1)-N(2)-C(7)	125.5(4)
C(1)-N(2)-C(3)	122.3(4)	C(7)-N(2)-C(3)	112.1(4)
C(1A)-N(2A)-C(7A)	124.5(4)	C(1A)-N(2A)-C(3A)	122.5(4)
C(7A)-N(2A)-C(3A)	113.0(3)	N(2A)-C(1A)-N(1A)	114.1(4)
N(2A)-C(1A)-S(1A)	116.1(3)	N(1A)-C(1A)-S(1A)	129.8(3)
C(2)-N(1)-C(1)	128.7(4)	N(2)-C(1)-N(1)	115.7(4)
N(2)-C(1)-S(1)	117.2(3)	N(1)-C(1)-S(1)	127.0(3)
O(1A)-C(2A)-N(1A)	130.3(4)	O(1A)-C(2A)-C(8A)	114.0(3)
N(1A)-C(2A)-C(8A)	115.6(4)	C(11)-C(8)-C(9)	113.0(10)
C(11)-C(8)-C(10)	107.9(11)	C(9)-C(8)-C(10)	107.0(9)
C(11)-C(8)-C(2)	107.8(5)	C(9)-C(8)-C(2)	111.7(4)
C(10)-C(8)-C(2)	109.3(5)	O(1)-C(2)-N(1)	129.6(4)
O(1)-C(2)-C(8)	114.7(4)	N(1)-C(2)-C(8)	115.6(4)
C(11A)-C(8A)-C(9A)	113.5(6)	C(11A)-C(8A)-C(10A)	109.6(7)
C(9A)-C(8A)-C(10A)	104.8(6)	C(11A)-C(8A)-C(2A)	107.9(4)
C(9A)-C(8A)-C(2A)	111.0(4)	C(10A)-C(8A)-C(2A)	110.1(4)
N(2A)-C(7A)-C(6A)	109.8(4)	N(2A)-C(3A)-C(4A)	110.1(4)
N(2)-C(3)-C(4)	110.1(5)	C(5A)-C(4A)-C(3A)	111.1(5)
C(7A)-C(6A)-C(5A)	111.3(4)	C(4A)-C(5A)-C(6A)	110.8(5)
C(3)-C(4)-C(5)	110.4(5)	C(4)-C(5)-C(6)	110.3(5)
N(2)-C(7)-C(6)	110.2(5)	C(7)-C(6)-C(5)	111.3(5)

Table A2.4 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$). The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pt(1)	27(1)	22(1)	25(1)	0(1)	2(1)	-2(1)
S(1A)	31(1)	26(1)	32(1)	2(1)	-2(1)	-5(1)
O(1)	41(2)	33(2)	38(2)	6(1)	-16(2)	-10(1)
S(1)	36(1)	27(1)	40(1)	5(1)	-1(1)	-7(1)
O(1A)	42(2)	28(2)	39(2)	5(1)	-7(1)	-13(1)
N(1A)	32(2)	24(2)	36(2)	5(1)	6(1)	-3(1)
N(2)	55(2)	27(2)	41(2)	9(2)	3(2)	-3(2)
N(2A)	30(2)	37(2)	44(2)	11(2)	0(2)	-4(2)
C(1A)	28(2)	31(2)	24(2)	1(2)	5(2)	2(2)
N(1)	40(2)	34(2)	31(2)	6(2)	-3(2)	-2(2)
C(1)	35(2)	31(2)	31(2)	5(2)	7(2)	-1(2)
C(2A)	35(2)	23(2)	32(2)	-1(2)	8(2)	-3(2)
C(8)	42(3)	44(3)	42(3)	4(2)	-11(2)	-6(2)
C(2)	29(2)	38(3)	27(2)	4(2)	-2(2)	1(2)
C(8A)	52(3)	28(2)	37(2)	1(2)	3(2)	-15(2)
C(7A)	35(2)	46(3)	36(2)	4(2)	-7(2)	-6(2)
C(3A)	36(2)	52(3)	50(3)	23(2)	1(2)	0(2)
C(3)	62(3)	37(3)	58(3)	22(2)	8(2)	11(2)
C(4A)	58(3)	50(3)	71(4)	17(3)	15(3)	16(3)
C(6A)	33(2)	66(4)	71(3)	0(3)	13(2)	-10(2)
C(5A)	37(3)	76(5)	97(5)	12(4)	11(3)	14(3)
C(4)	62(4)	52(4)	90(4)	23(3)	25(3)	9(3)
C(9A)	127(6)	77(5)	55(3)	-11(3)	9(4)	-70(5)
C(5)	102(5)	47(4)	104(5)	7(4)	57(4)	12(4)
C(11A)	165(8)	111(7)	129(6)	-69(6)	106(6)	-106(6)
C(10A)	100(6)	39(4)	215(11)	14(5)	-14(6)	-19(4)
C(7)	61(3)	25(2)	57(3)	4(2)	6(2)	-8(2)
C(6)	106(5)	37(3)	71(4)	-7(3)	35(3)	-17(3)
C(10)	304(17)	257(16)	41(4)	16(7)	-38(7)	-202(15)
C(9)	246(14)	60(6)	155(9)	-14(6)	-158(10)	-11(7)
C(11)	50(5)	390(30)	243(15)	-222(17)	-66(7)	59(9)

Table A2.5 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$)

	x	y	z	U(eq)
H(7A1)	-3550	9954	-548	50
H(7A2)	-3716	10375	-1348	50
H(3A1)	-2739	11876	-1419	58
H(3A2)	-1994	12351	-661	58
H(3A)	1748	6356	3372	64
H(3B)	2766	7150	3394	64
H(4A1)	-4108	12535	-359	72
H(4A2)	-4263	12926	-1168	72
H(6A1)	-5122	10951	-280	68
H(6A2)	-5840	10486	-1046	68
H(5A1)	-5457	11697	-1730	86
H(5A2)	-6193	12031	-1123	86
H(4A)	3767	5861	3090	81
H(4B)	3539	6531	2418	81
H(9A1)	1697	12660	2027	134
H(9A2)	2837	13139	1725	134
H(9A3)	2928	12122	1862	134
H(5A)	1783	5089	2477	95
H(5B)	2750	5165	1927	95
H(11A)	1704	12279	-136	183
H(11B)	2924	11883	500	183
H(11C)	2833	12900	364	183
H(10A)	-27	13325	1063	193
H(10B)	-77	13209	208	193
H(10C)	1093	13783	731	193
H(7A)	-512	6886	1597	59
H(7B)	-330	6216	2265	59
H(6A)	1394	6300	1258	83
H(6B)	383	5522	1301	83
H(10D)	2201	9596	4328	325
H(10E)	3778	9495	4757	325
H(10F)	2969	8703	4298	325
H(9A)	2643	10830	3665	290
H(9B)	3828	10817	3246	290
H(9C)	4206	10771	4129	290
H(11D)	4670	8603	3609	371
H(11E)	5464	9385	4091	371
H(11F)	5075	9432	3207	371

Table A2.6 Torsion angles (°) with estimated standard deviation in parentheses

Torsion angle	(°)	Torsion angle	(°)
O(1A)-Pt(1)-S(1A)-C(1A)	-3.83(17)	O(1)-Pt(1)-S(1A)-C(1A)	27.2(15)
S(1)-Pt(1)-S(1A)-C(1A)	177.33(14)	O(1A)-Pt(1)-O(1)-C(2)	177.5(4)
S(1A)-Pt(1)-O(1)-C(2)	146.3(13)	S(1)-Pt(1)-O(1)-C(2)	-3.8(4)
O(1A)-Pt(1)-S(1)-C(1)	9.6(17)	O(1)-Pt(1)-S(1)-C(1)	-12.63(19)
S(1A)-Pt(1)-S(1)-C(1)	169.42(15)	O(1)-Pt(1)-O(1A)-C(2A)	-174.7(4)
S(1A)-Pt(1)-O(1A)-C(2A)	3.2(4)	S(1)-Pt(1)-O(1A)-C(2A)	163.0(14)
C(2A)-N(1A)-C(1A)-N(2A)	-177.6(4)	C(2A)-N(1A)-C(1A)-S(1A)	2.9(6)
C(3A)-N(2A)-C(1A)-N(1A)	0.2(6)	C(7A)-N(2A)-C(1A)-N(1A)	-179.8(4)
C(3A)-N(2A)-C(1A)-S(1A)	179.8(3)	C(7A)-N(2A)-C(1A)-S(1A)	-0.2(6)
Pt(1)-S(1A)-C(1A)-N(1A)	2.1(4)	Pt(1)-S(1A)-C(1A)-N(2A)	-177.3(3)
C(7)-N(2)-C(1)-N(1)	-178.3(4)	C(3)-N(2)-C(1)-N(1)	-1.8(6)
C(7)-N(2)-C(1)-S(1)	5.8(6)	C(3)-N(2)-C(1)-S(1)	-177.8(4)
C(2)-N(1)-C(1)-N(2)	167.7(4)	C(2)-N(1)-C(1)-S(1)	-16.8(7)
Pt(1)-S(1)-C(1)-N(2)	-160.0(3)	Pt(1)-S(1)-C(1)-N(1)	24.6(4)
Pt(1)-O(1A)-C(2A)-N(1A)	1.2(7)	Pt(1)-O(1A)-C(2A)-C(8A)	-178.5(3)
C(1A)-N(1A)-C(2A)-O(1A)	-5.4(7)	C(1A)-N(1A)-C(2A)-C(8A)	174.4(4)
Pt(1)-O(1)-C(2)-N(1)	17.9(7)	Pt(1)-O(1)-C(2)-C(8)	-166.2(3)
C(1)-N(1)-C(2)-O(1)	-9.0(8)	C(1)-N(1)-C(2)-C(8)	175.1(4)
C(11)-C(8)-C(2)-O(1)	-107.2(10)	C(9)-C(8)-C(2)-O(1)	17.5(9)
C(10)-C(8)-C(2)-O(1)	135.7(9)	C(11)-C(8)-C(2)-N(1)	69.3(11)
C(9)-C(8)-C(2)-N(1)	-166.0(8)	C(10)-C(8)-C(2)-N(1)	-47.8(9)
O(1A)-C(2A)-C(8A)-C(11A)	96.6(7)	N(1A)-C(2A)-C(8A)-C(11A)	-83.2(6)
O(1A)-C(2A)-C(8A)-C(9A)	-28.2(6)	N(1A)-C(2A)-C(8A)-C(9A)	152.0(5)
O(1A)-C(2A)-C(8A)-C(10A)	-143.8(6)	N(1A)-C(2A)-C(8A)-C(10A)	36.4(7)
C(1A)-N(2A)-C(7A)-C(6A)	120.7(5)	C(3A)-N(2A)-C(7A)-C(6A)	-59.3(5)
C(1A)-N(2A)-C(3A)-C(4A)	-120.8(5)	C(7A)-N(2A)-C(3A)-C(4A)	59.2(6)
C(1)-N(2)-C(3)-C(4)	-116.3(5)	C(7)-N(2)-C(3)-C(4)	60.6(7)
N(2A)-C(3A)-C(4A)-C(5A)	-55.3(6)	N(2A)-C(7A)-C(6A)-C(5A)	55.6(6)
C(3A)-C(4A)-C(5A)-C(6A)	53.1(7)	C(7A)-C(6A)-C(5A)-C(4A)	-53.5(7)
N(2)-C(3)-C(4)-C(5)	-58.7(6)	C(3)-C(4)-C(5)-C(6)	55.5(7)
C(1)-N(2)-C(7)-C(6)	118.8(5)	C(3)-N(2)-C(7)-C(6)	-57.9(5)
N(2)-C(7)-C(6)-C(5)	54.1(6)	C(4)-C(5)-C(6)-C(7)	-53.3(7)

Appendix 3

Crystallographic data of the *N,S* coordinated *trans*-[bis(*N*-propyl-*N*³-butanoyl-thioureato)platinum(II)]

Table A3.1 Crystal data and structure refinement

Empirical formula	$C_{16}H_{30}N_4O_2PtS_2$	
Formula weight	569.65	
Temperature	293(2) K	
Wavelength	0.71070 Å	
Crystal system, space group	triclinic, $P \bar{1}$	
Unit cell dimensions	$a = 4.88130(10)$ Å	$\alpha = 71.5860(10)^\circ$
	$b = 9.7364(3)$ Å	$\beta = 87.312(2)^\circ$
	$c = 11.8767(4)$ Å	$\gamma = 89.368(2)^\circ$
Volume	$534.96(3)$ Å ³	
Z, Calculated density	1, 1.768 Mg/m ³	
Absorption coefficient	6.769 mm ⁻¹	
F(000)	280	
Crystal size	0.10 x 0.15 x 0.25 mm	
Theta range for data collection	3.26 to 28.73°	
Limiting indices	$-6 \leq h \leq 6$, $-13 \leq k \leq 13$, $-16 \leq l \leq 16$	
Reflections collected / unique	5367 / 2765 [$R(\text{int}) = 0.0328$]	
Completeness to $\theta = 28.73^\circ$	99.5 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2765 / 0 / 119	
Goodness-of-fit on F^2	1.093	
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0298$, $wR2 = 0.0705$	
R indices (all data)	$R1 = 0.0298$, $wR2 = 0.0705$	
Largest diff. peak and hole	2.040 and -2.573 e.Å ⁻³ (in vicinity of the platinum)	

Table A3.2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pt(1)	0	0	0	38(1)
S(1)	-1295(2)	2103(1)	-1457(1)	47(1)
O(11)	4688(7)	3188(4)	869(3)	55(1)
N(1)	1902(7)	1762(4)	191(3)	41(1)
N(3)	1702(8)	4221(4)	-1063(4)	49(1)
C(1)	998(8)	2840(4)	-735(3)	41(1)
C(11)	3751(8)	1986(4)	965(3)	41(1)
C(12)	4458(8)	642(5)	1944(4)	44(1)
C(13)	6304(11)	886(5)	2850(4)	54(1)
C(14)	6988(14)	-521(6)	3797(5)	67(1)
C(31)	633(10)	5288(5)	-2099(5)	54(1)
C(32)	2251(14)	5386(7)	-3229(5)	70(1)
C(33)	990(20)	6433(9)	-4308(7)	96(2)

Table A3.3a Bond lengths ($\text{\AA}$) with estimated standard deviations in parentheses

Bond	($\text{\AA}$)	Bond	($\text{\AA}$)
Pt(1)-N(1)	2.039(3)	Pt(1)-N(1)#1	2.039(3)
Pt(1)-S(1)#1	2.3285(10)	Pt(1)-S(1)	2.3285(10)
S(1)-C(1)	1.732(4)	O(11)-C(11)	1.230(5)
N(1)-C(1)	1.346(5)	N(1)-C(11)	1.385(5)
N(3)-C(1)	1.321(5)	N(3)-C(31)	1.452(6)
C(11)-C(12)	1.500(6)	C(12)-C(13)	1.511(5)
C(13)-C(14)	1.519(7)	C(31)-C(32)	1.502(8)
C(32)-C(33)	1.513(9)		

Symmetry transformations used to generate equivalent atoms:

#1 -x, -y, -z

Table A3.3b Bond angles (°) with estimated standard deviations in parentheses

Bond angle	(°)	Bond angle	(°)
N(1)-Pt(1)-N(1)#1	180.0(2)	N(1)-Pt(1)-S(1)#1	110.58(10)
N(1)#1-Pt(1)-S(1)#1	69.42(10)	N(1)-Pt(1)-S(1)	69.42(10)
N(1)#1-Pt(1)-S(1)	110.58(10)	S(1)#1-Pt(1)-S(1)	180.00(7)
C(1)-S(1)-Pt(1)	80.62(14)	C(1)-N(1)-C(11)	122.7(3)
C(1)-N(1)-Pt(1)	102.0(2)	C(11)-N(1)-Pt(1)	135.2(3)
C(1)-N(3)-C(31)	122.6(4)	N(3)-C(1)-N(1)	127.4(4)
N(3)-C(1)-S(1)	124.8(3)	N(1)-C(1)-S(1)	107.9(3)
O(11)-C(11)-N(1)	122.8(4)	O(11)-C(11)-C(12)	123.1(4)
N(1)-C(11)-C(12)	114.1(3)	C(11)-C(12)-C(13)	114.7(4)
C(12)-C(13)-C(14)	111.9(4)	N(3)-C(31)-C(32)	113.1(4)
C(31)-C(32)-C(33)	112.2(6)		

Symmetry transformations used to generate equivalent atoms:

#1 -x, -y, -z

Table A3.4 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$). The anisotropic displacement factor exponent takes the form: $-2p^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pt(1)	39(1)	34(1)	39(1)	-9(1)	-6(1)	-5(1)
S(1)	52(1)	39(1)	49(1)	-9(1)	-17(1)	-6(1)
O(11)	64(2)	41(2)	60(2)	-16(1)	-19(1)	-10(1)
N(1)	45(2)	36(2)	43(2)	-13(1)	-8(1)	-5(1)
N(3)	55(2)	37(2)	54(2)	-11(2)	-16(2)	-5(1)
C(1)	41(2)	38(2)	44(2)	-11(2)	-8(1)	-4(1)
C(11)	42(2)	42(2)	42(2)	-14(2)	-6(1)	-4(1)
C(12)	46(2)	41(2)	45(2)	-13(2)	-9(2)	-4(1)
C(13)	64(3)	49(2)	50(2)	-13(2)	-21(2)	-5(2)
C(14)	89(4)	55(3)	51(2)	-3(2)	-22(2)	-2(2)
C(31)	56(2)	36(2)	63(2)	-6(2)	-19(2)	1(2)
C(32)	79(3)	63(3)	60(3)	-5(2)	-13(2)	-6(3)
C(33)	135(7)	74(4)	68(4)	-1(3)	-31(4)	-22(4)

Table A3.5 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$)

	x	y	z	U(eq)
H(3N)	2900(130)	4380(70)	-710(60)	60(17)
H(12A)	5349	-31	1594	53
H(12B)	2771	191	2351	53
H(13A)	5404	1533	3225	65
H(13B)	7989	1348	2450	65
H(14A)	5331	-959	4220	81
H(14B)	8202	-326	4342	81
H(14C)	7862	-1169	3429	81
H(31A)	636	6229	-1979	64
H(31B)	-1254	5043	-2179	64
H(32A)	2348	4434	-3326	84
H(32B)	4107	5696	-3174	84
H(33A)	-794	6093	-4399	115
H(33B)	2139	6499	-5003	115
H(33C)	842	7370	-4205	115

Table A3.6 Torsion angles (°) with estimated standard deviation in parentheses

Torsion angle	(°)	Torsion angle	(°)
N(1)-Pt(1)-S(1)-C(1)	1.65(16)	N(1)#1-Pt(1)-S(1)-C(1)	-178.35(16)
S(1)#1-Pt(1)-S(1)-C(1)	-93(100)	N(1)#1-Pt(1)-N(1)-C(1)	8(68)
S(1)#1-Pt(1)-N(1)-C(1)	177.9(2)	S(1)-Pt(1)-N(1)-C(1)	-2.1(2)
N(1)#1-Pt(1)-N(1)-C(11)	-169(68)	S(1)#1-Pt(1)-N(1)-C(11)	0.4(4)
S(1)-Pt(1)-N(1)-C(11)	-179.6(4)	C(31)-N(3)-C(1)-N(1)	178.6(4)
C(31)-N(3)-C(1)-S(1)	-1.0(6)	C(11)-N(1)-C(1)-N(3)	1.1(6)
Pt(1)-N(1)-C(1)-N(3)	-176.8(4)	C(11)-N(1)-C(1)-S(1)	-179.3(3)
Pt(1)-N(1)-C(1)-S(1)	2.8(3)	Pt(1)-S(1)-C(1)-N(3)	177.2(4)
Pt(1)-S(1)-C(1)-N(1)	-2.5(2)	C(1)-N(1)-C(11)-O(11)	0.5(6)
Pt(1)-N(1)-C(11)-O(11)	177.5(3)	C(1)-N(1)-C(11)-C(12)	179.2(3)
Pt(1)-N(1)-C(11)-C(12)	-3.7(5)	O(11)-C(11)-C(12)-C(13)	3.2(6)
N(1)-C(11)-C(12)-C(13)	-175.6(4)	C(11)-C(12)-C(13)-C(14)	-178.7(4)
C(1)-N(3)-C(31)-C(32)	-86.1(6)	N(3)-C(31)-C(32)-C(33)	176.3(5)

Symmetry transformations used to generate equivalent atoms:
#1 -x, -y, -z

Table A3.7 Hydrogen bond lengths (Å) and angles (°) with estimated standard deviations in parentheses

Bond D-H...A	d(D-H) Å	d(H...A) Å	d(D...A) Å	<(DHA) °
N(3)-H(3N)...O(11)	0.78(6)	2.096(5)	2.687(5)	133(7)
N(3)-H(3N)...O(11)*	0.78(6)	2.602(5)	3.167(5)	131(6)

* via 1 - x, 1 - y, -z

Appendix 4

Crystallographic data of 1,4-bis(*N*-benzoylthiocarbamoyl)piperazine

Table A4.1 Crystal data and structure refinement

Empirical formula	$C_{20}H_{20}N_4O_2S_2$
Formula weight	412.52
Temperature	293(2) K
Wavelength	0.71070 Å
Crystal system	monoclinic
Space group	$P2_1$
Unit cell dimensions	$a = 5.21660(10)$ Å $\alpha = 90^\circ$ $b = 9.336(4)$ Å $\beta = 91.915(2)^\circ$ $c = 16.9443(6)$ Å $\gamma = 90^\circ$
Volume	$824.8(4)$ Å ³
Z	2
Calculated density	1.607 Mg/m ³
Absorption coefficient	0.352 mm ⁻¹
F(000)	432
Crystal size	0.10 x 0.10 x 0.20 mm ³
Theta range for data collection	3.91 to 32.53°
Index ranges	$0 \leq h \leq 6$, $0 \leq k \leq 14$, $-21 \leq l \leq 21$
Reflections collected / unique	2327 / 2327 [R(int) = 0.0000]
Completeness to 2theta = 32.53°	74.0%
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2327 / 1 / 261
Goodness-of-fit on F ²	1.016
Final R indices [I > 2sigma(I)]	R1 = 0.0365, wR2 = 0.0863
R indices (all data)	R1 = 0.0497, wR2 = 0.0919
Absolute structure parameter	0.10(7)
Largest diff. peak and hole	0.228 and -0.297 e.Å ⁻³

Table A4.2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(11)	11152(4)	3199(2)	4532(1)	29(1)
C(12)	10010(5)	1964(3)	4511(2)	32(1)
C(13)	10603(6)	1344(3)	3746(2)	36(1)
N(14)	9784(4)	2087(2)	3057(1)	31(1)
C(15)	10869(5)	3323(3)	3082(2)	33(1)
C(16)	10284(5)	3935(3)	3856(2)	33(1)
S(1A)	6658(2)	321(1)	2518(1)	48(1)
O(3A)	12126(3)	2591(2)	1532(1)	36(1)
N(2A)	7919(4)	2387(3)	1804(1)	27(1)
C(1A)	8245(5)	1638(3)	2486(2)	28(1)
C(3A)	9865(5)	2722(3)	1332(2)	29(1)
C(4A)	9108(5)	3305(3)	565(2)	28(1)
C(5A)	10765(5)	4187(3)	279(2)	37(1)
C(6A)	10196(6)	4784(4)	-426(2)	46(1)
C(7A)	7980(6)	4495(4)	-862(2)	46(1)
C(8A)	6353(5)	3618(4)	-583(2)	42(1)
C(9A)	6892(5)	3020(3)	122(2)	35(1)
S(1B)	14690(1)	4840(1)	4951(1)	37(1)
O(3B)	9040(3)	2894(2)	6093(1)	39(1)
N(2B)	13227(4)	2906(2)	5756(1)	28(1)
C(1B)	12895(4)	3599(3)	5064(1)	26(1)
C(3B)	11273(5)	2646(3)	6261(2)	30(1)
C(4B)	12048(5)	2050(3)	7019(2)	29(1)
C(5B)	10546(5)	2250(3)	7673(2)	39(1)
C(6B)	11156(6)	1685(4)	8378(2)	43(1)
C(7B)	13204(6)	903(3)	8451(2)	42(1)
C(8B)	14681(6)	690(3)	7808(2)	44(1)
C(9B)	14126(5)	1268(3)	7095(2)	38(1)

Table A4.3a Bond lengths (Å) with estimated standard deviations in parentheses

Bond	(Å)	Bond	(Å)
N(11)-C(12)	1.298(3)	N(11)-C(1B)	1.313(3)
N(11)-C(16)	1.398(3)	C(12)-C(13)	1.463(4)
C(13)-N(14)	1.411(3)	N(14)-C(15)	1.286(3)
N(14)-C(1A)	1.306(3)	C(15)-C(16)	1.472(4)
S(1A)-C(1A)	1.484(3)	O(3A)-C(3A)	1.223(3)
N(2A)-C(3A)	1.349(3)	N(2A)-C(1A)	1.357(3)
C(3A)-C(4A)	1.452(4)	C(4A)-C(5A)	1.299(4)
C(4A)-C(9A)	1.383(4)	C(5A)-C(6A)	1.342(4)
C(6A)-C(7A)	1.377(5)	C(7A)-C(8A)	1.281(4)
C(8A)-C(9A)	1.339(4)	S(1B)-C(1B)	1.506(3)
O(3B)-C(3B)	1.212(3)	N(2B)-C(1B)	1.345(3)
N(2B)-C(3B)	1.374(3)	C(3B)-C(4B)	1.446(4)
C(4B)-C(9B)	1.310(4)	C(4B)-C(5B)	1.391(4)
C(5B)-C(6B)	1.335(4)	C(6B)-C(7B)	1.297(4)
C(7B)-C(8B)	1.369(5)	C(8B)-C(9B)	1.346(4)

Table A4.3b Bond angles (°) with estimated standard deviations in parentheses

Bond angle	(°)	Bond angle	(°)
C(12)-N(11)-C(1B)	125.3(2)	C(12)-N(11)-C(16)	106.2(2)
C(1B)-N(11)-C(16)	128.4(2)	N(11)-C(12)-C(13)	105.4(2)
N(14)-C(13)-C(12)	118.2(2)	C(15)-N(14)-C(1A)	124.9(2)
C(15)-N(14)-C(13)	107.1(2)	C(1A)-N(14)-C(13)	128.1(2)
N(14)-C(15)-C(16)	105.8(2)	N(11)-C(16)-C(15)	118.0(2)
C(3A)-N(2A)-C(1A)	123.3(2)	N(14)-C(1A)-N(2A)	121.5(2)
N(14)-C(1A)-S(1A)	124.7(2)	N(2A)-C(1A)-S(1A)	113.8(2)
O(3A)-C(3A)-N(2A)	123.4(3)	O(3A)-C(3A)-C(4A)	121.1(2)
N(2A)-C(3A)-C(4A)	115.4(2)	C(5A)-C(4A)-C(9A)	118.3(3)
C(5A)-C(4A)-C(3A)	114.0(3)	C(9A)-C(4A)-C(3A)	127.7(2)
C(4A)-C(5A)-C(6A)	117.7(3)	C(5A)-C(6A)-C(7A)	123.5(3)
C(8A)-C(7A)-C(6A)	118.8(3)	C(7A)-C(8A)-C(9A)	118.3(3)
C(8A)-C(9A)-C(4A)	123.4(3)	C(1B)-N(2B)-C(3B)	123.4(2)
N(11)-C(1B)-N(2B)	121.8(2)	N(11)-C(1B)-S(1B)	123.4(2)
N(2B)-C(1B)-S(1B)	114.76(19)	O(3B)-C(3B)-N(2B)	123.2(2)
O(3B)-C(3B)-C(4B)	121.4(2)	N(2B)-C(3B)-C(4B)	115.5(2)
C(9B)-C(4B)-C(5B)	118.9(3)	C(9B)-C(4B)-C(3B)	120.5(2)
C(5B)-C(4B)-C(3B)	120.5(2)	C(6B)-C(5B)-C(4B)	122.4(3)
C(7B)-C(6B)-C(5B)	118.6(3)	C(6B)-C(7B)-C(8B)	119.4(3)
C(9B)-C(8B)-C(7B)	123.1(3)	C(4B)-C(9B)-C(8B)	117.7(3)

Table A4.4 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$). The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(11)	38(1)	21(1)	26(1)	2(1)	-4(1)	-5(1)
C(12)	43(1)	23(1)	31(2)	5(1)	-5(1)	-9(1)
C(13)	55(2)	21(1)	32(2)	7(1)	-11(1)	-1(1)
N(14)	47(1)	21(1)	26(1)	3(1)	-6(1)	-2(1)
C(15)	44(1)	24(1)	30(2)	2(1)	-3(1)	-6(1)
C(16)	46(2)	23(1)	30(2)	3(1)	-4(1)	0(1)
S(1A)	64(1)	32(1)	46(1)	5(1)	-13(1)	-15(1)
O(3A)	31(1)	43(1)	33(1)	6(1)	-1(1)	6(1)
N(2A)	29(1)	28(1)	25(1)	3(1)	-3(1)	1(1)
C(1A)	33(1)	25(1)	26(1)	-1(1)	0(1)	3(1)
C(3A)	34(1)	25(1)	28(2)	-4(1)	-2(1)	2(1)
C(4A)	35(1)	22(1)	29(1)	0(1)	2(1)	5(1)
C(5A)	38(1)	30(1)	42(2)	2(1)	-2(1)	-1(1)
C(6A)	56(2)	35(1)	48(2)	13(2)	2(1)	-1(1)
C(7A)	61(2)	40(2)	38(2)	15(1)	0(1)	12(1)
C(8A)	43(2)	47(2)	36(2)	1(1)	-8(1)	5(1)
C(9A)	37(1)	35(1)	33(2)	1(1)	-2(1)	-1(1)
S(1B)	41(1)	28(1)	42(1)	0(1)	0(1)	-7(1)
O(3B)	30(1)	48(1)	40(1)	8(1)	0(1)	6(1)
N(2B)	27(1)	28(1)	28(1)	2(1)	-3(1)	1(1)
C(1B)	28(1)	21(1)	28(1)	-2(1)	4(1)	3(1)
C(3B)	33(1)	28(1)	29(1)	-3(1)	0(1)	-1(1)
C(4B)	33(1)	23(1)	30(1)	0(1)	0(1)	-4(1)
C(5B)	46(2)	34(1)	36(2)	0(1)	7(1)	5(1)
C(6B)	53(2)	42(2)	34(2)	5(1)	8(1)	1(1)
C(7B)	53(2)	35(2)	37(2)	10(1)	-4(1)	-3(1)
C(8B)	49(2)	33(2)	48(2)	7(1)	-3(1)	9(1)
C(9B)	45(2)	31(1)	39(2)	2(1)	5(1)	7(1)

Table A4.5 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$)

	x	y	z	U(eq)
H(12A)	8173	2080	4557	39
H(12B)	10651	1357	4939	39
H(13A)	12450	1232	3731	43
H(13B)	9862	392	3721	43
H(15A)	10195	3930	2659	39
H(15B)	12708	3229	3030	39
H(16A)	10994	4895	3880	40
H(16B)	8436	4027	3878	40
H(2A)	6440(5)	2430(3)	1618(15)	20(7)
H(5A)	12293	4397	553	44
H(6A)	11360	5428	-631	56
H(7A)	7671	4928	-1350	56
H(8A)	4837	3402	-862	50
H(9A)	5714	2380	324	42
H(2B)	14630(6)	2990(4)	5920(2)	40(9)
H(5B)	9062	2798	7617	46
H(6B)	10133	1849	8808	51
H(7B)	13666	491	8935	50
H(8B)	16135	118	7867	52
H(9B)	15182	1118	6672	46

Table A4.6 Torsion angles (°) with estimated standard deviation in parentheses

Torsion angle	(°)	Torsion angle	(°)
C(1B)-N(11)-C(12)-C(13)	-121.1(3)	C(16)-N(11)-C(12)-C(13)	54.8(3)
N(11)-C(12)-C(13)-N(14)	-60.9(3)	C(12)-C(13)-N(14)-C(15)	60.4(3)
C(12)-C(13)-N(14)-C(1A)	-120.3(3)	C(1A)-N(14)-C(15)-C(16)	128.2(3)
C(13)-N(14)-C(15)-C(16)	-52.5(3)	C(12)-N(11)-C(16)-C(15)	-62.6(3)
C(1B)-N(11)-C(16)-C(15)	113.1(3)	N(14)-C(15)-C(16)-N(11)	61.0(3)
C(15)-N(14)-C(1A)-N(2A)	9.0(4)	C(13)-N(14)-C(1A)-N(2A)	-170.1(3)
C(15)-N(14)-C(1A)-S(1A)	-169.2(2)	C(13)-N(14)-C(1A)-S(1A)	11.6(4)
C(3A)-N(2A)-C(1A)-N(14)	57.9(4)	C(3A)-N(2A)-C(1A)-S(1A)	-123.6(3)
C(1A)-N(2A)-C(3A)-O(3A)	-12.2(4)	C(1A)-N(2A)-C(3A)-C(4A)	169.7(2)
O(3A)-C(3A)-C(4A)-C(5A)	-27.9(4)	N(2A)-C(3A)-C(4A)-C(5A)	150.2(3)
O(3A)-C(3A)-C(4A)-C(9A)	151.7(3)	N(2A)-C(3A)-C(4A)-C(9A)	-30.1(4)
C(9A)-C(4A)-C(5A)-C(6A)	1.0(4)	C(3A)-C(4A)-C(5A)-C(6A)	-179.3(3)
C(4A)-C(5A)-C(6A)-C(7A)	-1.0(5)	C(5A)-C(6A)-C(7A)-C(8A)	0.5(5)
C(6A)-C(7A)-C(8A)-C(9A)	-0.2(5)	C(7A)-C(8A)-C(9A)-C(4A)	0.3(5)
C(5A)-C(4A)-C(9A)-C(8A)	-0.7(4)	C(3A)-C(4A)-C(9A)-C(8A)	179.7(3)
C(12)-N(11)-C(1B)-N(2B)	-17.0(4)	C(16)-N(11)-C(1B)-N(2B)	168.2(3)
C(12)-N(11)-C(1B)-S(1B)	162.2(2)	C(16)-N(11)-C(1B)-S(1B)	-12.7(4)
C(3B)-N(2B)-C(1B)-N(11)	-53.2(4)	C(3B)-N(2B)-C(1B)-S(1B)	127.6(2)
C(1B)-N(2B)-C(3B)-O(3B)	7.5(4)	C(1B)-N(2B)-C(3B)-C(4B)	-172.4(2)
O(3B)-C(3B)-C(4B)-C(9B)	152.2(3)	N(2B)-C(3B)-C(4B)-C(9B)	-27.9(4)
O(3B)-C(3B)-C(4B)-C(5B)	-25.2(4)	N(2B)-C(3B)-C(4B)-C(5B)	154.7(3)
C(9B)-C(4B)-C(5B)-C(6B)	0.6(5)	C(3B)-C(4B)-C(5B)-C(6B)	178.1(3)
C(4B)-C(5B)-C(6B)-C(7B)	-1.1(5)	C(5B)-C(6B)-C(7B)-C(8B)	0.4(5)
C(6B)-C(7B)-C(8B)-C(9B)	0.7(5)	C(5B)-C(4B)-C(9B)-C(8B)	0.5(4)
C(3B)-C(4B)-C(9B)-C(8B)	-177.0(3)	C(7B)-C(8B)-C(9B)-C(4B)	-1.1(5)

Table A4.7 Hydrogen bond lengths (Å) and angles (°) with estimated standard deviations in parentheses

Bond D-H...A	d(D-H) Å	d(H...A) Å	d(D...A) Å	<(DHA) °
N(2A)-H(2A)...O(3A)*	0.82(3)	2.256(3)	3.047(3)	161(2)
N(2B)-H(2B)...O(3B)**	0.78(3)	2.312(3)	3.067(3)	165(3)

* via x - 1, y, z

** via x + 1, y, z

Appendix 5

Crystallographic data of *cis*-[(3,3,3',3'-tetrabutyl-1,1'-terephthaloylbis(thioureato))-platinum(II)]₃

Table A5.1 Crystal data and structure refinement

Empirical formula	(C ₂₆ H ₄₀ N ₄ O ₂ Pt S ₂) ₃ · 2CHCl ₃ · CH ₃ CH ₂ OH · 2H ₂ O
Formula weight	2420.41
Temperature	293(2) K
Wavelength	0.71070 Å
Crystal system	monoclinic
Space group	P2 ₁ /c
Unit cell dimensions	a = 17.6110(10) Å α = 90° b = 23.293(2) Å β = 94.261(2)° c = 26.0330(10) Å γ = 90°
Volume	10649.6(12) Å ³
Z	4
Calculated density	1.525 Mg/m ³
Absorption coefficient	4.253 mm ⁻¹
F(000)	4944
Crystal size	0.10 x 0.11 x 0.16 mm ³
Theta range for data collection	2.96 to 28.27°
Limiting indices	0 ≤ h ≤ 22, 0 ≤ k ≤ 30, -34 ≤ l ≤ 33
Reflections collected / unique	25105 / 25105 [R(int) = 0.0000]
Completeness to theta = 28.27	95.1 %
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	25105 / 0 / 758
Goodness-of-fit on F ²	1.099
Final R indices [I > 2σ(I)]	R1 = 0.0617, wR2 = 0.1713
R indices (all data)	R1 = 0.0934, wR2 = 0.1972
Largest diff. peak and hole	2.406 and -1.551 e.Å ⁻³

Table A5.2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Pt(1A)	1542(1)	298(1)	156(1)	51(1)
O(2A)	1000(3)	-276(3)	587(3)	61(2)
C(3A)	1255(5)	-736(4)	788(3)	51(2)
N(4A)	1911(4)	-1008(3)	735(3)	56(2)
C(5A)	2476(5)	-860(4)	434(3)	52(2)
S(6A)	2541(1)	-272(1)	47(1)	61(1)
N(5A)	3061(4)	-1228(4)	454(3)	55(2)
C(5A1)	3693(5)	-1187(4)	129(4)	57(2)
C(5A2)	4392(5)	-895(5)	388(4)	62(2)
C(5A3)	5026(6)	-910(5)	23(4)	70(3)
C(5A4)	5780(7)	-696(6)	267(5)	90(4)
C(5A5)	3090(6)	-1730(4)	813(4)	62(2)
C(5A6)	2667(7)	-2242(5)	609(5)	80(3)
C(5A7)	2714(9)	-2719(7)	986(6)	104(4)
C(5A8)	2297(12)	-3247(10)	816(9)	149(8)
S(7A)	2106(1)	962(1)	-307(1)	62(1)
C(8A)	1605(5)	1587(4)	-263(4)	54(2)
N(9A)	944(4)	1684(4)	-46(3)	56(2)
C(10A)	516(5)	1307(4)	171(3)	51(2)
O(11A)	618(3)	787(3)	274(3)	64(2)
N(8A)	1902(4)	2067(4)	-470(3)	61(2)
C(8A1)	1509(6)	2631(5)	-443(4)	65(2)
C(8A2)	918(7)	2721(5)	-881(5)	76(3)
C(8A3)	481(9)	3297(7)	-826(6)	98(4)
C(8A4)	-70(11)	3423(9)	-1307(8)	134(6)
C(8A5)	2590(6)	2062(5)	-759(4)	63(2)
C(8A6)	3299(7)	2248(5)	-453(5)	74(3)
C(8A7)	3957(7)	2329(6)	-779(5)	78(3)
C(8A8)	4671(8)	2575(7)	-477(6)	101(4)
C(3A1)	727(4)	-1036(4)	1119(4)	52(2)
C(3A2)	-34(5)	-885(4)	1101(4)	54(2)
C(3A3)	-519(5)	-1172(4)	1415(4)	53(2)
C(3A4)	-245(4)	-1614(4)	1746(4)	52(2)
C(3A5)	527(5)	-1746(5)	1770(5)	70(3)
C(3A6)	1002(5)	-1476(4)	1456(4)	65(3)
Pt(1B)	-2394(1)	-2252(1)	2185(1)	47(1)
O(2B)	-2959(3)	-1531(3)	1948(3)	61(2)
C(3B)	-3662(4)	-1427(4)	1932(3)	47(2)
N(4B)	-4242(4)	-1764(3)	2029(3)	52(2)
C(5B)	-4226(5)	-2310(4)	2185(3)	49(2)
S(6B)	-3438(1)	-2747(1)	2336(1)	61(1)
N(5B)	-4906(4)	-2559(3)	2213(3)	53(2)
N(5B1)	-5609(6)	-2247(4)	2088(4)	62(2)

Table A5.2 continued

	x	y	z	U(eq)
C(5B2)	-5904(7)	-1929(5)	2533(5)	75(3)
C(5B3)	-6659(8)	-1662(6)	2373(6)	91(4)
C(5B4)	-7005(13)	-1351(11)	2779(9)	168(9)
C(5B5)	-5008(6)	-3148(4)	2370(4)	61(2)
C(5B6)	-5077(8)	-3560(6)	1911(5)	85(3)
C(5B7)	-5235(9)	-4181(7)	2062(6)	103(4)
C(5B8)	-6047(11)	-4294(9)	2134(8)	139(7)
S(7B)	-1720(1)	-3028(1)	2448(1)	62(1)
C(8B)	-801(6)	-2775(5)	2588(4)	62(2)
N(9B)	-455(4)	-2350(4)	2347(3)	57(2)
C(10B)	-781(5)	-1937(4)	2052(4)	51(2)
O(11B)	-1464(3)	-1789(3)	2001(3)	62(2)
N(8B)	-362(5)	-3071(4)	2929(3)	64(2)
C(8B1)	438(7)	-2881(6)	3073(5)	84(3)
C(8B2)	1010(8)	-3165(6)	2754(6)	90(4)
C(8B3)	1801(10)	-2886(8)	2839(7)	119(5)
C(8B4)	2424(13)	-3248(11)	2600(10)	170(9)
C(8B5)	-602(8)	-3583(6)	3200(5)	90(4)
C(8B6)	-515(12)	-4125(9)	2805(8)	136(6)
C(8B7)	-577(19)	-4651(13)	3109(13)	214(13)
C(8B8)	-635(13)	-5106(10)	2681(9)	156(8)
C(3B1)	-3878(5)	-823(3)	1777(4)	50(2)
C(3B2)	-3338(5)	-458(4)	1593(4)	61(2)
C(3B3)	-3526(5)	97(4)	1458(4)	57(2)
C(3B4)	-4258(5)	307(4)	1499(3)	50(2)
C(3B5)	-4810(5)	-67(4)	1670(4)	59(2)
C(3B6)	-4605(5)	-626(4)	1819(4)	59(2)
Pt(1C)	-3910(1)	2056(1)	1050(1)	47(1)
O(2C)	-2809(3)	1900(2)	916(3)	55(2)
C(3C)	-2324(5)	2269(4)	771(3)	48(2)
N(4C)	-2352(5)	2831(3)	737(3)	59(2)
C(5C)	-2954(6)	3168(4)	775(4)	58(2)
S(6C)	-3896(2)	2979(1)	824(1)	71(1)
N(5C)	-2799(5)	3729(3)	750(4)	70(2)
C(5C1)	-2007(7)	3924(6)	694(5)	88(4)
C(5C2)	-1531(9)	3911(8)	1235(7)	114(5)
C(5C3)	-706(13)	4106(11)	1134(10)	156(8)
C(5C4)	-340(30)	3960(20)	1610(20)	420(30)
C(5C5)	-3366(8)	4192(6)	786(5)	89(4)
C(5C6)	-3634(12)	4465(9)	283(8)	136(6)
C(5C7)	-4001(15)	4112(12)	-30(11)	177(9)
C(5C8)	-4329(18)	4405(14)	-566(12)	223(13)
S(7C)	-5133(1)	2194(1)	1180(1)	66(1)

Table A5.2 continued

	x	y	z	U(eq)
C(8C)	-5543(5)	1523(4)	1221(4)	53(2)
N(9C)	-5199(4)	1029(3)	1332(3)	55(2)
C(10C)	-4467(4)	908(4)	1345(3)	48(2)
O(11C)	-3902(3)	1215(3)	1245(3)	60(2)
N(8C)	-6308(4)	1499(4)	1135(4)	70(2)
C(8C1)	-6782(10)	1965(7)	962(7)	109(5)
C(8C2)	-7431(8)	2124(6)	1170(6)	90(4)
C(8C3)	-7849(8)	2641(6)	997(6)	95(4)
C(8C4)	-8540(13)	2780(9)	1179(9)	147(8)
C(8C5)	-6713(7)	944(5)	1155(5)	80(3)
C(8C6)	-6861(8)	777(6)	1692(6)	94(4)
C(8C7)	-7361(15)	234(11)	1721(10)	167(9)
C(8C8)	-6985(16)	-211(12)	1737(11)	192(11)
C(3C1)	-1589(5)	2000(4)	625(3)	49(2)
C(3C2)	-1451(4)	1425(4)	665(3)	49(2)
C(3C3)	-773(5)	1181(4)	528(4)	52(2)
C(3C4)	-232(5)	1548(4)	327(3)	51(2)
C(3C5)	-374(6)	2133(5)	277(5)	70(3)
C(3C6)	-1042(6)	2358(4)	437(5)	73(3)
C(1G)	-5614(11)	-6288(9)	1334(8)	128(6)
Cl(1G)	-5142(4)	-5663(3)	1528(2)	172(2)
Cl(2G)	-5997(3)	-6252(3)	703(2)	171(2)
Cl(3G)	-6322(4)	-6410(3)	1713(3)	195(2)
C(1H)	-2614(14)	6027(11)	1511(10)	164(8)
Cl(1H)	-3244(4)	5525(3)	1811(3)	205(2)
Cl(2H)	-1869(4)	5612(3)	1371(3)	215(3)
Cl(3H)	-3170(5)	6162(4)	896(3)	242(3)
C(1J)	1751(8)	4374(6)	2383(5)	84(3)
C(2J)	1046(9)	4179(7)	2032(6)	105(4)
O(2J)	2403(13)	4691(10)	2073(9)	234(9)
O(1K)	-8503(7)	-4902(5)	2974(5)	122(4)
O(1L)	-8612(11)	-4527(8)	2003(8)	197(7)

Table A5.3a Bond lengths (Å) with estimated standard deviations in parentheses

Bond	(Å)	Bond	(Å)
Pt(1A)-O(11A)	2.028(6)	Pt(1A)-O(2A)	2.031(6)
Pt(1A)-S(7A)	2.238(2)	Pt(1A)-S(6A)	2.238(2)
O(2A)-C(3A)	1.259(11)	C(3A)-N(4A)	1.335(11)
C(3A)-C(3A1)	1.489(11)	N(4A)-C(5A)	1.356(11)
C(5A)-N(5A)	1.339(11)	C(5A)-S(6A)	1.709(10)
N(5A)-C(5A1)	1.451(11)	N(5A)-C(5A5)	1.494(13)
C(5A1)-C(5A2)	1.520(13)	C(5A2)-C(5A3)	1.519(14)
C(5A3)-C(5A4)	1.514(16)	C(5A5)-C(5A6)	1.485(16)
C(5A6)-C(5A7)	1.481(19)	C(5A7)-C(5A8)	1.48(2)
S(7A)-C(8A)	1.710(10)	C(8A)-N(9A)	1.351(11)
C(8A)-N(8A)	1.362(12)	N(9A)-C(10A)	1.312(11)
C(10A)-O(11A)	1.252(11)	C(10A)-C(3C4)	1.515(12)
N(8A)-C(8A5)	1.472(12)	N(8A)-C(8A1)	1.490(13)
C(8A1)-C(8A2)	1.501(15)	C(8A2)-C(8A3)	1.559(18)
C(8A3)-C(8A4)	1.55(2)	C(8A5)-C(8A6)	1.494(15)
C(8A6)-C(8A7)	1.500(16)	C(8A7)-C(8A8)	1.542(18)
C(3A1)-C(3A2)	1.382(12)	C(3A1)-C(3A6)	1.413(13)
C(3A2)-C(3A3)	1.395(12)	C(3A3)-C(3A4)	1.405(12)
C(3A4)-C(3A5)	1.391(12)	C(3A4)-C(10B)	1.485(12)
C(3A5)-C(3A6)	1.364(13)	Pt(1B)-O(2B)	2.027(6)
Pt(1B)-O(11B)	2.049(6)	Pt(1B)-S(6B)	2.230(2)
Pt(1B)-S(7B)	2.240(2)	O(2B)-C(3B)	1.260(9)
C(3B)-N(4B)	1.328(10)	C(3B)-C(3B1)	1.504(11)
N(4B)-C(5B)	1.335(11)	C(5B)-N(5B)	1.338(11)
C(5B)-S(6B)	1.742(9)	N(5B)-C(5B5)	1.446(12)
N(5B)-C(5B1)	1.452(12)	C(5B1)-C(5B2)	1.498(15)
C(5B2)-C(5B3)	1.500(17)	C(5B3)-C(5B4)	1.45(2)
C(5B5)-C(5B6)	1.530(16)	C(5B6)-C(5B7)	1.531(19)
C(5B7)-C(5B8)	1.48(2)	S(7B)-C(8B)	1.736(11)
C(8B)-N(8B)	1.327(12)	C(8B)-N(9B)	1.342(13)

Table A5.3a continued

Bond	(Å)	Bond	(Å)
N(9B)-C(10B)	1.334(11)	C(10B)-O(11B)	1.248(10)
N(8B)-C(8B5)	1.462(15)	N(8B)-C(8B1)	1.498(15)
C(8B1)-C(8B2)	1.506(18)	C(8B2)-C(8B3)	1.54(2)
C(8B3)-C(8B4)	1.55(3)	C(8B5)-C(8B6)	1.64(2)
C(8B6)-C(8B7)	1.47(3)	C(8B7)-C(8B8)	1.53(3)
C(3B1)-C(3B6)	1.373(12)	C(3B1)-C(3B2)	1.387(12)
C(3B2)-C(3B3)	1.372(13)	C(3B3)-C(3B4)	1.391(12)
C(3B4)-C(3B5)	1.402(13)	C(3B4)-C(10C)	1.494(12)
C(3B5)-C(3B6)	1.397(13)	Pt(1C)-O(11C)	2.025(6)
Pt(1C)-O(2C)	2.027(6)	Pt(1C)-S(7C)	2.229(2)
Pt(1C)-S(6C)	2.228(3)	O(2C)-C(3C)	1.288(10)
C(3C)-N(4C)	1.312(11)	C(3C)-C(3C1)	1.512(11)
N(4C)-C(5C)	1.330(12)	C(5C)-N(5C)	1.338(12)
C(5C)-S(6C)	1.730(10)	N(5C)-C(5C1)	1.483(15)
N(5C)-C(5C5)	1.477(15)	C(5C1)-C(5C2)	1.59(2)
C(5C2)-C(5C3)	1.56(3)	C(5C3)-C(5C4)	1.40(6)
C(5C5)-C(5C6)	1.50(2)	C(5C6)-C(5C7)	1.30(3)
C(5C7)-C(5C8)	1.62(3)	S(7C)-C(8C)	1.728(10)
C(8C)-N(9C)	1.324(11)	C(8C)-N(8C)	1.350(12)
N(9C)-C(10C)	1.318(10)	C(10C)-O(11C)	1.268(10)
N(8C)-C(8C1)	1.422(17)	N(8C)-C(8C5)	1.479(15)
C(8C1)-C(8C2)	1.35(2)	C(8C2)-C(8C3)	1.465(19)
C(8C3)-C(8C4)	1.38(2)	C(8C5)-C(8C6)	1.493(18)
C(8C6)-C(8C7)	1.55(3)	C(8C7)-C(8C8)	1.23(3)
C(3C1)-C(3C2)	1.364(12)	C(3C1)-C(3C6)	1.391(13)
C(3C2)-C(3C3)	1.393(11)	C(3C3)-C(3C4)	1.408(12)
C(3C4)-C(3C5)	1.389(14)	C(3C5)-C(3C6)	1.380(14)
C(1G)-Cl(3G)	1.67(2)	C(1G)-Cl(1G)	1.73(2)
C(1G)-Cl(2G)	1.73(2)	C(1H)-Cl(2H)	1.69(2)
C(1H)-Cl(3H)	1.84(3)	C(1H)-Cl(1H)	1.83(2)
C(1J)-C(2J)	1.55(2)	C(1J)-O(2J)	1.63(3)

Table A5.3b Bond angles (°) with estimated standard deviations in parentheses

Bond angle	(°)	Bond angle	(°)
O(11A)-Pt(1A)-O(2A)	82.5(3)	O(11A)-Pt(1A)-S(7A)	94.99(19)
O(2A)-Pt(1A)-S(7A)	177.42(19)	O(11A)-Pt(1A)-S(6A)	177.4(2)
O(2A)-Pt(1A)-S(6A)	94.91(18)	S(7A)-Pt(1A)-S(6A)	87.56(9)
C(3A)-O(2A)-Pt(1A)	128.4(5)	O(2A)-C(3A)-N(4A)	130.3(8)
O(2A)-C(3A)-C(3A1)	114.8(7)	N(4A)-C(3A)-C(3A1)	114.9(8)
C(3A)-N(4A)-C(5A)	128.1(8)	N(5A)-C(5A)-N(4A)	114.1(8)
N(5A)-C(5A)-S(6A)	117.0(7)	N(4A)-C(5A)-S(6A)	128.9(7)
C(5A)-S(6A)-Pt(1A)	108.3(3)	C(5A)-N(5A)-C(5A1)	123.7(8)
C(5A)-N(5A)-C(5A5)	121.1(8)	C(5A1)-N(5A)-C(5A5)	115.2(7)
N(5A)-C(5A1)-C(5A2)	113.7(8)	C(5A1)-C(5A2)-C(5A3)	108.7(8)
C(5A4)-C(5A3)-C(5A2)	113.1(10)	C(5A6)-C(5A5)-N(5A)	114.3(9)
C(5A7)-C(5A6)-C(5A5)	111.3(11)	C(5A6)-C(5A7)-C(5A8)	115.0(15)
C(8A)-S(7A)-Pt(1A)	107.4(3)	N(9A)-C(8A)-N(8A)	113.3(8)
N(9A)-C(8A)-S(7A)	129.5(7)	N(8A)-C(8A)-S(7A)	117.1(7)
C(10A)-N(9A)-C(8A)	127.4(9)	O(11A)-C(10A)-N(9A)	131.5(8)
O(11A)-C(10A)-C(3C4)	114.5(8)	N(9A)-C(10A)-C(3C4)	114.0(8)
C(10A)-O(11A)-Pt(1A)	128.0(6)	C(8A)-N(8A)-C(8A5)	123.4(9)
C(8A)-N(8A)-C(8A1)	120.7(8)	C(8A5)-N(8A)-C(8A1)	115.8(8)
N(8A)-C(8A1)-C(8A2)	112.7(9)	C(8A1)-C(8A2)-C(8A3)	111.7(10)
C(8A2)-C(8A3)-C(8A4)	111.8(13)	N(8A)-C(8A5)-C(8A6)	114.4(9)
C(8A5)-C(8A6)-C(8A7)	112.7(10)	C(8A6)-C(8A7)-C(8A8)	113.1(11)
C(3A2)-C(3A1)-C(3A6)	119.5(8)	C(3A2)-C(3A1)-C(3A)	120.4(8)
C(3A6)-C(3A1)-C(3A)	120.0(8)	C(3A1)-C(3A2)-C(3A3)	119.5(9)
C(3A2)-C(3A3)-C(3A4)	120.9(8)	C(3A5)-C(3A4)-C(3A3)	118.6(8)
C(3A5)-C(3A4)-C(10B)	121.5(8)	C(3A3)-C(3A4)-C(10B)	119.9(7)
C(3A6)-C(3A5)-C(3A4)	120.9(9)	C(3A5)-C(3A6)-C(3A1)	120.6(8)
O(2B)-Pt(1B)-O(11B)	82.8(2)	O(2B)-Pt(1B)-S(6B)	95.16(17)
O(11B)-Pt(1B)-S(6B)	176.4(2)	O(2B)-Pt(1B)-S(7B)	177.43(18)
O(11B)-Pt(1B)-S(7B)	94.73(19)	S(6B)-Pt(1B)-S(7B)	87.37(9)
C(3B)-O(2B)-Pt(1B)	129.0(5)	O(2B)-C(3B)-N(4B)	130.4(8)
O(2B)-C(3B)-C(3B1)	114.6(7)	N(4B)-C(3B)-C(3B1)	115.0(7)
C(3B)-N(4B)-C(5B)	128.5(7)	N(4B)-C(5B)-N(5B)	115.5(8)
N(4B)-C(5B)-S(6B)	128.7(6)	N(5B)-C(5B)-S(6B)	115.8(6)
C(5B)-S(6B)-Pt(1B)	108.1(3)	C(5B)-N(5B)-C(5B5)	123.8(8)
C(5B)-N(5B)-C(5B1)	121.5(8)	C(5B5)-N(5B)-C(5B1)	114.7(7)
N(5B)-C(5B1)-C(5B2)	114.3(9)	C(5B3)-C(5B2)-C(5B1)	110.0(10)
C(5B4)-C(5B3)-C(5B2)	114.6(15)	N(5B)-C(5B5)-C(5B6)	112.3(9)
C(5B7)-C(5B6)-C(5B5)	113.5(11)	C(5B8)-C(5B7)-C(5B6)	113.3(14)
C(8B)-S(7B)-Pt(1B)	104.8(4)	N(8B)-C(8B)-N(9B)	115.7(9)
N(8B)-C(8B)-S(7B)	116.9(8)	N(9B)-C(8B)-S(7B)	126.9(7)
C(10B)-N(9B)-C(8B)	127.7(8)	O(11B)-C(10B)-N(9B)	129.1(8)
O(11B)-C(10B)-C(3A4)	116.6(8)	N(9B)-C(10B)-C(3A4)	114.3(7)
C(10B)-O(11B)-Pt(1B)	127.5(6)	C(8B)-N(8B)-C(8B5)	124.8(10)

Table A5.3b continued

Bond angle	(°)	Bond angle	(°)
C(8B)-N(8B)-C(8B1)	120.3(9)	C(8B5)-N(8B)-C(8B1)	114.9(9)
N(8B)-C(8B1)-C(8B2)	112.8(11)	C(8B1)-C(8B2)-C(8B3)	111.7(12)
C(8B2)-C(8B3)-C(8B4)	111.9(15)	N(8B)-C(8B5)-C(8B6)	106.4(12)
C(8B7)-C(8B6)-C(8B5)	107.0(19)	C(8B6)-C(8B7)-C(8B8)	101(2)
C(3B6)-C(3B1)-C(3B2)	119.3(8)	C(3B6)-C(3B1)-C(3B)	120.6(8)
C(3B2)-C(3B1)-C(3B)	120.1(7)	C(3B3)-C(3B2)-C(3B1)	120.4(8)
C(3B2)-C(3B3)-C(3B4)	121.3(8)	C(3B3)-C(3B4)-C(3B5)	118.2(8)
C(3B3)-C(3B4)-C(10C)	121.4(8)	C(3B5)-C(3B4)-C(10C)	120.4(7)
C(3B6)-C(3B5)-C(3B4)	119.8(8)	C(3B1)-C(3B6)-C(3B5)	120.8(8)
O(11C)-Pt(1C)-O(2C)	83.1(2)	O(11C)-Pt(1C)-S(7C)	95.17(18)
O(2C)-Pt(1C)-S(7C)	177.55(19)	O(11C)-Pt(1C)-S(6C)	178.7(2)
O(2C)-Pt(1C)-S(6C)	95.64(18)	S(7C)-Pt(1C)-S(6C)	86.03(9)
C(3C)-O(2C)-Pt(1C)	126.4(5)	O(2C)-C(3C)-N(4C)	131.6(8)
O(2C)-C(3C)-C(3C1)	113.3(7)	N(4C)-C(3C)-C(3C1)	115.0(7)
C(3C)-N(4C)-C(5C)	127.5(8)	N(4C)-C(5C)-N(5C)	114.0(9)
N(4C)-C(5C)-S(6C)	129.0(7)	N(5C)-C(5C)-S(6C)	117.0(7)
C(5C)-S(6C)-Pt(1C)	107.2(3)	C(5C)-N(5C)-C(5C1)	120.0(9)
C(5C)-N(5C)-C(5C5)	124.6(9)	C(5C1)-N(5C)-C(5C5)	115.4(10)
N(5C)-C(5C1)-C(5C2)	110.2(11)	C(5C1)-C(5C2)-C(5C3)	106.4(15)
C(5C4)-C(5C3)-C(5C2)	99(3)	N(5C)-C(5C5)-C(5C6)	115.1(13)
C(5C7)-C(5C6)-C(5C5)	113(2)	C(5C6)-C(5C7)-C(5C8)	114(2)
C(8C)-S(7C)-Pt(1C)	107.0(3)	N(9C)-C(8C)-N(8C)	115.8(8)
N(9C)-C(8C)-S(7C)	127.8(7)	N(8C)-C(8C)-S(7C)	116.4(7)
C(8C)-N(9C)-C(10C)	128.5(8)	O(11C)-C(10C)-N(9C)	131.0(8)
O(11C)-C(10C)-C(3B4)	113.7(7)	N(9C)-C(10C)-C(3B4)	115.4(8)
C(10C)-O(11C)-Pt(1C)	127.3(5)	C(8C)-N(8C)-C(8C1)	125.2(10)
C(8C)-N(8C)-C(8C5)	120.6(9)	C(8C1)-N(8C)-C(8C5)	113.9(10)
C(8C2)-C(8C1)-N(8C)	125.2(14)	C(8C1)-C(8C2)-C(8C3)	121.6(14)
C(8C4)-C(8C3)-C(8C2)	121.7(16)	N(8C)-C(8C5)-C(8C6)	112.3(11)
C(8C5)-C(8C6)-C(8C7)	113.5(15)	C(8C8)-C(8C7)-C(8C6)	113(2)
C(3C2)-C(3C1)-C(3C6)	119.4(8)	C(3C2)-C(3C1)-C(3C)	122.6(7)
C(3C6)-C(3C1)-C(3C)	118.0(8)	C(3C1)-C(3C2)-C(3C3)	122.2(8)
C(3C2)-C(3C3)-C(3C4)	117.7(8)	C(3C5)-C(3C4)-C(3C3)	120.5(8)
C(3C5)-C(3C4)-C(10A)	119.4(8)	C(3C3)-C(3C4)-C(10A)	120.1(8)
C(3C6)-C(3C5)-C(3C4)	119.8(9)	C(3C5)-C(3C6)-C(3C1)	120.4(9)
Cl(3G)-C(1G)-Cl(1G)	109.5(12)	Cl(3G)-C(1G)-Cl(2G)	108.3(11)
Cl(1G)-C(1G)-Cl(2G)	112.4(12)	Cl(2H)-C(1H)-Cl(3H)	106.2(14)
Cl(2H)-C(1H)-Cl(1H)	103.4(14)	Cl(3H)-C(1H)-Cl(1H)	100.4(12)
C(2J)-C(1J)-O(2J)	113.8(13)		

Table A5.4 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$). The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + \dots + 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pt(1A)	34(1)	60(1)	61(1)	5(1)	8(1)	-1(1)
O(2A)	45(3)	59(4)	83(5)	16(3)	24(3)	3(3)
C(3A)	38(4)	57(5)	59(5)	-1(4)	12(3)	-4(3)
N(4A)	37(4)	66(5)	66(5)	6(4)	13(3)	4(3)
C(5A)	38(4)	65(6)	55(5)	-6(4)	5(3)	1(3)
S(6A)	41(1)	64(1)	81(2)	6(1)	21(1)	3(1)
N(5A)	41(4)	69(5)	57(4)	-5(4)	10(3)	7(3)
S(7A)	43(1)	71(2)	76(2)	18(1)	19(1)	4(1)
C(8A)	45(5)	60(5)	56(5)	3(4)	1(4)	-5(4)
N(9A)	44(4)	65(5)	58(4)	5(4)	6(3)	-3(3)
C(10A)	44(4)	60(5)	49(5)	2(4)	5(3)	2(4)
O(11A)	37(3)	64(4)	92(5)	17(4)	18(3)	10(3)
N(8A)	50(4)	70(5)	65(5)	5(4)	16(3)	-5(4)
C(3A1)	35(4)	61(5)	61(5)	4(4)	12(3)	-4(3)
C(3A2)	41(4)	57(5)	65(6)	0(4)	6(4)	-2(3)
C(3A3)	36(4)	60(5)	66(5)	7(4)	13(4)	4(3)
C(3A4)	35(4)	60(5)	63(5)	8(4)	7(3)	7(3)
C(3A5)	36(5)	82(7)	94(8)	31(6)	14(4)	9(4)
C(3A6)	40(5)	63(6)	94(8)	9(5)	11(4)	11(4)
Pt(1B)	41(1)	46(1)	55(1)	11(1)	11(1)	5(1)
O(2B)	38(3)	49(4)	96(5)	24(3)	14(3)	8(2)
C(3B)	41(4)	43(4)	58(5)	7(4)	12(3)	6(3)
N(4B)	49(4)	42(4)	66(5)	6(3)	11(3)	2(3)
C(5B)	47(4)	49(5)	51(5)	4(4)	9(3)	-2(3)
S(6B)	46(1)	49(1)	87(2)	22(1)	12(1)	2(1)
N(5B)	45(4)	49(4)	64(5)	8(3)	8(3)	-1(3)
S(7B)	51(1)	54(1)	82(2)	22(1)	8(1)	9(1)
C(8B)	57(5)	78(7)	51(5)	13(5)	1(4)	11(5)

Table A5.4 continued

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
N(9B)	42(4)	72(5)	58(4)	13(4)	3(3)	4(3)
C(10B)	40(4)	51(5)	62(5)	3(4)	10(3)	-1(3)
O(11B)	41(3)	57(4)	89(5)	19(3)	16(3)	1(3)
N(8B)	55(5)	65(5)	71(5)	20(4)	4(4)	12(4)
C(3B1)	47(4)	38(4)	65(5)	6(4)	12(4)	7(3)
C(3B2)	39(5)	59(6)	87(7)	15(5)	14(4)	10(4)
C(3B3)	39(4)	47(5)	85(7)	15(4)	9(4)	1(3)
C(3B4)	48(5)	51(5)	53(5)	-2(4)	10(3)	9(3)
C(3B5)	47(5)	50(5)	81(7)	0(4)	14(4)	8(4)
C(3B6)	48(5)	45(5)	86(7)	5(4)	20(4)	2(4)
Pt(1C)	42(1)	41(1)	59(1)	2(1)	6(1)	6(1)
O(2C)	42(3)	42(3)	80(4)	2(3)	7(3)	-1(2)
C(3C)	42(4)	49(5)	53(5)	0(4)	8(3)	1(3)
N(4C)	57(5)	51(4)	70(5)	0(4)	13(4)	2(3)
C(5C)	64(6)	44(5)	67(6)	1(4)	17(4)	9(4)
S(6C)	56(1)	44(1)	115(2)	13(1)	13(1)	9(1)
N(5C)	71(5)	43(4)	98(7)	11(4)	24(5)	2(4)
S(7C)	48(1)	51(1)	102(2)	9(1)	20(1)	14(1)
C(8C)	38(4)	58(5)	64(5)	6(4)	10(3)	7(3)
N(9C)	44(4)	52(4)	69(5)	5(4)	11(3)	5(3)
C(10C)	35(4)	47(5)	61(5)	1(4)	7(3)	6(3)
O(11C)	41(3)	44(3)	95(5)	15(3)	8(3)	9(2)
N(8C)	45(4)	69(6)	98(7)	26(5)	17(4)	13(4)
C(3C1)	40(4)	56(5)	50(5)	1(4)	2(3)	0(3)
C(3C2)	38(4)	52(5)	57(5)	2(4)	9(3)	-1(3)
C(3C3)	44(4)	49(5)	66(5)	-1(4)	7(4)	-1(3)
C(3C4)	40(4)	60(5)	52(5)	-3(4)	7(3)	-4(3)
C(3C5)	47(5)	65(6)	101(8)	20(6)	21(5)	5(4)
C(3C6)	65(6)	49(5)	109(9)	13(5)	34(6)	2(4)

Table A5.5 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$)

	x	y	z	U(eq)
H(5A2)	3528	-975	-180	68
H(5A1)	3832	-1570	25	68
H(5A4)	4552	-1092	706	75
H(5A3)	4273	-500	470	75
H(5A6)	5088	-1301	-94	84
H(5A5)	4879	-676	-276	84
H(5A9)	5906	-902	581	108
H(5A8)	5742	-294	341	108
H(5A7)	6170	-757	34	108
H(5AY)	3618	-1835	894	75
H(5AX)	2882	-1614	1132	75
H(5AA)	2137	-2141	527	96
H(5AZ)	2877	-2367	293	96
H(5AC)	2516	-2585	1303	125
H(5AB)	3246	-2816	1063	125
H(5AF)	2210	-3246	448	179
H(5AE)	1817	-3260	969	179
H(5AD)	2594	-3578	923	179
H(8A2)	1884	2936	-445	78
H(8A1)	1268	2654	-120	78
H(8A4)	558	2405	-891	91
H(8A3)	1161	2722	-1203	91
H(8A6)	846	3609	-778	118
H(8A5)	193	3280	-523	118
H(8A9)	-482	3152	-1321	161
H(8A8)	200	3389	-1612	161
H(8A7)	-269	3805	-1284	161
H(8AY)	2507	2312	-1055	75
H(8AX)	2666	1676	-886	75
H(8AA)	3433	1962	-191	89
H(8AZ)	3201	2606	-280	89
H(8AC)	3805	2587	-1061	94
H(8AB)	4085	1962	-927	94
H(8AF)	4816	2327	-191	121
H(8AE)	4560	2951	-351	121
H(8AD)	5080	2599	-699	121
H(3A2)	-221	-595	881	65
H(3A3)	-1030	-1068	1405	64
H(3A5)	722	-2021	2002	84
H(3A6)	1512	-1584	1465	78
H(5B2)	-5995	-2516	1955	75
H(5B1)	-5526	-1974	1816	75
H(5B4)	-5959	-2192	2816	90

Table A5.5 continued

	x	y	z	U(eq)
H(5B3)	-5544	-1633	2649	90
H(5B6)	-6594	-1400	2090	109
H(5B5)	-7006	-1962	2246	109
H(5B9)	-6665	-1054	2909	202
H(5B8)	-7102	-1611	3053	202
H(5B7)	-7475	-1183	2643	202
H(5BY)	-5463	-3175	2557	73
H(5BX)	-4577	-3262	2602	73
H(5BA)	-5486	-3429	1669	102
H(5BZ)	-4608	-3548	1738	102
H(5BC)	-5071	-4435	1796	124
H(5BB)	-4935	-4271	2379	124
H(5BF)	-6351	-4187	1827	167
H(5BE)	-6200	-4073	2420	167
H(5BD)	-6117	-4695	2201	167
H(8B2)	566	-2968	3434	101
H(8B1)	470	-2468	3031	101
H(8B4)	836	-3137	2392	108
H(8B3)	1048	-3569	2843	108
H(8B6)	1930	-2843	3206	143
H(8B5)	1786	-2506	2686	143
H(8B9)	2264	-3338	2249	204
H(8B8)	2504	-3598	2792	204
H(8B7)	2891	-3034	2612	204
H(8BY)	-1126	-3544	3285	108
H(8BX)	-283	-3640	3515	108
H(8BA)	-914	-4112	2527	164
H(8BZ)	-26	-4110	2657	164
H(8BC)	-1028	-4648	3301	256
H(8BB)	-130	-4710	3344	256
H(8BF)	-136	-5249	2628	187
H(8BE)	-853	-4936	2368	187
H(8BD)	-952	-5416	2781	187
H(3B2)	-2846	-590	1560	74
H(3B3)	-3157	337	1338	69
H(3B5)	-5310	55	1683	71
H(3B6)	-4966	-867	1949	71
H(5C2)	-2013	4311	556	106
H(5C1)	-1769	3675	454	106
H(5C4)	-1525	3527	1379	137
H(5C3)	-1752	4170	1475	137
H(5C6)	-507	3895	852	187
H(5C5)	-680	4515	1067	187

Table A5.5 continued

	x	y	z	U(eq)
H(5C9)	-146	3574	1594	501
H(5C8)	-687	3986	1873	501
H(5C7)	82	4218	1687	501
H(5CY)	-3147	4488	1013	107
H(5CX)	-3805	4037	943	107
H(5CA)	-3963	4786	349	164
H(5CZ)	-3198	4614	120	164
H(5CC)	-4422	3949	140	213
H(5CB)	-3663	3800	-108	213
H(5CF)	-3922	4455	-787	267
H(5CE)	-4547	4772	-495	267
H(5CD)	-4714	4162	-732	267
H(8C2)	-6458	2302	976	130
H(8C1)	-6921	1894	600	130
H(8C4)	-7310	2164	1537	107
H(8C3)	-7782	1804	1123	107
H(8C6)	-7512	2965	1073	114
H(8C5)	-7929	2618	625	114
H(8C9)	-8460	2926	1524	177
H(8C8)	-8855	2444	1179	177
H(8C7)	-8786	3068	962	177
H(8CY)	-6412	648	1005	97
H(8CX)	-7194	971	949	97
H(8CA)	-7109	1094	1853	113
H(8CZ)	-6377	710	1886	113
H(8CC)	-7645	256	2026	200
H(8CB)	-7725	223	1423	200
H(8CF)	-6539	-162	1968	230
H(8CE)	-6835	-299	1398	230
H(8CD)	-7286	-520	1856	230
H(3C2)	-1822	1188	788	58
H(3C3)	-680	790	567	63
H(3C5)	-21	2371	136	84
H(3C6)	-1127	2752	418	87

Table A5.6 Torsion angles (°) with estimated standard deviation in parentheses

Torsion angle	(°)	Torsion angle	(°)
O(11A)-Pt(1A)-O(2A)-C(3A)	-168.2(9)	S(7A)-Pt(1A)-O(2A)-C(3A)	-152(5)
S(6A)-Pt(1A)-O(2A)-C(3A)	11.7(8)	Pt(1A)-O(2A)-C(3A)-N(4A)	-7.9(15)
Pt(1A)-O(2A)-C(3A)-C(3A1)	175.1(6)	O(2A)-C(3A)-N(4A)-C(5A)	-1.6(17)
C(3A1)-C(3A)-N(4A)-C(5A)	175.4(9)	C(3A)-N(4A)-C(5A)-N(5A)	-178.6(9)
C(3A)-N(4A)-C(5A)-S(6A)	2.3(15)	N(5A)-C(5A)-S(6A)-Pt(1A)	-174.4(6)
N(4A)-C(5A)-S(6A)-Pt(1A)	4.6(10)	O(11A)-Pt(1A)-S(6A)-C(5A)	-7(5)
O(2A)-Pt(1A)-S(6A)-C(5A)	-8.6(4)	S(7A)-Pt(1A)-S(6A)-C(5A)	170.7(3)
N(4A)-C(5A)-N(5A)-C(5A1)	173.9(8)	S(6A)-C(5A)-N(5A)-C(5A1)	-6.9(12)
N(4A)-C(5A)-N(5A)-C(5A5)	-4.3(12)	S(6A)-C(5A)-N(5A)-C(5A5)	175.0(7)
C(5A)-N(5A)-C(5A1)-C(5A2)	97.7(11)	C(5A5)-N(5A)-C(5A1)-C(5A2)	-84.0(10)
N(5A)-C(5A1)-C(5A2)-C(5A3)	176.6(8)	C(5A1)-C(5A2)-C(5A3)-C(5A4)	-172.8(10)
C(5A)-N(5A)-C(5A5)-C(5A6)	84.5(12)	C(5A1)-N(5A)-C(5A5)-C(5A6)	-93.8(11)
N(5A)-C(5A5)-C(5A6)-C(5A7)	-179.5(10)	C(5A5)-C(5A6)-C(5A7)-C(5A8)	179.1(14)
O(11A)-Pt(1A)-S(7A)-C(8A)	9.4(4)	O(2A)-Pt(1A)-S(7A)-C(8A)	-7(5)
S(6A)-Pt(1A)-S(7A)-C(8A)	-170.5(3)	Pt(1A)-S(7A)-C(8A)-N(9A)	-6.9(10)
Pt(1A)-S(7A)-C(8A)-N(8A)	172.9(6)	N(8A)-C(8A)-N(9A)-C(10A)	178.0(9)
S(7A)-C(8A)-N(9A)-C(10A)	-2.2(15)	C(8A)-N(9A)-C(10A)-O(11A)	6.5(17)
C(8A)-N(9A)-C(10A)-C(3C4)	-174.0(8)	N(9A)-C(10A)-O(11A)-Pt(1A)	1.6(15)
C(3C4)-C(10A)-O(11A)-Pt(1A)	-177.8(6)	O(2A)-Pt(1A)-O(11A)-C(10A)	170.3(9)
S(7A)-Pt(1A)-O(11A)-C(10A)	-9.0(8)	S(6A)-Pt(1A)-O(11A)-C(10A)	169(5)
N(9A)-C(8A)-N(8A)-C(8A5)	-175.7(8)	S(7A)-C(8A)-N(8A)-C(8A5)	4.6(13)
N(9A)-C(8A)-N(8A)-C(8A1)	0.6(13)	S(7A)-C(8A)-N(8A)-C(8A1)	-179.2(7)
C(8A)-N(8A)-C(8A1)-C(8A2)	-86.7(12)	C(8A5)-N(8A)-C(8A1)-C(8A2)	89.8(11)
N(8A)-C(8A1)-C(8A2)-C(8A3)	176.6(10)	C(8A1)-C(8A2)-C(8A3)-C(8A4)	173.9(12)
C(8A)-N(8A)-C(8A5)-C(8A6)	-99.8(12)	C(8A1)-N(8A)-C(8A5)-C(8A6)	83.8(11)
N(8A)-C(8A5)-C(8A6)-C(8A7)	-170.6(10)	C(8A5)-C(8A6)-C(8A7)-C(8A8)	174.7(11)
O(2A)-C(3A)-C(3A1)-C(3A2)	14.3(13)	N(4A)-C(3A)-C(3A1)-C(3A2)	-163.1(9)
O(2A)-C(3A)-C(3A1)-C(3A6)	-165.5(9)	N(4A)-C(3A)-C(3A1)-C(3A6)	17.0(13)
C(3A6)-C(3A1)-C(3A2)-C(3A3)	-0.1(15)	C(3A)-C(3A1)-C(3A2)-C(3A3)	-180.0(9)
C(3A1)-C(3A2)-C(3A3)-C(3A4)	-0.6(15)	C(3A2)-C(3A3)-C(3A4)-C(3A5)	2.6(15)
C(3A2)-C(3A3)-C(3A4)-C(10B)	-176.3(9)	C(3A3)-C(3A4)-C(3A5)-C(3A6)	-4.0(17)
C(10B)-C(3A4)-C(3A5)-C(3A6)	174.8(10)	C(3A4)-C(3A5)-C(3A6)-C(3A1)	3.3(18)
C(3A2)-C(3A1)-C(3A6)-C(3A5)	-1.3(16)	C(3A)-C(3A1)-C(3A6)-C(3A5)	178.6(10)
O(11B)-Pt(1B)-O(2B)-C(3B)	-179.5(9)	S(6B)-Pt(1B)-O(2B)-C(3B)	3.4(8)
S(7B)-Pt(1B)-O(2B)-C(3B)	-166(4)	Pt(1B)-O(2B)-C(3B)-N(4B)	-5.4(15)
Pt(1B)-O(2B)-C(3B)-C(3B1)	174.9(6)	O(2B)-C(3B)-N(4B)-C(5B)	2.1(17)
C(3B1)-C(3B)-N(4B)-C(5B)	-178.2(9)	C(3B)-N(4B)-C(5B)-N(5B)	-175.0(9)
C(3B)-N(4B)-C(5B)-S(6B)	2.8(15)	N(4B)-C(5B)-S(6B)-Pt(1B)	-3.1(9)
N(5B)-C(5B)-S(6B)-Pt(1B)	174.6(6)	O(2B)-Pt(1B)-S(6B)-C(5B)	0.3(4)
O(11B)-Pt(1B)-S(6B)-C(5B)	-54(3)	S(7B)-Pt(1B)-S(6B)-C(5B)	179.9(3)
N(4B)-C(5B)-N(5B)-C(5B5)	179.5(8)	S(6B)-C(5B)-N(5B)-C(5B5)	1.5(12)
N(4B)-C(5B)-N(5B)-C(5B1)	-0.8(13)	S(6B)-C(5B)-N(5B)-C(5B1)	-178.8(7)
C(5B)-N(5B)-C(5B1)-C(5B2)	-88.3(12)	C(5B5)-N(5B)-C(5B1)-C(5B2)	91.4(11)

Table A5.6 continued

Torsion angle	(°)	Torsion angle	(°)
N(5B)-C(5B1)-C(5B2)-C(5B3)	-175.5(10)	C(5B1)-C(5B2)-C(5B3)-C(5B4)	178.9(14)
C(5B)-N(5B)-C(5B5)-C(5B6)	-92.8(11)	C(5B1)-N(5B)-C(5B5)-C(5B6)	87.5(11)
N(5B)-C(5B5)-C(5B6)-C(5B7)	-176.4(10)	C(5B5)-C(5B6)-C(5B7)-C(5B8)	81.6(17)
O(2B)-Pt(1B)-S(7B)-C(8B)	8(5)	O(11B)-Pt(1B)-S(7B)-C(8B)	21.0(4)
S(6B)-Pt(1B)-S(7B)-C(8B)	-161.9(4)	Pt(1B)-S(7B)-C(8B)-N(8B)	154.4(8)
Pt(1B)-S(7B)-C(8B)-N(9B)	-33.9(10)	N(8B)-C(8B)-N(9B)-C(10B)	-168.7(10)
S(7B)-C(8B)-N(9B)-C(10B)	19.5(16)	C(8B)-N(9B)-C(10B)-O(11B)	13.3(18)
C(8B)-N(9B)-C(10B)-C(3A4)	-166.6(10)	C(3A5)-C(3A4)-C(10B)-O(11B)	-179.4(10)
C(3A3)-C(3A4)-C(10B)-O(11B)	-0.6(14)	C(3A5)-C(3A4)-C(10B)-N(9B)	0.5(14)
C(3A3)-C(3A4)-C(10B)-N(9B)	179.3(9)	N(9B)-C(10B)-O(11B)-Pt(1B)	-18.7(15)
C(3A4)-C(10B)-O(11B)-Pt(1B)	161.2(6)	O(2B)-Pt(1B)-O(11B)-C(10B)	177.6(9)
S(6B)-Pt(1B)-O(11B)-C(10B)	-128(3)	S(7B)-Pt(1B)-O(11B)-C(10B)	-1.8(8)
N(9B)-C(8B)-N(8B)-C(8B5)	-174.1(10)	S(7B)-C(8B)-N(8B)-C(8B5)	-1.5(15)
N(9B)-C(8B)-N(8B)-C(8B1)	7.5(15)	S(7B)-C(8B)-N(8B)-C(8B1)	-179.8(8)
C(8B)-N(8B)-C(8B1)-C(8B2)	-93.2(14)	C(8B5)-N(8B)-C(8B1)-C(8B2)	88.3(14)
N(8B)-C(8B1)-C(8B2)-C(8B3)	169.7(12)	C(8B1)-C(8B2)-C(8B3)-C(8B4)	168.5(15)
C(8B)-N(8B)-C(8B5)-C(8B6)	82.6(15)	C(8B1)-N(8B)-C(8B5)-C(8B6)	-99.0(13)
N(8B)-C(8B5)-C(8B6)-C(8B7)	166.9(18)	C(8B5)-C(8B6)-C(8B7)-C(8B8)	170.0(17)
O(2B)-C(3B)-C(3B1)-C(3B6)	-170.2(9)	N(4B)-C(3B)-C(3B1)-C(3B6)	10.1(13)
O(2B)-C(3B)-C(3B1)-C(3B2)	9.4(13)	N(4B)-C(3B)-C(3B1)-C(3B2)	-170.3(9)
C(3B6)-C(3B1)-C(3B2)-C(3B3)	0.7(16)	C(3B)-C(3B1)-C(3B2)-C(3B3)	-178.9(10)
C(3B1)-C(3B2)-C(3B3)-C(3B4)	-0.5(17)	C(3B2)-C(3B3)-C(3B4)-C(3B5)	-1.6(15)
C(3B2)-C(3B3)-C(3B4)-C(10C)	-179.0(10)	C(3B3)-C(3B4)-C(3B5)-C(3B6)	3.4(15)
C(10C)-C(3B4)-C(3B5)-C(3B6)	-179.2(9)	C(3B2)-C(3B1)-C(3B6)-C(3B5)	1.1(16)
C(3B)-C(3B1)-C(3B6)-C(3B5)	-179.2(9)	C(3B4)-C(3B5)-C(3B6)-C(3B1)	-3.2(16)
O(11C)-Pt(1C)-O(2C)-C(3C)	-177.7(8)	S(7C)-Pt(1C)-O(2C)-C(3C)	136(5)
S(6C)-Pt(1C)-O(2C)-C(3C)	2.9(7)	Pt(1C)-O(2C)-C(3C)-N(4C)	10.0(15)
Pt(1C)-O(2C)-C(3C)-C(3C1)	-171.0(5)	O(2C)-C(3C)-N(4C)-C(5C)	-10.8(18)
C(3C1)-C(3C)-N(4C)-C(5C)	170.3(9)	C(3C)-N(4C)-C(5C)-N(5C)	176.7(10)
C(3C)-N(4C)-C(5C)-S(6C)	-6.3(16)	N(4C)-C(5C)-S(6C)-Pt(1C)	16.8(11)
N(5C)-C(5C)-S(6C)-Pt(1C)	-166.2(7)	O(11C)-Pt(1C)-S(6C)-C(5C)	-37(10)
O(2C)-Pt(1C)-S(6C)-C(5C)	-12.2(4)	S(7C)-Pt(1C)-S(6C)-C(5C)	169.6(4)
N(4C)-C(5C)-N(5C)-C(5C1)	-1.0(15)	S(6C)-C(5C)-N(5C)-C(5C1)	-178.4(9)
N(4C)-C(5C)-N(5C)-C(5C5)	-179.6(10)	S(6C)-C(5C)-N(5C)-C(5C5)	3.0(15)
C(5C)-N(5C)-C(5C1)-C(5C2)	-80.3(14)	C(5C5)-N(5C)-C(5C1)-C(5C2)	98.4(14)
N(5C)-C(5C1)-C(5C2)-C(5C3)	178.5(14)	C(5C1)-C(5C2)-C(5C3)-C(5C4)	-168(3)
C(5C)-N(5C)-C(5C5)-C(5C6)	-102.6(16)	C(5C1)-N(5C)-C(5C5)-C(5C6)	78.7(17)
N(5C)-C(5C5)-C(5C6)-C(5C7)	64(2)	C(5C5)-C(5C6)-C(5C7)-C(5C8)	177.3(19)
O(11C)-Pt(1C)-S(7C)-C(8C)	-14.5(4)	O(2C)-Pt(1C)-S(7C)-C(8C)	32(5)
S(6C)-Pt(1C)-S(7C)-C(8C)	164.9(4)	Pt(1C)-S(7C)-C(8C)-N(9C)	21.2(10)
Pt(1C)-S(7C)-C(8C)-N(8C)	-159.5(7)	N(8C)-C(8C)-N(9C)-C(10C)	167.1(10)
S(7C)-C(8C)-N(9C)-C(10C)	-13.6(16)	C(8C)-N(9C)-C(10C)-O(11C)	-2.1(18)
C(8C)-N(9C)-C(10C)-C(3B4)	178.4(9)	C(3B3)-C(3B4)-C(10C)-O(11C)	-8.9(13)

Table A5.6 continued

Torsion angle	(°)	Torsion angle	(°)
C(3B5)-C(3B4)-C(10C)-O(11C)	173.8(9)	C(3B3)-C(3B4)-C(10C)-N(9C)	170.6(9)
C(3B5)-C(3B4)-C(10C)-N(9C)	-6.7(13)	N(9C)-C(10C)-O(11C)-Pt(1C)	3.2(15)
C(3B4)-C(10C)-O(11C)-Pt(1C)	-177.4(6)	O(2C)-Pt(1C)-O(11C)-C(10C)	-171.7(8)
S(7C)-Pt(1C)-O(11C)-C(10C)	6.5(8)	S(6C)-Pt(1C)-O(11C)-C(10C)	-147(9)
N(9C)-C(8C)-N(8C)-C(8C1)	-173.6(12)	S(7C)-C(8C)-N(8C)-C(8C1)	7.0(16)
N(9C)-C(8C)-N(8C)-C(8C5)	-1.3(15)	S(7C)-C(8C)-N(8C)-C(8C5)	179.3(8)
C(8C)-N(8C)-C(8C1)-C(8C2)	-132.6(16)	C(8C5)-N(8C)-C(8C1)-C(8C2)	55(2)
N(8C)-C(8C1)-C(8C2)-C(8C3)	174.4(15)	C(8C1)-C(8C2)-C(8C3)-C(8C4)	174.9(18)
C(8C)-N(8C)-C(8C5)-C(8C6)	83.0(14)	C(8C1)-N(8C)-C(8C5)-C(8C6)	-103.9(14)
N(8C)-C(8C5)-C(8C6)-C(8C7)	173.6(14)	C(8C5)-C(8C6)-C(8C7)-C(8C8)	88(3)
O(2C)-C(3C)-C(3C1)-C(3C2)	-2.7(12)	N(4C)-C(3C)-C(3C1)-C(3C2)	176.4(9)
O(2C)-C(3C)-C(3C1)-C(3C6)	176.6(9)	N(4C)-C(3C)-C(3C1)-C(3C6)	-4.3(13)
C(3C6)-C(3C1)-C(3C2)-C(3C3)	0.6(14)	C(3C)-C(3C1)-C(3C2)-C(3C3)	179.9(8)
C(3C1)-C(3C2)-C(3C3)-C(3C4)	-2.0(14)	C(3C2)-C(3C3)-C(3C4)-C(3C5)	0.9(14)
C(3C2)-C(3C3)-C(3C4)-C(10A)	-179.9(8)	O(11A)-C(10A)-C(3C4)-C(3C5)	173.9(9)
N(9A)-C(10A)-C(3C4)-C(3C5)	-5.7(13)	O(11A)-C(10A)-C(3C4)-C(3C3)	-5.4(12)
N(9A)-C(10A)-C(3C4)-C(3C3)	175.1(8)	C(3C3)-C(3C4)-C(3C5)-C(3C6)	1.7(17)
C(10A)-C(3C4)-C(3C5)-C(3C6)	-177.6(10)	C(3C4)-C(3C5)-C(3C6)-C(3C1)	-3.1(19)
C(3C2)-C(3C1)-C(3C6)-C(3C5)	2.0(17)	C(3C)-C(3C1)-C(3C6)-C(3C5)	-177.3(10)

Appendix 6

Crystallographic data of *cis*-[(3,3,3',3'-tetraethyl-1,1'-isophthaloylbis(thioureato))-platinum(II)]₂

Table A6.1 Crystal data and structure refinement

Empirical formula	(C ₁₈ H ₂₄ N ₄ O ₂ Pt S ₂) ₂
Formula weight	1175.24
Temperature	293(2) K
Wavelength	0.71070 Å
Crystal system,	triclinic
Space group	P $\bar{1}$
Unit cell dimensions	a = 8.3986(2) Å α = 80.512(2)° b = 9.7283(3) Å β = 82.187(2)° c = 13.0248(4) Å γ = 84.719(2)°
Volume	1037.24(5) Å ³
Z	1
Calculated density	1.881 Mg/m ³
Absorption coefficient	6.986 mm ⁻¹
F(000)	572
Crystal size	0.20 x 0.10 x 0.10 mm ³
Theta range for data collection	2.13 to 26.35°
Limiting indices	-10 ≤ h ≤ 10, -12 ≤ k ≤ 12, -16 ≤ l ≤ 16
Reflections collected / unique	7930 / 4227 [R(int) = 0.0170]
Completeness to theta = 26.35°	99.4 %
Max. and min. transmission	0.5418 and 0.3355
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4227. / 0 / 244
Goodness-of-fit on F ²	1.003
Final R indices [I > 2σ(I)]	R1 = 0.0197, wR2 = 0.0494
R indices (all data)	R1 = 0.0222, wR2 = 0.0512
Largest diff. peak and hole	0.717 and -0.750 e.Å ⁻³

Table A6.2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
Pt(1)	2990(1)	2441(1)	-1834(1)	34(1)
O(2)	2693(3)	1496(3)	-313(2)	39(1)
C(3)	3719(4)	1360(3)	338(2)	34(1)
N(4)	5178(3)	1806(3)	239(2)	38(1)
C(5)	5872(4)	2715(3)	-547(3)	36(1)
N(5)	7400(3)	2949(3)	-470(2)	42(1)
C(51)	8304(4)	3986(4)	-1221(3)	46(1)
C(52)	7900(6)	5494(5)	-1034(4)	66(1)
C(53)	8228(4)	2186(4)	414(3)	50(1)
C(54)	7905(7)	2875(6)	1367(4)	75(1)
S(6)	5036(1)	3638(1)	-1619(1)	49(1)
S(7)	3358(1)	3404(1)	-3513(1)	52(1)
C(8)	1975(4)	2798(4)	-4153(3)	44(1)
N(8)	2176(4)	3115(4)	-5192(2)	59(1)
C(81)	1117(5)	2560(5)	-5852(3)	65(1)
C(82)	-265(7)	3605(7)	-5997(5)	88(2)
C(83)	3456(5)	3959(5)	-5786(3)	62(1)
C(84)	4988(7)	3064(6)	-6051(4)	90(2)
N(9)	701(4)	2073(4)	-3743(2)	48(1)
C(10)	331(4)	1477(4)	-2773(3)	38(1)
O(11)	1080(3)	1369(3)	-1975(2)	42(1)
C(31)	3185(4)	563(3)	1384(2)	33(1)
C(32)	1715(4)	-41(3)	1587(2)	35(1)
C(33)	1229(4)	-795(3)	2563(2)	36(1)
C(34)	2248(4)	-943(4)	3349(3)	43(1)
C(35)	3706(4)	-348(4)	3156(3)	46(1)
C(36)	4199(4)	384(4)	2180(3)	40(1)

Table A6.3a Bond lengths (Å) with estimated standard deviations in parentheses

Bond	(Å)	Bond	(Å)
Pt(1)-O(2)	2.035(2)	Pt(1)-O(11)	2.036(2)
Pt(1)-S(7)	2.2248(10)	Pt(1)-S(6)	2.2346(9)
O(2)-C(3)	1.272(4)	C(3)-N(4)	1.320(4)
C(3)-C(31)	1.486(4)	N(4)-C(5)	1.343(4)
C(5)-N(5)	1.343(4)	C(5)-S(6)	1.728(3)
N(5)-C(51)	1.471(4)	N(5)-C(53)	1.484(4)
C(51)-C(52)	1.526(6)	C(53)-C(54)	1.488(6)
S(7)-C(8)	1.716(4)	C(8)-N(8)	1.328(4)
C(8)-N(9)	1.337(5)	N(8)-C(83)	1.468(5)
N(8)-C(81)	1.507(5)	C(81)-C(82)	1.481(7)
C(83)-C(84)	1.517(7)	N(9)-C(10)	1.309(4)
C(10)-O(11)	1.271(4)	C(10)-C(33)#1	1.496(4)
C(31)-C(32)	1.390(4)	C(31)-C(36)	1.408(4)
C(32)-C(33)	1.388(4)	C(33)-C(34)	1.403(4)
C(33)-C(10)#1	1.496(4)	C(34)-C(35)	1.377(5)
C(35)-C(36)	1.381(5)		

Symmetry transformations used to generate equivalent atoms:

#1 -x, -y, -z

Table A6.3b Bond angles (°) with estimated standard deviations in parentheses

Bond angle	(°)	Bond angle	(°)
O(2)-Pt(1)-O(11)	84.25(9)	O(2)-Pt(1)-S(7)	177.96(7)
O(11)-Pt(1)-S(7)	95.36(7)	O(2)-Pt(1)-S(6)	94.10(7)
O(11)-Pt(1)-S(6)	177.77(7)	S(7)-Pt(1)-S(6)	86.34(4)
C(3)-O(2)-Pt(1)	126.7(2)	O(2)-C(3)-N(4)	130.8(3)
O(2)-C(3)-C(31)	114.6(3)	N(4)-C(3)-C(31)	114.7(3)
C(3)-N(4)-C(5)	127.6(3)	N(4)-C(5)-N(5)	115.2(3)
N(4)-C(5)-S(6)	128.2(2)	N(5)-C(5)-S(6)	116.5(2)
C(5)-N(5)-C(51)	122.5(3)	C(5)-N(5)-C(53)	120.3(3)
C(51)-N(5)-C(53)	117.1(3)	N(5)-C(51)-C(52)	114.5(3)
N(5)-C(53)-C(54)	112.8(3)	C(5)-S(6)-Pt(1)	106.01(11)
C(8)-S(7)-Pt(1)	108.14(12)	N(8)-C(8)-N(9)	115.7(3)
N(8)-C(8)-S(7)	115.8(3)	N(9)-C(8)-S(7)	128.5(3)
C(8)-N(8)-C(83)	123.9(3)	C(8)-N(8)-C(81)	121.1(3)
C(83)-N(8)-C(81)	115.0(3)	C(82)-C(81)-N(8)	106.9(4)
N(8)-C(83)-C(84)	111.8(4)	C(10)-N(9)-C(8)	128.5(3)
O(11)-C(10)-N(9)	131.0(3)	O(11)-C(10)-C(33)#1	114.1(3)
N(9)-C(10)-C(33)#1	114.9(3)	C(10)-O(11)-Pt(1)	126.8(2)
C(32)-C(31)-C(36)	119.1(3)	C(32)-C(31)-C(3)	121.2(3)
C(36)-C(31)-C(3)	119.7(3)	C(33)-C(32)-C(31)	121.0(3)
C(32)-C(33)-C(34)	119.0(3)	C(32)-C(33)-C(10)#1	121.0(3)
C(34)-C(33)-C(10)#1	120.0(3)	C(35)-C(34)-C(33)	120.5(3)
C(34)-C(35)-C(36)	120.5(3)	C(35)-C(36)-C(31)	119.9(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x, -y, -z

Table A6.4 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$). The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pt(1)	31(1)	40(1)	30(1)	3(1)	-4(1)	-12(1)
O(2)	33(1)	53(1)	30(1)	5(1)	-5(1)	-17(1)
C(3)	32(2)	34(2)	35(2)	-4(1)	-4(1)	-5(1)
N(4)	32(1)	44(2)	38(1)	1(1)	-2(1)	-14(1)
C(5)	33(2)	38(2)	36(2)	-2(1)	-3(1)	-11(1)
N(5)	35(1)	50(2)	40(1)	2(1)	-3(1)	-17(1)
C(51)	37(2)	56(2)	43(2)	2(2)	1(1)	-17(2)
C(52)	69(3)	58(2)	72(3)	-7(2)	-3(2)	-25(2)
C(53)	33(2)	62(2)	55(2)	-2(2)	-7(2)	-9(2)
C(54)	83(3)	91(4)	58(3)	-5(2)	-20(2)	-31(3)
S(6)	47(1)	53(1)	46(1)	15(1)	-16(1)	-26(1)
S(7)	52(1)	70(1)	34(1)	15(1)	-10(1)	-34(1)
C(8)	40(2)	56(2)	35(2)	4(2)	-6(1)	-18(2)
N(8)	63(2)	82(2)	32(2)	11(2)	-7(1)	-40(2)
C(81)	64(3)	84(3)	45(2)	-5(2)	-1(2)	-15(2)
C(82)	70(3)	116(5)	76(3)	-6(3)	-11(3)	-4(3)
C(83)	66(3)	82(3)	36(2)	11(2)	0(2)	-40(2)
C(84)	93(4)	94(4)	80(3)	-23(3)	32(3)	-40(3)
N(9)	51(2)	63(2)	29(1)	9(1)	-7(1)	-28(2)
C(10)	39(2)	43(2)	31(2)	1(1)	-5(1)	-13(1)
O(11)	36(1)	57(2)	32(1)	8(1)	-8(1)	-22(1)
C(31)	33(2)	34(2)	31(1)	-4(1)	-1(1)	-9(1)
C(32)	35(2)	40(2)	30(1)	0(1)	-6(1)	-9(1)
C(33)	35(2)	42(2)	31(2)	-3(1)	-3(1)	-11(1)
C(34)	45(2)	52(2)	31(2)	2(1)	-8(1)	-18(2)
C(35)	47(2)	57(2)	35(2)	0(2)	-16(1)	-16(2)
C(36)	33(2)	50(2)	37(2)	1(1)	-7(1)	-16(1)

Table A6.5 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$)

	x	y	z	U(eq)
H(51A)	8093	3915	-1923	55
H(51B)	9447	3758	-1188	55
H(52A)	6769	5729	-1056	99
H(52B)	8503	6107	-1570	99
H(52C)	8174	5593	-360	99
H(53A)	9380	2118	195	60
H(53B)	7876	1244	587	60
H(54A)	8279	3799	1207	113
H(54B)	8459	2339	1915	113
H(54C)	6767	2933	1594	113
H(81A)	1711	2430	-6526	78
H(81B)	741	1668	-5502	78
H(82A)	-902	3657	-5332	132
H(82B)	-915	3332	-6470	132
H(82C)	127	4502	-6282	132
H(83A)	3685	4648	-5377	74
H(83B)	3087	4453	-6430	74
H(84A)	5394	2621	-5414	134
H(84B)	5780	3643	-6466	134
H(84C)	4759	2364	-6439	134
H(32)	1048	62	1062	42
H(34)	1937	-1447	4006	51
H(35)	4363	-440	3687	55
H(36)	5199	760	2049	48

Table A6.6 Torsion angles (°) with estimated standard deviation in parentheses

Torsion angle	(°)	Torsion angle	(°)
O(11)-Pt(1)-O(2)-C(3)	162.1(3)	S(7)-Pt(1)-O(2)-C(3)	83.1(18)
S(6)-Pt(1)-O(2)-C(3)	-19.4(3)	Pt(1)-O(2)-C(3)-N(4)	2.5(5)
Pt(1)-O(2)-C(3)-C(31)	-177.4(2)	O(2)-C(3)-N(4)-C(5)	10.9(6)
C(31)-C(3)-N(4)-C(5)	-169.2(3)	C(3)-N(4)-C(5)-N(5)	-177.6(3)
C(3)-N(4)-C(5)-S(6)	3.8(5)	N(4)-C(5)-N(5)-C(51)	-175.5(3)
S(6)-C(5)-N(5)-C(51)	3.2(4)	N(4)-C(5)-N(5)-C(53)	2.3(5)
S(6)-C(5)-N(5)-C(53)	-179.0(3)	C(5)-N(5)-C(51)-C(52)	79.2(4)
C(53)-N(5)-C(51)-C(52)	-98.8(4)	C(5)-N(5)-C(53)-C(54)	-85.7(4)
C(51)-N(5)-C(53)-C(54)	92.3(4)	N(4)-C(5)-S(6)-Pt(1)	-22.9(3)
N(5)-C(5)-S(6)-Pt(1)	158.6(2)	O(2)-Pt(1)-S(6)-C(5)	23.79(15)
O(11)-Pt(1)-S(6)-C(5)	65.7(18)	S(7)-Pt(1)-S(6)-C(5)	-154.22(13)
O(2)-Pt(1)-S(7)-C(8)	77.1(17)	O(11)-Pt(1)-S(7)-C(8)	-1.80(18)
S(6)-Pt(1)-S(7)-C(8)	179.64(16)	Pt(1)-S(7)-C(8)-N(8)	-170.8(3)
Pt(1)-S(7)-C(8)-N(9)	10.8(4)	N(9)-C(8)-N(8)-C(83)	177.1(4)
S(7)-C(8)-N(8)-C(83)	-1.5(6)	N(9)-C(8)-N(8)-C(81)	-5.8(6)
S(7)-C(8)-N(8)-C(81)	175.6(3)	C(8)-N(8)-C(81)-C(82)	91.2(5)
C(83)-N(8)-C(81)-C(82)	-91.5(5)	C(8)-N(8)-C(83)-C(84)	88.2(5)
C(81)-N(8)-C(83)-C(84)	-89.1(5)	N(8)-C(8)-N(9)-C(10)	170.6(4)
S(7)-C(8)-N(9)-C(10)	-11.0(7)	C(8)-N(9)-C(10)-O(11)	-3.1(7)
C(8)-N(9)-C(10)-C(33)#1	177.5(4)	N(9)-C(10)-O(11)-Pt(1)	13.4(6)
C(33)#1-C(10)-O(11)-Pt(1)	-167.2(2)	O(2)-Pt(1)-O(11)-C(10)	173.5(3)
S(7)-Pt(1)-O(11)-C(10)	-8.5(3)	S(6)-Pt(1)-O(11)-C(10)	131.5(16)
O(2)-C(3)-C(31)-C(32)	3.6(4)	N(4)-C(3)-C(31)-C(32)	-176.3(3)
O(2)-C(3)-C(31)-C(36)	-177.9(3)	N(4)-C(3)-C(31)-C(36)	2.2(4)
C(36)-C(31)-C(32)-C(33)	0.9(5)	C(3)-C(31)-C(32)-C(33)	179.4(3)
C(31)-C(32)-C(33)-C(34)	-0.1(5)	C(31)-C(32)-C(33)-C(10)#1	-178.3(3)
C(32)-C(33)-C(34)-C(35)	0.1(5)	C(10)#1-C(33)-C(34)-C(35)	178.4(3)
C(33)-C(34)-C(35)-C(36)	-1.1(6)	C(34)-C(35)-C(36)-C(31)	1.9(5)
C(32)-C(31)-C(36)-C(35)	-1.9(5)	C(3)-C(31)-C(36)-C(35)	179.6(3)
O(2)-O(11)-O(2)#1-O(11)#1	0.0		

Appendix 7

Crystallographic data of *cis*-[3,3,3',3'-tetrabutyl-1,1'-isophthaloylbis(thioureato))-palladium(II)]₂

Table A7.1 Crystal data and structure refinement

Empirical formula	(C ₂₆ H ₄₀ N ₄ O ₂ Pd S ₂) ₂	
Formula weight	1222.28	
Temperature	213(2) K	
Wavelength	0.71070 Å	
Crystal system	Triclinic	
Space group	P $\bar{1}$	
Unit cell dimensions	a = 9.767(1) Å	α = 62.39(1)°.
	b = 12.502(1) Å	β = 79.71(1)°.
	c = 13.373(1) Å	γ = 80.349(10)°.
Volume	1416.9(2) Å ³	
Z	1	
Density (calculated)	1.432 Mg/m ³	
Absorption coefficient	0.832 mm ⁻¹	
F(000)	636	
Crystal size	0.30 x 0.35 x 0.26 mm ³	
Theta range for data collection	2.13 to 26.95°.	
Index ranges	-11 ≤ h ≤ 10, -14 ≤ k ≤ 12, -16 ≤ l ≤ 15	
Reflections collected	8077	
Independent reflections	4668 [R(int) = 0.0331]	
Completeness to theta = 26.95°	76.0 %	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4668 / 25 / 317	
Goodness-of-fit on F ²	1.017	
Final R indices [I > 2σ(I)]	R1 = 0.0345, wR2 = 0.0875	
R indices (all data)	R1 = 0.0416, wR2 = 0.0918	
Extinction coefficient	0.0015(8)	
Largest diff. peak and hole	0.957 and -0.640 e.Å ⁻³	

Table A7.2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
Pd(1)	2627(1)	1376(1)	6904(1)	29(1)
S(1)	450(1)	1214(1)	7813(1)	34(1)
S(2)	7195(1)	-2701(1)	2444(1)	44(1)
O(2)	5409(2)	-1495(2)	3914(2)	37(1)
O(1)	2478(2)	214(2)	6268(2)	36(1)
N(4)	371(3)	-629(2)	7219(2)	29(1)
N(3)	4568(3)	-3011(2)	3681(2)	29(1)
N(1)	5613(3)	-4494(3)	3201(3)	37(1)
N(2)	-1228(3)	-521(3)	8628(2)	31(1)
C(7)	2925(3)	-1248(3)	5179(3)	26(1)
C(2)	3079(3)	-1898(3)	4552(3)	27(1)
C(8)	1491(3)	-434(3)	6471(3)	29(1)
C(6)	1654(3)	-1099(3)	5771(3)	26(1)
C(3)	1909(3)	-2363(3)	4485(3)	31(1)
C(12)	5695(4)	-3418(3)	3175(3)	30(1)
C(4)	624(4)	-2180(3)	5042(3)	34(1)
C(5)	497(3)	-1587(3)	5707(3)	29(1)
C(10)	-123(3)	-61(3)	7870(3)	28(1)
C(22)	-2815(4)	-1199(3)	7793(3)	35(1)
C(1)	4478(3)	-2130(3)	3981(3)	27(1)
C(17)	6756(4)	-5131(4)	2757(4)	50(1)
C(23)	-3310(4)	-2301(3)	7822(4)	45(1)
C(21)	-1829(4)	-1553(3)	8680(3)	33(1)
C(25)	-1927(4)	-21(3)	9408(3)	36(1)
C(14)	3192(4)	-4695(4)	2983(4)	46(1)
C(13)	4342(4)	-5131(3)	3746(3)	38(1)
C(26)	-3094(4)	962(4)	8942(3)	45(1)
C(24)	-4287(5)	-1948(4)	6930(4)	58(1)
C(27)	-3886(5)	1376(5)	9818(5)	69(1)
C(15)	1882(5)	-5327(4)	3628(5)	75(2)
C(28)	-3016(6)	1950(5)	10208(4)	73(1)
C(19)	8006(7)	-5710(7)	1246(6)	118(3)
C(16)	698(6)	-4871(6)	2966(8)	134(3)
C(18)	6762(6)	-4881(4)	1547(4)	69(1)
C(20)	8220(9)	-5442(8)	112(8)	141(3)

Table A7.3a Bond lengths (Å) with estimated standard deviations in parentheses

Bond	(Å)	Bond	(Å)
Pd(1)-O(2)#1	2.024(2)	Pd(1)-O(1)	2.029(2)
Pd(1)-S(2)#1	2.2417(9)	Pd(1)-S(1)	2.2431(9)
S(1)-C(10)	1.740(3)	S(2)-C(12)	1.739(3)
S(2)-Pd(1)#1	2.2417(9)	O(2)-C(1)	1.269(4)
O(2)-Pd(1)#1	2.024(2)	O(1)-C(8)	1.274(4)
N(4)-C(8)	1.315(4)	N(4)-C(10)	1.343(4)
N(3)-C(1)	1.321(4)	N(3)-C(12)	1.339(4)
N(1)-C(12)	1.345(4)	N(1)-C(17)	1.462(5)
N(1)-C(13)	1.476(4)	N(2)-C(10)	1.342(4)
N(2)-C(25)	1.467(4)	N(2)-C(21)	1.473(4)
C(7)-C(6)	1.382(5)	C(7)-C(2)	1.389(4)
C(2)-C(3)	1.400(4)	C(2)-C(1)	1.495(5)
C(8)-C(6)	1.490(5)	C(6)-C(5)	1.403(4)
C(3)-C(4)	1.382(5)	C(4)-C(5)	1.378(5)
C(22)-C(23)	1.516(5)	C(22)-C(21)	1.520(5)
C(17)-C(18)	1.499(6)	C(23)-C(24)	1.519(6)
C(25)-C(26)	1.507(5)	C(14)-C(13)	1.513(5)
C(14)-C(15)	1.522(6)	C(26)-C(27)	1.530(6)
C(27)-C(28)	1.490(7)	C(15)-C(16)	1.458(8)
C(19)-C(20)	1.377(10)	C(19)-C(18)	1.582(7)

Symmetry transformations used to generate equivalent atoms:

#1 -x + 1, -y, -z + 1

Table A7.3b Bond angles (°) with estimated standard deviations in parentheses

Bond angle	(°)	Bond angle	(°)
O(2)#1-Pd(1)-O(1)	84.70(9)	O(2)#1-Pd(1)-S(2)#1	94.43(7)
O(1)-Pd(1)-S(2)#1	178.39(7)	O(2)#1-Pd(1)-S(1)	179.07(7)
O(1)-Pd(1)-S(1)	94.47(7)	S(2)#1-Pd(1)-S(1)	86.40(3)
C(10)-S(1)-Pd(1)	106.94(11)	C(12)-S(2)-Pd(1)#1	106.85(11)
C(1)-O(2)-Pd(1)#1	129.1(2)	C(8)-O(1)-Pd(1)	128.7(2)
C(8)-N(4)-C(10)	128.1(3)	C(1)-N(3)-C(12)	127.1(3)
C(12)-N(1)-C(17)	123.8(3)	C(12)-N(1)-C(13)	120.3(3)
C(17)-N(1)-C(13)	115.8(3)	C(10)-N(2)-C(25)	123.2(3)
C(10)-N(2)-C(21)	120.1(3)	C(25)-N(2)-C(21)	116.6(3)
C(6)-C(7)-C(2)	121.0(3)	C(7)-C(2)-C(3)	119.1(3)
C(7)-C(2)-C(1)	120.8(3)	C(3)-C(2)-C(1)	120.1(3)
O(1)-C(8)-N(4)	130.2(3)	O(1)-C(8)-C(6)	114.7(3)
N(4)-C(8)-C(6)	115.1(3)	C(7)-C(6)-C(5)	119.1(3)
C(7)-C(6)-C(8)	121.3(3)	C(5)-C(6)-C(8)	119.6(3)
C(4)-C(3)-C(2)	120.1(3)	N(1)-C(12)-N(3)	115.0(3)
N(1)-C(12)-S(2)	116.7(3)	N(3)-C(12)-S(2)	128.2(3)
C(5)-C(4)-C(3)	120.4(3)	C(4)-C(5)-C(6)	120.2(3)
N(2)-C(10)-N(4)	114.9(3)	N(2)-C(10)-S(1)	116.9(2)
N(4)-C(10)-S(1)	128.2(3)	C(23)-C(22)-C(21)	111.8(3)
O(2)-C(1)-N(3)	130.3(3)	O(2)-C(1)-C(2)	115.0(3)
N(3)-C(1)-C(2)	114.7(3)	N(1)-C(17)-C(18)	116.1(4)
C(24)-C(23)-C(22)	111.9(3)	N(2)-C(21)-C(22)	114.0(3)
N(2)-C(25)-C(26)	114.4(3)	C(13)-C(14)-C(15)	110.6(4)
N(1)-C(13)-C(14)	113.6(3)	C(25)-C(26)-C(27)	112.8(4)
C(28)-C(27)-C(26)	113.9(4)	C(16)-C(15)-C(14)	113.1(5)
C(20)-C(19)-C(18)	113.6(7)	C(17)-C(18)-C(19)	108.8(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x + 1, -y, -z + 1

Table A7.4 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$). The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd(1)	26(1)	35(1)	35(1)	-24(1)	0(1)	-10(1)
S(1)	29(1)	46(1)	42(1)	-30(1)	4(1)	-13(1)
S(2)	39(1)	59(1)	58(1)	-46(1)	13(1)	-23(1)
O(2)	27(1)	47(1)	54(2)	-37(1)	8(1)	-17(1)
O(1)	27(1)	48(1)	51(2)	-37(1)	6(1)	-16(1)
N(4)	28(2)	35(2)	31(2)	-18(1)	0(1)	-10(1)
N(3)	30(2)	31(1)	34(2)	-19(1)	-1(1)	-10(1)
N(1)	38(2)	39(2)	47(2)	-29(2)	-2(1)	-9(1)
N(2)	31(2)	38(2)	29(2)	-18(1)	1(1)	-11(1)
C(7)	28(2)	21(2)	32(2)	-12(1)	-6(1)	-8(1)
C(2)	31(2)	26(2)	25(2)	-11(1)	-5(1)	-8(1)
C(8)	23(2)	32(2)	34(2)	-15(2)	-6(1)	-4(1)
C(6)	26(2)	25(2)	29(2)	-11(1)	-4(1)	-7(1)
C(3)	33(2)	30(2)	36(2)	-18(2)	-5(2)	-10(1)
C(12)	36(2)	32(2)	32(2)	-20(2)	-6(2)	-8(1)
C(4)	28(2)	38(2)	44(2)	-22(2)	-4(2)	-14(2)
C(5)	24(2)	34(2)	34(2)	-19(2)	0(1)	-7(1)
C(10)	25(2)	36(2)	26(2)	-14(2)	-4(1)	-7(1)
C(22)	33(2)	40(2)	38(2)	-21(2)	-5(2)	-6(2)
C(1)	29(2)	31(2)	25(2)	-13(1)	-3(1)	-10(1)
C(17)	49(2)	47(2)	74(3)	-45(2)	-2(2)	-7(2)
C(23)	47(2)	40(2)	55(2)	-24(2)	-12(2)	-8(2)
C(21)	32(2)	35(2)	31(2)	-13(2)	0(1)	-12(1)
C(25)	39(2)	47(2)	26(2)	-19(2)	5(2)	-15(2)
C(14)	46(2)	42(2)	54(2)	-25(2)	-3(2)	-12(2)
C(13)	49(2)	33(2)	41(2)	-21(2)	-1(2)	-14(2)
C(26)	40(2)	54(2)	53(2)	-34(2)	-5(2)	-6(2)
C(24)	63(3)	53(3)	75(3)	-36(2)	-25(2)	-9(2)
C(27)	55(3)	85(4)	93(4)	-64(3)	10(3)	-14(3)
C(15)	43(3)	55(3)	115(5)	-28(3)	-1(3)	-16(2)
C(28)	88(4)	79(3)	72(3)	-54(3)	-8(3)	1(3)
C(19)	109(5)	192(8)	94(5)	-98(5)	32(4)	-59(5)
C(16)	69(4)	83(4)	215(9)	-21(5)	-51(5)	-17(3)
C(18)	87(4)	66(3)	65(3)	-45(3)	21(3)	-22(3)
C(20)	137(7)	153(7)	174(9)	-119(7)	26(6)	-27(6)

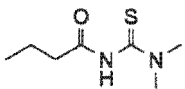
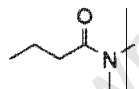
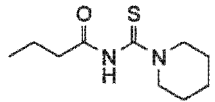
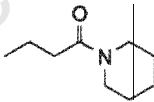
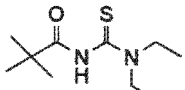
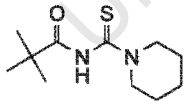
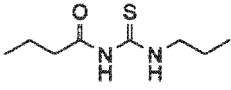
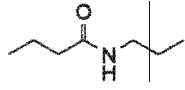
Table A7.5 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$)

	x	y	z	U(eq)
H(7)	3689	-908	5201	31
H(3)	1997	-2796	4065	37
H(4)	-158	-2459	4968	41
H(5)	-359	-1509	6115	35
H(22A)	-3619	-690	7927	42
H(22B)	-2341	-730	7045	42
H(17A)	6724	-5996	3232	59
H(17B)	7633	-4921	2829	59
H(23A)	-2506	-2813	7694	54
H(23B)	-3791	-2765	8569	54
H(21A)	-2332	-1969	9428	40
H(21B)	-1072	-2120	8583	40
H(25A)	-1236	304	9603	43
H(25B)	-2303	-675	10103	43
H(14A)	3507	-4861	2334	55
H(14B)	2977	-3825	2704	55
H(13A)	3990	-5023	4423	46
H(13B)	4588	-5992	3983	46
H(26A)	-3745	665	8682	54
H(26B)	-2708	1653	8292	54
H(24A)	-4566	-2667	6967	88
H(24B)	-3813	-1490	6190	88
H(24C)	-5099	-1464	7070	88
H(27A)	-4672	1951	9490	83
H(27B)	-4258	680	10472	83
H(15A)	2089	-6189	3855	90
H(15B)	1626	-5220	4314	90
H(28A)	-3574	2180	10758	109
H(28B)	-2668	2656	9571	109
H(28C)	-2244	1383	10547	109
H(19A)	8858	-5619	1465	142
H(19B)	7814	-6551	1688	142
H(16A)	-101	-5288	3419	201
H(16B)	928	-5008	2303	201
H(16C)	486	-4018	2739	201
H(18A)	6880	-4033	1047	83
H(18B)	5880	-5056	1445	83
H(20A)	8983	-5976	-14	211
H(20B)	8439	-4617	-331	211
H(20C)	7388	-5545	-110	211

Appendix 8

IUPAC Nomenclature* of some *N*-substituted *N'*-acyl- and *N'*-aroylthioureas and the associated amide side-products

Table A8.1 IUPAC nomenclature of some simple *N*-substituted *N'*-acyl- and *N'*-aroylthioureas and the associated amide side-products

<i>N</i> -substituted <i>N'</i> -acyl- and <i>N'</i> -aroylthioureas	<i>N</i> -substituted amides
 3-Butyryl-1,1-diethyl-thiourea	 <i>N,N</i>-Dimethyl-butylamide
 <i>N</i>-(Piperidine-1-carbothioyl)-butylamide	 1-Piperidin-1-yl-butan-1-one
 3-(2,2-Dimethyl-propionyl)-1,1-diethyl-thiourea	
 2,2-Dimethyl-<i>N</i>-(piperidine-1-carbothioyl)-propionamide	
 1-Butyryl-3-propyl-thiourea	 <i>N</i>-Propyl-butylamide

* Systematic names derived with the aid of AutoNom 2.1 software package, available from Beilstein Informations Systems at website <http://www.ChemWeb.com>

Table A8.1 continued

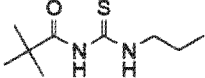
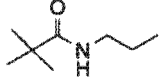
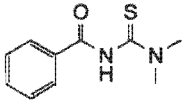
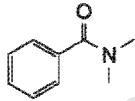
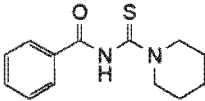
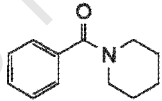
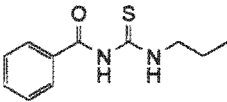
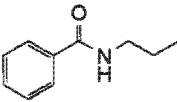
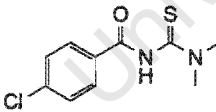
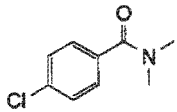
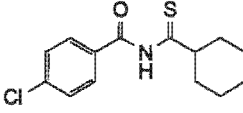
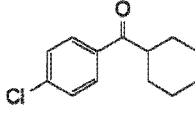
<i>N</i> -substituted <i>N'</i> -acyl- and <i>N'</i> -aroylthioureas	<i>N</i> -substituted amides
 1-Butyl-3-(2,2-dimethyl-propionyl)-thiourea	 <i>N</i>-Butyl-2,2-dimethyl-propionamide
 3-Benzoyl-1,1-dimethyl-thiourea	 <i>N,N</i>-Dimethyl-benzamide
 <i>N</i>-(Piperidine-1-carbothioid)-benzamide	 Phenyl-piperidin-1-yl-methanone
 1-Benzoyl-3-propyl-thiourea	 <i>N</i>-Propyl-benzamide
 3-(4-Chloro-benzoyl)-1,1-dimethyl-thiourea	 4-Chloro-<i>N,N</i>-dimethyl-benzamide
 4-Chloro-<i>N</i>-(piperidine-1-carbothioid)-benzamide	 (4-Chloro-phenyl)-piperidin-1-yl-methanone

Table A8.2 IUPAC nomenclature of some bipodal thioureas and the associated amidic side-products

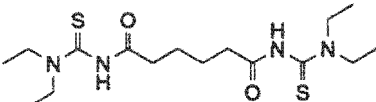
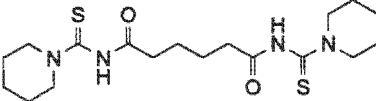
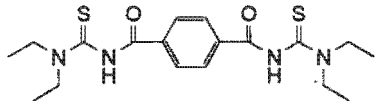
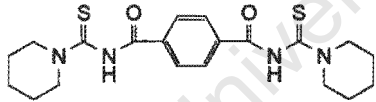
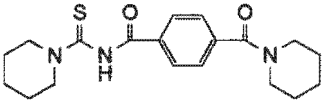
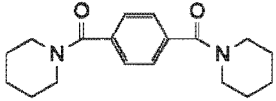
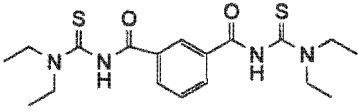
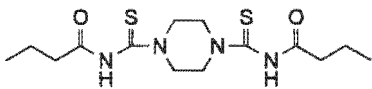
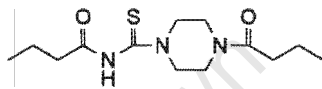
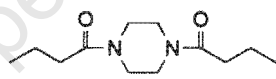
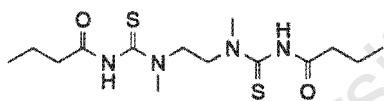
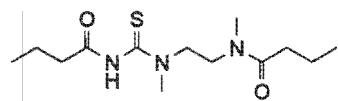
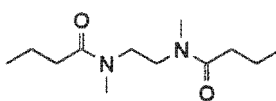
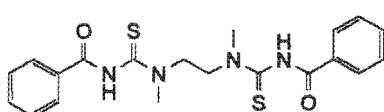
Bipodal thioureas	Amidic products
 3-[6-(3,3-Diethyl-thioureido)-6-oxo-hexanoyl]-1,1-diethyl-thiourea	
 Hexanedioic acid bis-[(piperidine-1-carbothioid)-amide]	
 3-[4-(3,3-Diethyl-thioureidocarbonyl)-benzoyl]-1,1-diethyl-thiourea	
 <i>N,N'</i>-Bis-(piperidine-1-carbothioid)-terephthalamide	 4-(Piperidine-1-carbonyl)-<i>N</i>-(piperidine-1-carbothioid)-benzamide
	 [4-(Pyrrolidine-1-carbonyl)-phenyl]-pyrrolidin-1-yl-methanone

Table A8.2 continued

Bipodal thioureas	Amidic products
 3-[3-(3,3-Diethyl-thioureidocarbonyl)-benzoyl]-1,1-diethyl-thiourea	
 <i>N</i>-(4-Propionylaminocarbothioid-piperazine-1-carbothioid)-propionamide	 <i>N</i>-(4-Propionyl-piperazine-1-carbothioid)-propionamide
	 1-(4-Propionyl-piperazin-1-yl)-propan-1-one
 3-Butyryl-1-[2-(3-butyryl-1-methyl-thioureido)-ethyl]-1-methyl-thiourea	 <i>N</i>-[2-(3-Butyryl-1-methyl-thioureido)-ethyl]-<i>N</i>-methyl-butyramide
	 <i>N</i>-[2-(Butyryl-methyl-amino)-ethyl]-<i>N</i>-methyl-butyramide
 3-Benzoyl-1-[2-[(3-benzoyl-1-methyl-thioureido)-ethyl]-1-methyl-thiourea	