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Metal Ion Interactions of Phenothiazine Drugs

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Abstract

Phenothiazine drugs are versatile antihistamine and anticholinergic compounds. The drugs are based on the phenothiazine heterocycle with an N(10) substituent consisting of a two or three carbon atom chain terminating in a quaternary nitrogen, which is usually present as the hydrochloride salt.

When reacted with K_2MCl_4 (M=Pd,Pt) phenothiazine and non-drug ligands react thus:-

$$K_2MCl_4 + 2L \rightarrow ML_2Cl_2 + 2KCl$$

Far infrared and ^{13}C n.m.r. spectroscopy confirm that ML_2Cl_2 is a cis square planar complex, the ligand being bonded to the metal ion through the sulphur atom of the heterocycle.

The drug hydrochloride ligands (LH.Cl) react differently:-

$$K_2MCl_4 + LH.Cl \rightarrow M(LH)Cl_3 + 2KCl$$

$M(LH)Cl_3$ is also a square planar compound with the ligand sulphur bonded to the MCl_3^- anion. The charge on the anion is balanced by the quaternary exocyclic nitrogen located at the end of the N(10) side chain of the drug.

By X-ray crystallography it was found that the N(10) side chain is bent back over the heterocycle in a unique scorpion conformation facilitating the hydrogen bonding interaction between the quaternary nitrogen and the $PdCl_3^-$ anion. This scorpion conformation is quite different from that found in the uncomplexed drug.

Using ^1H n.m.r. spectroscopy it has been found that this scorpion conformation is maintained in dmf solution. These results are discussed in the context of the current receptor blocking theory of the action of the drugs. The results obtained appear to be validated for all phenothiazine drugs despite a wide range of 2 and 10 position substituents on these drugs.

No reaction was found for phenothiazine and related non-drug ligands with divalent cobalt, nickel and copper chlorides. However these metal ions do react with the drug hydrochlorides thus:-

$$MCl_2 + 2LH.Cl \rightarrow (LH^+)_2(MCl_4)^{2-}; \text{ (M=Co,Ni and Cu)}$$

The species $(LH^+)_2(MCl_4)^{2-}$ involves a hydrogen bonded interaction similar to that seen for the Pd and Pt complexes but no sulphur bonding or any coordination of the heterocycle is present for M=Co,Ni or Cu.

$FeCl_3$ oxidises both the drug and non-drug ligands to cation radicals. $FeCl_2$, $MnCl_2$ and $ZnCl_2$ show no reaction with either the drug or non-drug ligands.

Abbreviations

General

Me - methyl

Et - ethyl

Ph - phenyl

L - neutral unidentate ligand

dmf - dimethylformamide

LH - protonated unidentate ligand

dmso - dimethylsulphoxide

M - metal atom or ion

ptz - phenothiazine

X - halogen

pmz - promethazine

tdz - thioridazine

cpz - chlorpromazine

eptz - N-ethylphenothiazine

dptz - N- dimethylcarbamoylphenothiazine

Crystallographic

Å - Angstrom

R - refinement factor

Dm - measured density

F_o - observed structure factor

Dc - calculated density

Z - number of molecules/unit cell

F(000) - no. of electrons

I - intensity of a reflection

Class 1 ligands are those without an exocyclic quaternary nitrogen on the N(10) side chain, e.g. phenothiazine.

Class 2 ligands are those with a quaternary nitrogen on the N(10) side chain, e.g. chlorpromazine.

Class 1 and 2 complexes are those involving Class 1 and 2 ligands respectively.

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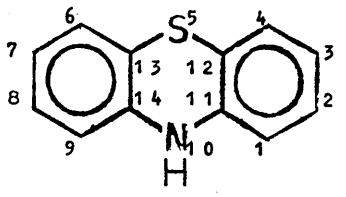
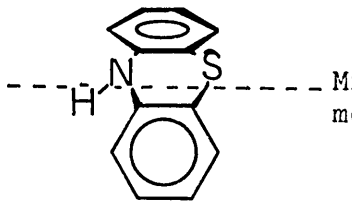
1:1 Historical Introduction.

Phenothiazine (ptz) was first synthesised by Bernthsen in 1881.[1] The chemistry of the heterocycle has been extensively reviewed by Bodea and Silberg.[2] The accepted numbering scheme is given below:-



Phenothiazine

The molecule is not planar, but folded along the N-S axis with a dihedral angle of 158.5°.[3]



Mid-line of phenyl ring mean planes.

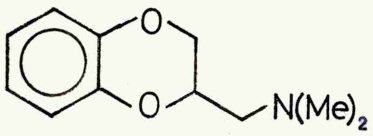
Fig. 1:1:1

Folding of the phenothiazine heterocycle

However, as can be seen from Fig. 1:1:1 the N and S atoms are significantly above the mean planes of the phenyl rings (0.18 Å for the S atom and 0.03 Å for the N atom) and the hydrogen atom of the secondary amine is on the opposite side of the planes from the N and S atoms. This is the "H *intra*" configuration that has been calculated as the energetically most probable one from molecular orbital calculations by Malrieu and Pullman.[4] The C-S bond length {1.770(5) Å} and the C-S-C bond angle {100.9(3)°} are both contracted from the

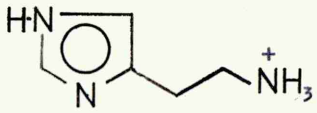
expected values. The central ring has little aromatic character.[2]

In the 1930's phenothiazine became one of the first generation of anthelmintics, being used in the treatment of worms in sheep. Also during the same decade the original antihistamine drugs (benzodioxanes) were first synthesised.



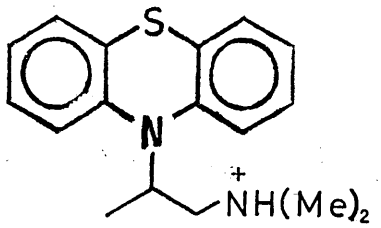
Benzodioxane

Histamine is a naturally occuring amine found in an inactive form in most body tissues. Pharmacologically active free histamine is released in response to injury.



Protonated histamine

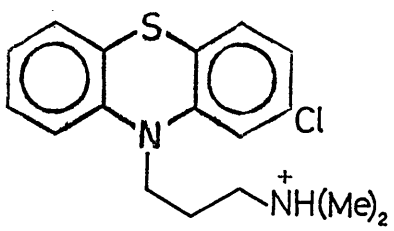
The release of histamine by tissue injury has harmful effects including skin itching and headaches, and for this reason it was thought that histamine antagonists might have therapeutic importance, especially in allergic conditions. The effect of histamine can be opposed in a variety of ways but the benzodioxanes are believed to function by preventing histamine from reaching its site of action i.e. by competition. However, early antihistamines did not block some of the effects of histamine, especially in the stomach. These drugs were called H_1 receptor blockers because it seemed that there must be more than one type of histamine receptor. Over the next decade structural modifications were carried out by various research groups in search of other types of antihistamine agents. One of these was promethazine.[5]



Protonated promethazine.(pmzH)

The above diagram shows the drug in its protonated form. It is usually supplied in this form as the hydrochloride salt, since the free base is an oily liquid. It is thought that the drug interacts with the receptor site in the protonated form. For clarity the counter-ion will always be omitted from diagrams of the drugs in the running text, and the drugs will always be shown in the protonated form. Drug abbreviations will only be given when the drugs are also ligands used in this project. The abbreviations used will include the letter H, when the ligand being discussed is in the protonated form.

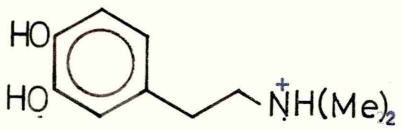
Promethazine, like benzodioxane, is an H_1 receptor blocker and as such blocks all the effects of histamine except that on acid and pepsin content of gastric juices. However, the term antihistamine is unsatisfactory as promethazine has numerous other activities and is used in hypnotics, motion sickness remedies, antitussives, expectorants and antiparkinsonian remedies (see below). In an effort to enhance the hypnotic or sedative effect of promethazine, the Rhone-Poulenc research group studied many modifications of promethazine, one of which led to the synthesis of chlorpromazine:-



Protonated chlorpromazine.(cpzH)

Chlorpromazine has diminished antihistamine activity but pronounced sedative and antipsychotic activity. In psychotic states (severe manic depressive illness and schizophrenia), drugs are used to reduce aggression, hyperactivity and manic behaviour, and these drugs are classified as antipsychotics.

Antipsychotic drugs are thought to act by blocking dopamine (catecholamine) transport mechanisms.



Protonated dopamine

Dopamine is one of the monoamine family of neurotransmitters. These molecules are responsible for electrical messages in the nervous system, being able to cross the synapse (the gap between one nerve cell and the next). Any blocking of the dopamine receptor sites would exert a calming effect in an agitated patient.

The conformation of chlorpromazine in the solid state shows an orientation of the side chain of the drug away from the mid-line towards the chlorine substituted ring. The X-ray analysis of dopamine shows the side chain fully extended and in a plane above the phenyl ring. Fig. 1:1:2 shows that dopamine can be partially superimposed upon a portion of the chlorpromazine molecule.

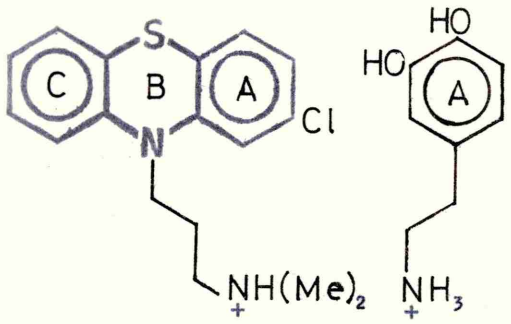


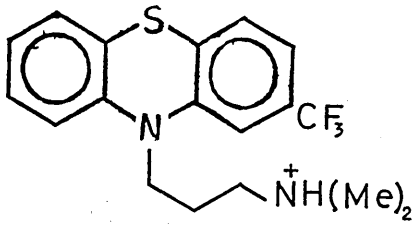
Fig 1:1:2 Superimposition of cpzH and dopamine.

The aromatic ring of dopamine lies over the A ring of the heterocycle such that the meta-hydroxyl group overlays the sulphur atom of the chlorpromazine. The primary amine group of the fully extended dopamine side chain would then be superimposed upon the tertiary amine group of the chlorpromazine side chain.

It was soon realised that the chlorine substituent in the 2 position on the A ring was important in the sedative action of the drug, since promazine has little sedative effect.

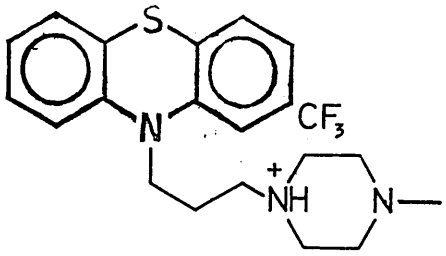
Protonated promazine

It has been postulated that the substituent is important in attracting the amine side chain and increasing dopamine mimicry.[6] To test this hypothesis phenothiazine drugs have been synthesised with 2 and 10 position substituents that would increase the interaction between the 2 position substituent and the amine side chain, and these prove to be more potent drugs than chlorpromazine e.g. trifluprom azine is a more potent sedative than chlorpromazine.



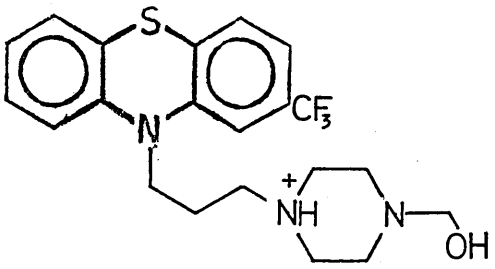
Protonated
Triflupromazine

Molecular models and computer calculations indicate that the CF_3 group approaches more closely the amine side chain, and thus the drug should be more potent in binding to the dopamine receptor. Likewise trifluoperazine is more potent than triflupromazine.



Protonated
trifluoperazine

The simple perazine side chain offers more points of attraction to the CF_3 group than the alkyl amino side chain. One of the most potent phenothiazine drugs is fluphenazine.



Protonated
fluphenazine

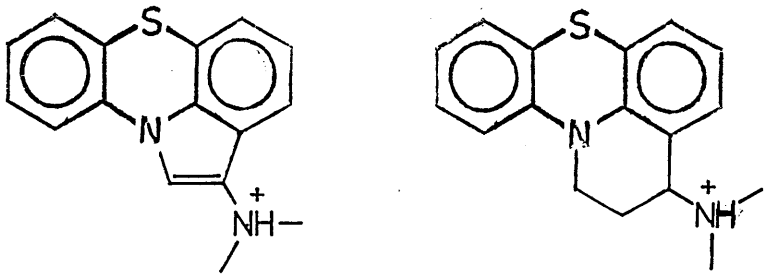
The side chain here has still more attractive possibilities than the simple perazine side chain. In Table 1:1:1 the relative potencies of the drugs mentioned above are listed.[7]

Table 1:1:1

Drug Listed in approx descending order of potency in treating schizophrenia in patients.	Relative potency in competing for dopamine receptor binding in vitro.
Fluphenazine	465
Trifluoperazine	181
Triflupromazine	214
Chlorpromazine	100
Promazine	27

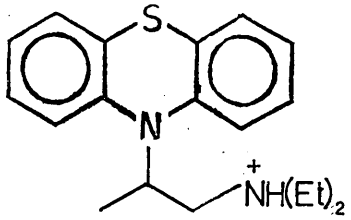
Thus by designing drugs which more accurately mimic dopamine conformation in the solid state, it has been possible to obtain progressively more potent drugs.

However despite the elegance of this theory of solid state dopamine mimicry it must be emphasised that the solid state structure is not the conformation that interacts with the receptor site. This is demonstrated by the synthesis of the following molecules.[8]



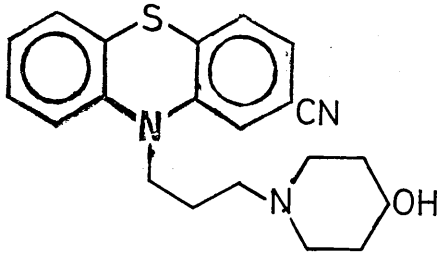
Both these molecules, in the solid state, mimic dopamine closely and would be expected to have a clinical potency similar to that of promazine; however the compounds exhibit no sedative or neuroleptic properties. These aspects of structure activity relationships will be considered again in Sec. 2:2:9.

In large doses chlorpromazine causes a Parkinsonian syndrome (uncontrollable shaking of the limbs), but small doses can sometimes relieve Parkinsonian tremor. The mechanism of control is believed to be the blocking of another neuro-transmitter acetylcholine ($CH_3COOCH_2CH_2\overset{+}{N}(CH_3)_3.\overset{-}{O}H$). The basal ganglia control movement by two balanced systems, one cholinergic, the other dopaminergic, in which the chemical transmitters are acetylcholine and dopamine respectively. In Parkinsonism the dopaminergic system is defective, so that the cholinergic system is dominant. There are thus two ways to restore the balance; to reduce cholinergic activity (by anticholinergic drugs) or to enhance dopaminergic activity by treatment with levodopa, a precursor of dopamine. The former involves the use of drugs like ethopropazine.

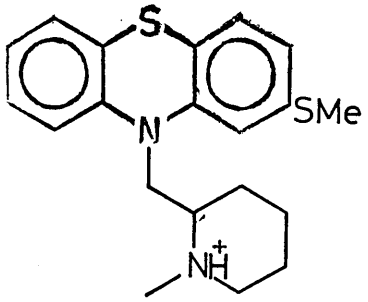


Protonated ethopropazine (epzH)

Two other drugs that are used in this project are pericyazine and thioridazine, both used as alternatives to chlorpromazine.



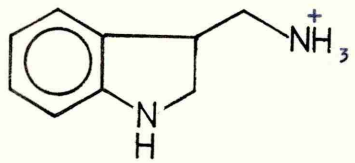
Pericyazine(pcyz)



Protonated thioridazine (tdzH)

Pericyazine is one of the few phenothiazine drugs not supplied as the hydrochloride salt, being a solid in the free base form.

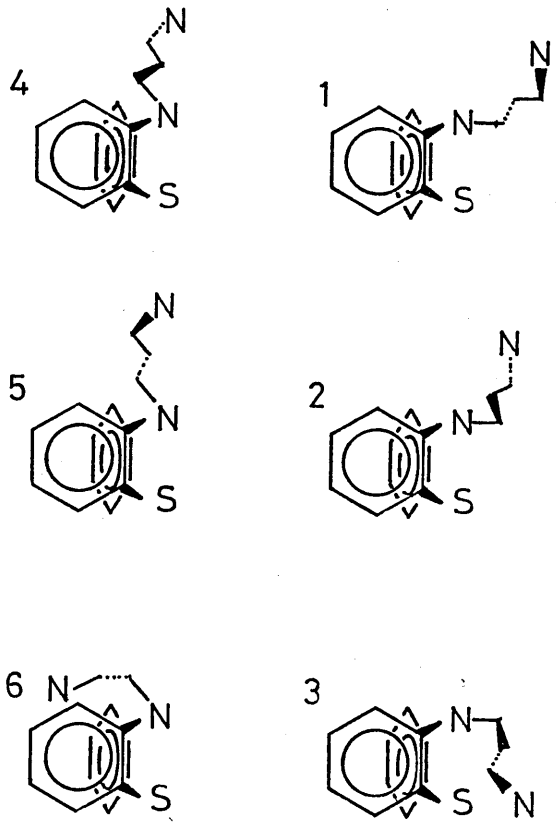
Thus the phenothiazine drugs (all having an N(10) substituent consisting of a two or three carbon atom chain terminating in a quaternary nitrogen) all show a range of activity including blocking at dopamine, acetylcholine, histamine, and serotonin receptors.



Protonated serotonin

As mentioned in relation to promethazine none of the drugs are specific to one sort of neurotransmitter receptor site so all of them show all or some of the above properties to a greater or lesser degree. In an attempt to explain this polybiovalency (the ability of a drug to exhibit more than one type of action) Barbe[9] has studied the conformation of drugs in solution. In the solid state the drugs have only one conformation, that in which the side chain extends away from the heterocycle along the N-S axis in a quasi-equatorial conformation. In the liquid state the drugs are able to undergo inversion to the quasi-axial conformer. Barbe has used both dipole moment measurements and high resolution n.m.r. to study the preferred conformation in solution, using a wide range of phenothiazine drugs, with a wide variety of pharmacological actions. By using high resolution n.m.r. it was possible to study the conformational changes in the N(10) side chain. He found that each drug had a preference for a given type of side chain orientation as shown in Fig. 1:1:3, and by assessing the

Structure number	Activity
1	Sedation
2	Sympathetic receptor
3	Histamine receptor (H_1)
4	Cholinergic receptor
5	Serotonin receptor
6*	Dopamine receptor



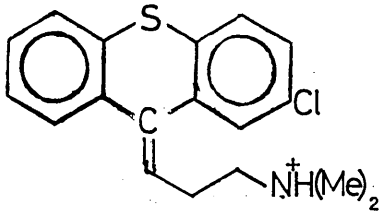
* Because of steric hindrance this structure can only be observed with an ethyldialkylamino side chain.

Fig. 1:1:3

Solution conformation of phenothiazine drugs related to their activity.

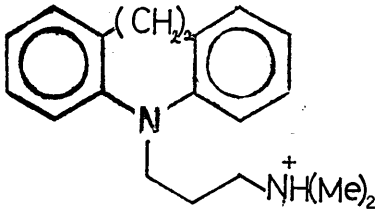
drug's major and minor pharmacological properties he was able to propose a theory of polybiovalency, which may be described as the ability of a particular phenothiazine drug to exhibit a variety of physiological effects depending on its conformation in solution. Thus promethazine is both a sedative and anti-histamine but shows few anticholinergic properties, and these properties will be determined by the proportion of the drug in conformations 1 and 3 illustrated in Fig. 1:1:3.

Finally, a brief mention needs to be made of the two classes of drugs that are structurally similar to phenothiazines but do not have the same heterocyclic ring system as phenothiazines. They are the thioxanthenes and the dibenzazepines.



Protonated chlorprothixene

Chlorprothixene is an example of the former. The thioxanthenes have the endocyclic nitrogen of phenothiazine replaced by an sp^2 hybridised carbon atom and are neuroleptic drugs.

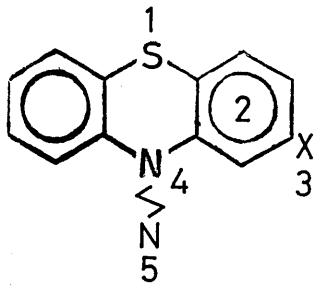


Protonated imipramine

Imipramine is a typical dibenzazepine where the ring sulphur of phenothiazine is replaced by a $-CH_2\,CH_2-$ group. This alters the pharmacology of the drugs, and they are classified as antidepressants used for treating depression.

1:2 Possible sites of metal interactions on the drug molecule

The sites available on the drug molecule can be broken down into five types: the ring sulphur, the aryl rings, the 2-position substituent, the endocyclic nitrogen and the exocyclic nitrogen.

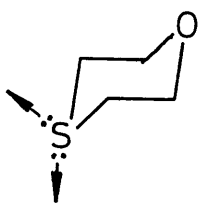


1:2:1 The ring sulphur

According to Pearson's [10] classification sulphur is a soft base. This is because it is of low electronegativity, high polarizability and is easy to oxidise. As such it would be expected to coordinate to soft acids such as Cu(I), Ag(I), Au(I), Tl(I), Hg(I), Pd(II), Cd(II), Pt(II), Hg(II) and perhaps some of the larger borderline acids such as Rh(III) and Ir(III).

In a recent review [11] it was stated that in all complexes of thioethers, the bond angles about the sulphur are approximately tetrahedral, consistent with the presence of one lone pair of electrons in an orbital that can roughly be described as sp^3 hybridised. Distortions from the ideal tetrahedral angle would be expected and are indeed found when the sulphur atom forms part of a ring, as in phenothiazine.

In a ring system, the metal may coordinate either pseudo-axially or pseudo-equatorially e.g.:-



1,4 thioxane.

In thioethers, sulphur is usually found to coordinate pseudo-equatorially as in trans dibromobis(1,4 thioxane) platinum (II).[12] It has been suggested that the platinum halide system would interact with the ring protons if axially coordinated. This suggestion is supported by the observation that when sulphur is replaced by selenium the bonding is axial, presumably because of the increased Pt-Se distance and reduced steric interaction. Also it is observed that cyclic ether ligands always coordinate equatorially.

One of the most characteristic properties of alkyl thioethers is their power to form well defined crystalline complexes with the salts of heavy metals. The most common complexes are those with $PtCl_4$, AuCl, $AuCl_3$, $SnCl_4$, $HgCl_2$, $PtCl_2$ and $ZnCl_2$. However this property is not shared by aryl thioethers, the only metal ions that form complexes with aryl thioethers (as established by X-ray studies) being Pt(II) and Hg(II).[13]

1:2:2. The aryl rings.

Various aryl rings have been found to coordinate to transition metal atoms, of low or zero oxidation number, via the π ring electrons. The first of these synthesised, ferrocene, involves an iron atom sandwiched between two cyclopentadienyl (C_5H_5) rings. Phenothiazine itself has been used as one slice of an iron sandwich system.[14] This aspect of phenothiazine metal interactions is not likely to be of biological significance.

1:2:3. The 2-position substituent

On some of the drugs the 2 position substituent contains atoms that might coordinate to metal ions. One example is the sulphur of the $-SCH_3$ substituent on thioridazine. This is effectively a half alkyl, half aryl thioether and hence might be expected to coordinate with metal ions rather better than full aryl thioethers.

1:2:4 The endocyclic nitrogen.

Nitrogen is usually classified as a hard base, the lone pair of electrons being tightly bound, although pyridine is classified as a borderline base. The endocyclic nitrogen on phenothiazine, however, is not really analagous to pyridine because the central ring is not planar (Fig. 1:1:1) and has little aromatic character. In the phenothiazine drugs the nitrogen is considered to be sp^2 hybridised and to have low basicity. This is reflected in the pKa value of 2.32 for the endocyclic nitrogen of imipramine measured in 2-methoxyethanol,[15] a low value for an amine nitrogen (see below). Despite this apparent lack of availability the endocyclic nitrogen has been frequently implicated in chelation by various authors, see Sec. 1:4.

1:2:5 The exocyclic nitrogen.

The pKa of the exocyclic nitrogen measured under the same conditions as above is 7.71. This is a typical value for such an amine and similar values would be expected for nitrogen with diethyl groups attached or nitrogens that are part of a

piperidine or piperazine ring. The availability of the nitrogen lone pair is reflected in the ease of formation of the hydrochloride salts of the drugs. It is thought that the drug interacts with the receptor site in the protonated form.[16] Tertiary amines coordinate with a wide variety of metal ions including Pt(II),[17] Ni(II),[18] Cu(II),[19] Ti(III),[20] Cr(III),[20] Mn(II),[21] Mg(II),[22] and Al(III),[23], However, compared to primary and secondary amines they are rather weak ligands.[15]

Since the drugs are protonated under physiological conditions it is sensible to consider interactions involving quaternary nitrogens with metal halide systems. It is possible for a protonated quaternary nitrogen to interact, via hydrogen bonding, to a chlorine atom on a metal system such as MCl_4^{2-}. This type of interaction has been observed for M=Cu and Co, where the nitrogen is part of a piperazine ring.[24,25]

1:2:6. Chelation

It can be shown by molecular models that a metal bonded to the ring sulphur or the 2 position substituent would also be able to interact with the exocyclic nitrogen, either directly or by hydrogen bonding.

It has been postulated for thianthrene and phenoxathiin (analagous to phenothiazine with the N(10) nitrogen replaced by S and O respectively) that chelation could occur via both heteroatoms.[26] This is unlikely for phenothiazine for the reasons given in Sec 1:2:4.

1:3 *In vivo* interactions with metals of biological significance.

Soon after the discovery of chlorpromazine in 1951 clinicians were noticing alterations in the concentrations of first row transition metals in the blood and urine of patients treated with phenothiazine drugs. Azima [27] reported that copper in blood plasma gradually rose to abnormal levels during a course of treatment with chlorpromazine. Nunez [28] found that under the same conditions of treatment, blood plasma copper concentrations dropped in all types of mental patient except manic depressives. Later Terada [29,30] found that chlorpromazine decreased the blood iron concentration temporarily and inhibited the natural diurnal variations of blood iron concentrations. Schiller [31] discovered that before administration of chlorpromazine the blood copper concentrations of schizophrenics was high and decreased after administration. Daily intramuscular injections of chlorpromazine and perphenazine (analagous to fluphenazine with the 2 position CF_3 group replaced by Cl) caused increases in the copper concentrations found in the caudate nuclei and cerebellar cortex of guinea pigs.[32] Copper at 10^{-5}M reversed the swelling of rat liver mitochondria induced by 10^{-3}M chlorpromazine.[33]

Manganese has also been studied extensively and is perhaps the most interesting of the first row transition metals because manganese poisoning exhibits extrapyramidal (Parkinson like) tremors similar to that seen in patients on high dose chlorpromazine therapy. [34] Dialysed mouse brain homogenates were found to concentrate Mn(II) and on treatment with chlorpromazine the brain was less able to bind manganese. This was assumed to be due to competitive metal complexing by chlorpromazine. [35] However subsequent work using radioactive

manganese (^{54}Mn) found that chlorpromazine did not influence manganese absorption in the mouse brain, liver or kidneys.[36] Bird [37] reported that phenothiazine therapy increased manganese concentration in the basal ganglia but that results taken over one year did not show a significant increase of manganese in the putamen.

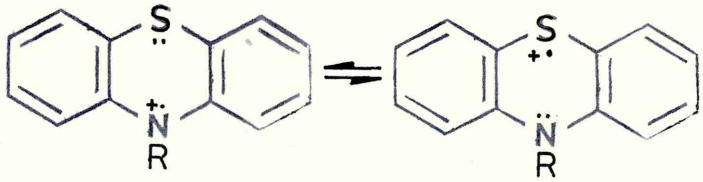
Lanthanum has also been studied in its trivalent state and evidence has been presented by Mela [38] that La(III) is a powerful inhibitor of the Ca(II) and Mn(II) uptake in rat liver mitochondria, while chlorpromazine increases the rate and extent of the La(III) induced membrane pH gradient.

Radioactive caesium (^{137}Cs) has been used to study caesium retention in the body. When chlorpromazine was administered before the caesium, the retention of caesium in the body was lowered. When the drug was administered after caesium exposure, increased caesium retention was observed.[39] Likewise using radioactive zinc (^{65}Zn) it was found that whole brain uptake of Zn was increased after treatment with perphenazine.[40]

1:4 *In vitro* interactions with metals of biological significance.

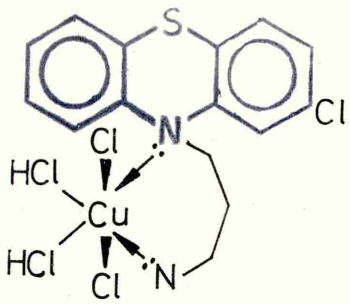
Many of the studies reported in Sec. 1:3 led to attempts to examine metal ion-phenothiazine interactions *in vitro*, with various theories being proposed and structures suggested for species observed or compounds isolated.

Chlorpromazine was found to produce a red species when reacted with Fe(III), and the product was said to be a complex and not an oxidation product.[41] Mn(II) was not found to react with chlorpromazine unless the acidity was altered to pH 7 and then back to pH 2. Under these conditions the red species (λmax 530 nm) mentioned above was again observed.[42] It has since been established that this species is a cation radical and plays a prominent role in phenothiazine-metal ion interactions (see Sec. 1:5 esp Table 1:5:1). The cation radical was found to be produced by a variety of metal ions, the structure being a resonance hybrid:-



The authors could find no link between the reaction of Mn(II) with chlorpromazine and drug action.[42] Indeed it was later established that chlorpromazine, after forming the cation radical, disproportionates into the sulphoxide and the unoxidised drug. The sulphoxide shows no anticholinergic activity.[43]

Much work has been published on Cu(II) and its reaction with various phenothiazine drugs. Huang [44] isolated a solid complex from the reaction of chlorpromazine with $CuCl_2$. The following structure was proposed:-

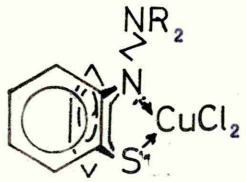


(cpz) $CuCl_2$ 2HCl

In the above stucture it was proposed that the copper was in an octahedral environment with the two nitrogens cis to one another. The product was a red crystalline material having an e.s.r. and UV solution spectra very similar to those of the chlorpromazine cation radical. No e.s.r. spectrum was observed in the solid state. The compound had a melting point of 147°C. The above structure was proposed on the basis of changes in the infrared spectra of the drug upon complexation.

Gowda [45] isolated several complexes of phenothiazine drugs, including cpz and pmz, with Cu(II). Both drugs were found to form complexes of the type $L.CuCl_2.2H_2O$, L=cpz,pmz. The complexes were brown with melting points of 141 and 112°C for L=cpz and pmz respectively. The complexes were found to be 1:1 electrolytes in dmf and methanol.

Cimpu [46] has studied promethazine interactions with a wide variety of metal ions (see Sec. 1:5) and for Cu(II) has proposed the possibility of a range of products between $CuCl_2$ and promethazine, one of which has the proposed structure and formula:-



(pmz) $CuCl_2$ $2H_2O$

The complex was light green in colour with a melting point of 92°C and was a non-electrolyte in dmf.

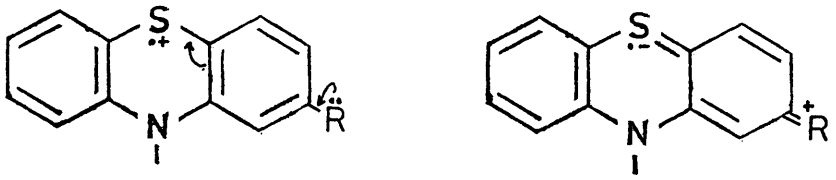
All the above three reports agree in some detail but are contradictory in others. This is surprising since the experimental detail of all three reports are similar. Huang's work was followed up by Harris [47] who gave a brief report of a crystal structure of a 1:1 adduct of chlorpromazine and $CuCl_2$. The structure discussed involved electrostatic interaction between $CuCl_4^{2-}$, present as a flattened tetrahedra, and protonated chlorpromazine. The report ended with the promise of a full publication of crystal data but this has not been reported yet.

The chelate structures proposed above are all solely based on the interpretation of changes in the infrared spectra; this approach has also been used by the same authors to propose the same structures for Pd(II) complexes with phenothiazine drugs (see Sec.1:5:3) and these proposals have been shown to be erroneous by this project.

1:5 Phenothiazine-metal ion interactions in analytical chemistry

1:5:1 Redox reactions

Alongside the investigation of the reaction with metals of physiological significance there has been extensive research into the analytical applications of various phenothiazine-metal ion reactions. Some of these involve oxidation of the drug to a cation radical (as seen for Fe(III) in Sec. 1:4) and subsequent determination by spectrophotometry at the appropriate wavelength. This wavelength is dependent on the 2 position substituent on the heterocycle, and the results are summarised in Table 1:5:1. For the various substituents in the 2 position the wavelengths found were: $-SCH_3$, 640 nm; $-OCH_3$, 570 nm; -Cl, 530 nm; -H, 515 nm; $-CF_3$, 505 nm. This trend is presumably due to an electron releasing effect of the 2 position substituent similar to that seen for aromatic substituents in electrophilic substitution on benzenoid systems. The canonical forms in this case would be:-



Thus systems having R=SCH_3 or OCH_3 in the 2 position have lone pairs available for stabilization of the cation radical, while CF_3 would withdraw electrons, thus destabilizing the cation radical. Not included in Table 1:5:1 are a variety of redox interactions including the use of the drugs as redox indicators [69–74] and the production of a stable ion pair between $SbCl_4^-$ and phenothiazine cation radical.[75] The kinetics of drug-Co(III) redox interactions have been studied.[76]

Table 1:5:1

Table of metal ion-phenothiazine interactions producing cation radical species (from the literature).

Author and reference		drug	metal system	λ max /nm	2 position substituent
Gowda	48	methiomeprazine	Au(III)	630	$-SCH_3$
Gowda	49	thioridazine	Ru(III)	640	$-SCH_3$
Gowda	50	thioridazine	Os(VIII)	640	$-SCH_3$
Rieder	51	thioridazine	Fe(III)	644	$-SCH_3$
Tarasiewicz	52	thioridazine	Fe(III)	640	$-SCH_3$
Tarasiewicz	52	levomeprazine	Fe(III)	560	$-OCH_3$
Rieder	51	levomeprazine	Fe(III)	570	$-OCH_3$
Pelizetti	53	methoxypromazine	Co(III)	566	$-OCH_3$
Pelizetti	53	hydroxypromazine	Co(III)	562	-OH
Gowda	54	prochlorperazine	Ru(III)	530	-Cl
Gowda	48	prochlorperazine	Au(III)	530	-Cl
Gowda	55	prochlorperazine	Os(VIII)	530	-Cl
Gowda	56	chlorpromazine	Ru(III)	530	-Cl
Rieder	51	chlorpromazine	Fe(III)	528	-Cl
Tarasiewicz	52	chlorpromazine	Fe(III)	525	-Cl
Tarasiewicz	52	perphenazine	Fe(III)	525	-Cl
Rieder	51	perphenazine	Fe(III)	528	-Cl
Gowda	57	promethazine	Ru(III)	516	-H
Gowda	58	promethazine	Au(III)	517	-H
Gowda	59	promethazine	Os(VIII)	515	-H
Gowda	51	promethazine	Fe(III)	512	-H
Gowda	60	mepazine	Ru(III)	514	-H
Gowda	58	mepazine	Au(III)	514	-H
Rieder	51	mepazine	Fe(III)	512	-H
Gowda	61	promazine	Ru(III)	515	-H
Rieder	51	promazine	Fe(III)	510	-H
Gowda	52	promazine	Fe(III)	510	-H
Gowda	62	diethazine	Ru(III)	515	-H
Gowda	63	diethazine	V(V)	515	-H
Gowda	48	diethazine	Au(III)	518	-H
Gowda	64	diethazine	Os(VIII)	515	-H
Tarasiewicz	52	perazine	Fe(III)	510	-H
Rieder	51	acetylpromazine	Fe(III)	513	$-COCH_3$
Gowda	65	fluphenazine	Ce(IV)	500	$-CF_3$
Rieder	51	fluphenazine	Fe(III)	500	$-CF_3$
Gowda	66	trifluoperazine	Ru(III)	500	$-CF_3$
Gowda	67	trifluoperazine	Os(VIII)	502	$-CF_3$
Gowda	48	trifluoperazine	Au(III)	502	$-CF_3$
Gowda	68	triflupromazine	Ce(IV)	503	$-CF_3$
Gowda	58	triflupromazine	Au(III)	503	$-CF_3$

1:5:2 Complex metal anions

Another interaction observed involves the use of a metal within a stable complex anion e.g. $\{M(SCN)_4\}^{2-}$ or $(MI_4)^{2-}$ (where M is a wide variety of divalent metal ions) which precipitates the drug as the protonated counter ion in an insoluble salt. Examples of this are given in Table 1:5:2. The precipitate is determined either gravimetrically or, following solvent extraction, spectrophotometrically. An alternative method involves the back titration of unused metal reagent.

1:5:3 Divalent palladium

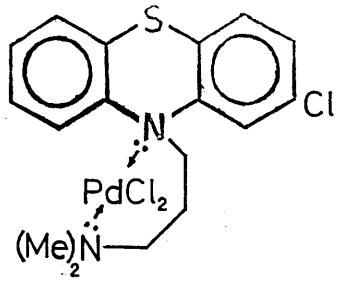
The earliest reported use of phenothiazine complexation in an analytical application was by Overholser and Yoe [98] who used $PdCl_2$ to determine phenothiazine in animal feedstuffs by measurement of the absorption, at 550 nm, of the species produced in ethanol. When drugs are reacted with $PdCl_2$ they produce species with a maximum absorbance in the visible region around 480 nm. This particular reaction has been extensively used in the determination of both the drugs and divalent palladium. It is significant that all phenothiazine ligands that are not drugs (e.g. ptz, N-ethylptz, 2-chloroptz) produce species with their λ max in the visible region around 550 nm. Because this distinction is observed in other areas of metal interaction and because it will form a major part of the discussion later, it will be convenient to denote the non-drug ligands as Class 1 ligands and the drug ligands as Class 2 ligands. These differences, which are reflected in

Table 1:5:2

Table of metal ion-phenothiazine interactions involving the production of an insoluble product via a complex anion and protonated drug.

Author and reference		drug	metal system
Basinska	77,78	chlorpromazine	$(BiI_6)^{3-}$
Basinska	79	perazine	$(HgI_4)^{2-}$
Basinska	80	various	$(CdI_4)^{2-}$
Cimpu	81	promethazine	$\{M(SCN)_4\}^{2-}$ M=Pd,Co,Fe
Ciszewska	82	chlorpromazine	lead picrates
Dembinski	83	various	$(CdI_4)^{2-}$
Dembinski	84	various	$\{Zn(SCN)_4\}^{2-}$
Dima	85	chlorpromazine	$(VO_3)^{-}$
Gajewska	86,87	various	Pb,Cu,Cd,and Zn picrates
Gowda	88	chlorpromazine	$\{W(SCN)_4\}^{-}$
Gowda	89	promethazine	$\{Co(SCN)_4\}^{2-}$
Grecu	90	various	$(TeCl_6)^{2-}$
Griffiths	91	various	$(VO_3)^{-}$
Hentrich	92	promethazine	$\{Hg(SCN)_4\}^{2-}$
Khakimov	93	diethazine	$(MCl_4)^{2-}$ M=Cu,Co
Nowakowski	94	various	$(PbI_4)^{2-}$
Olech	95	chlorpromazine	$\{Cr(SCN)_6\}^{3-}$
Tarasiewicz	96	various	$M(SCN)_4^{2-}$ M=Co,Pd $M(SCN)_6^{3-}$ M=Fe $M(SCN)_4^{-}$ M=Bi,Ru $M(SCN)_6^{2-}$ M=Ti $M(SCN)_5^{2-}$ M=W
Yung	97	various	$\{Cr(SCN)_6\}^{3-}$

Table 1:5:3, have been mentioned before but erroneously explained as the difference between bidentate (Class 2) and monodentate (Class 1) coordination.[99] The bidentate complex is the same as that postulated for the complex of $CuCl_2$ with chlorpromazine (see Sec. 1:4) :-



(cpz) $PdCl_2$

Cimpu has also proposed three different complexes for the reaction between divalent palladium and promethazine. These are $Pd(pmz)Cl_2$, $Pd(pmz)_4Cl_2$ and $Pd(pmz)_2PdCl_4$.[100] There have been 3 studies of the visible spectra of the drug-palladium complexes in a variety of ligand-metal ratios and pH.[101–103] All the above observations will be discussed in context with the results of this project in Sec. 2:2:9.

Unlike Table 1:5:1 there is no observable trend in Table 1:5:3 of the effect of the 2 position substituent on the λ max value of the visible spectra. Not included in Table 1:5:3 are a range of analytical applications reported in the literature, including using $PdCl_2$ to indicate the position of chlorpromazine on thin layer chromatography plates,[115,116] and the sorting and classifying of antihistamines before modern instrumental techniques were available.[117]

Table 1:5:3

Table of Pd(II) interactions with phenothiazines, involving species in solution. (Aqueous unless otherwise noted)

Author and reference		ligand	ligand/ metal mole ratio	λ max /nm
Gowda	99 '	phenothiazine	2:1	530
Gowda	99 '	2-Cl-phenothiazine	2:1	535
Gowda	104	2-Cl-phenothiazine	2:1	525
Overholser	98	phenothiazine	2:1	550
Lee	101	chlorpromazine	2:1	565
Puzanowska-Tarasiewicz	102	promazine	2:1	540
Tarasiewicz	103	chlorpromazine	2:1	580
Gowda	105	promethazine	1:1	470
Gowda	99 '	promethazine	1:1	430
Cavatorta	106 "	promethazine	1:1	440
Cavatorta	106 "	promazine	1:1	440
Gowda	99 '	promazine	1:1	440
Puzanowska-Tarasiewicz	103	promazine	1:1	460
Cavatorta	106 "	chlorpromazine	1:1	440
Lee	101	chlorpromazine	1:1	458
Gowda	107	chlorpromazine	1:1	495
Gowda	99 '	chlorpromazine	1:1	430
Tarasiewicz	103	chlorpromazine	1:1	465
Munoz Leva	108	chlorpromazine	1:1	484
Gowda	109	diethazine	1:1	490
Gowda	99 '	diethazine	1:1	410
Gowda	110	prochlorperazine	1:1	480
Gowda	111	trifluoperazine	1:1	480
Gowda	99 '	trifluoperazine	1:1	420
Gowda	112	triflupromazine	1:1	480
Gowda	113	thioridazine	1:1	490
Gowda	65	fluphenazine	1:1	480
Gowda	99 '	fluphenazine	1:1	440
Jovanic	114	fluphenazine	1:1	495
Jovanic	114	levomeprazine	1:1	510
Gowda	99 '	methiomeprazine	1:1	440

' spectra obtained in dmf solution
" spectra obtained in $CHCl_3$ solution

2-Cl-phenothiazine= 2-chlorophenothiazine.

1:5:4 Tetravalent platinum

There has been an interesting spectrophotometric study of Pt(IV) interactions with phenothiazine drugs. The results are summarised in Table 1:5:4. It is of interest to note the difference in the observed spectra between those drugs with alkylamino side chains and those with alkylperazine side chains, the former having a λ max around 400 nm the latter having a λ max around 500 nm in the visible region. No theory has been put forward about this phenomenon and it has not received any further study in this project.

Not included in Table 1:5:4 are a group of studies involving gravimetric determination of the product of the reaction between Pt(IV) and phenothiazine [126,127] and chlorpromazine.[128]

1:5:5 Miscellaneous interactions

These interactions are listed in Table 1:5:5 and include all those reactions not easily discussed in the previous four sections. They include a number of papers on $Co(SCN)_2$ and $CuCl_2$ complexes of phenothiazine and drugs for which the conclusions are doubtful.

Table 1:5:4

Table of Pt(IV) interactions with phenothiazine and drugs

Ligand	λ max /nm	reference
trifluoperazine	504	118
perphenazine	528	119
perazine	512	120
diethazine	404	121
profenamine	400	122
chlorpromazine	400	123
promethazine	406	124
phenothiazine	440	125

Table 1:5:5

Miscellaneous metal ion-phenothiazine reactions.

Author and reference	interaction	comments
Abdel-Wahib 129	$SbCl_5$/drugs	antimalarial preparations
Akbaev 130	$3CuCl_2$ 4ptz	antimicrobial compounds
Barbe 131-133	$Co(SCN)_2$/drugs	no solid complexes obtained
Hojman 134	$NiCl_2$/drugs	solution chemistry
Kniasseff 135	$CuCl_2$/ptz	det^{n} of ptz
Lagabeau 136	$Co(SCN)_2$/drugs	poor analytical data
Lee 137	Ferrocene/ptz	sandwich compound
Lind 138	$NiCl_2$/ptz	electroplating brightener
Mesnard 139,140	$Co(SCN)_2$/drugs	dubious formulae
Pellerin 141	Bi(III)/drugs	Bi(III) solvent extraction
Tanaka 142	Cu(II)/drugs	det^{n} of saccharin
Tribalat 143	$(HReCl_6)^-$/cpz	MIBK extraction of Re
Varhelyi 144	$K_2\{Cr(NCS)_6\}$/drug	colorimetric det^{n} of drugs
Weinberg 145	$SnCl_2$/ptz	anthelmintic compounds

MIBK = methyl isobutyl ketone (4-methyl-2-pentanone)

1:6 Objectives of the project

It is clear from the foregoing sections that despite some forty years of investigation of metal-ion phenothiazine interactions, no solid complexes with reliable analytical data had been isolated and structurally characterised (up to the end of 1981). Neither had any attempt been made to rationalise many of the solution effects observed in the analytical applications of the interactions.

The structures proposed for solid complexes are usually unlikely from a chemical point of view, since they involve the endocyclic nitrogen in coordination, this nitrogen being insufficiently basic to support such bonding.

The published analytical data have not been sufficiently accurate or useful in distinguishing between $PdLCl_2$ and $PdLHCl_3$ (L=drug).[99]

Although, according to current theories of phenothiazine drug action, first row transiton metal ions are no longer implicated in the mechanism of action of the drugs, the drugs have as yet unexplained side effects including pigmentation of the skin and eyes, so any stable complexes formed between physiologically active metal ions and the drugs might be significant in these side effects.

The importance of drug conformation on their physiological activity has been discussed in Sec. 1:1; it is possible that coordination might induce such conformational changes in the body, especially as it is known that metal complexes of ligands having biological activity are more active than the free ligands.[146]

Thus the possible aims of the project were:-

1:6:1 To obtain solid complexes with "soft" metals especially divalent palladium and platinum, and to obtain reliable analytical data on these complexes.

1:6:2 To use the data from 1:6:1 together with techniques outlined in Sec. 1:7 to propose structures of the drug-metal complexes.

1:6:3 To rationalise the solution chemistry of the drug interactions with divalent palladium using data from 1:6:2.

1:6:4 To use the expertise gained from the above, to investigate in a similar way the interaction of biologically significant first row transition metal ions with the drugs.

1:6:5 To ascertain if any such interactions, either in the solid state or in solution could be involved in, or help the understanding of, the mode of action, side effects or metabolism of the drugs.

1:6:6 To test any solid complexes obtained for possible biological activity if theoretically justified.

1:7 Techniques used for the elucidation of the composition and structure of metal complexes

1:7:1 Conductance measurements

The type of bonding present in a compound determines the species present in solution, when that compound is dissolved in a solvent. Covalent compounds exist in solution in almost the same form as in their pure state. Ionic compounds however, when dissolved in a polar solvent (e.g. water), will dissociate into their constituent ions. The properties of a solution in which dissociation occurs are radically different from those of a solution in which no dissociation occurs. The conductance of pure water is much lower than that of water containing a trace of an ionic salt. Most ions, with the exception of hydrogen, hydroxyl and long chain ions have ion conductances of about 6×10^{-3} $Sm^2 mol^{-1}$ at 25°C, and this fact may be utilised to throw light on the valency of the ions present in a solution and their mode of ionisation. By measuring the conductance of an inorganic compound it is possible to determine the the valency of the ions e.g. [147]

Electrolyte type	Molar conductance x 10^2 (in water at 25°C)
1:1	1.2 $Sm^2 mol^{-1}$
2:1	2.4 "
3:1	3.6 "
4:1	4.8 "

The technique is particularly useful in determining whether a halogen atom, or other negative group, is attached in a covalent or ionic manner:-

$\{Pt(NH_3)_4\}^{2+}2Cl^-$	2.6×10^{-2} Sm^2mol^{-1}
$\{Pt(NH_3)_3Cl\}^+Cl^-$	1.16 " " "
$K^+\{Pt(NH_3)Cl_3\}^-$	1.07 " " "
$2K^+\{PtCl_4\}^{2-}$	2.67 " " "

The other member of this group, $Pt(NH_3)_2Cl_2$ is a non-electrolyte and so produces no ions in solution; the two chlorine atoms are thus held to the central platinum atom by covalent forces.

1:7:2 Electronic spectroscopy

The visible and ultraviolet regions of the electromagnetic spectrum, that is 1000-200 nm (10 000- 50 000 cm^{-1}), are those in which electronic excitations within a molecule usually occur. Light of these wavelengths may be absorbed by a complex for a variety of reasons.

1:7:2:1 Ligand spectra

Organic molecules especially those with conjugated double bonds or aromatic rings,possess characteristic absorption bands,normally in the UV. These bands remain in the spectra of the complexes but may be shifted from their original position.

1:7:2:2 Counter-ion spectra

A complex ion must be associated with a counter-ion; a knowledge of the spectrum of this counter-ion is necessary

in order to interpret the spectrum due to the complex-ion.

1:7:2:3 Ligand field spectra

These arise from transitions between the d-orbitals of the metal that have been split in a ligand field; they are usually known as d-d spectra. For many first row transition metal ions a choice of configuration (e.g. octahedral or tetrahedral) is available. Such configurations have different ligand fields and as such would be expected to lead to different electronic spectra. The classic example of this is seen in the chemistry of divalent cobalt, where the majority of octahedral complexes are pink and the majority oftetrahedral ones are blue.

1:7:2:4 Charge transfer spectra

A requirement forusing d-d spectra to elucidate the configuration of a metal ion is that the relatively weak d-d transitions ($\epsilon \simeq 10$ $dm^{-3}mol^{-1}cm^{-1}$ in octahedral Co(II) complexes) are not masked by the more intense charge transfer spectra.

These spectra can occur even with transition metal ions having d^0 or d^{10} electron configuration e.g. Hg(II)iodide, a deep brick red colour. In such cases the colour arises, at least in part, by the absorption of light which occurs when an electron is transferred from an orbital lying principally on the ligand to an orbital principally on the metal or vice versa.

The bands are intense ($\epsilon > 1000$ $dm^{-3}mol^{-1}cm^{-1}$) and usually lie in the UV region.

1:7:3 Infrared spectroscopy

For metal complexes of organic ligands there are three areas of diagnostic interest (a) the far infrared region (400-40 cm^{-1}) (b) the fingerprint region (1400-400 cm^{-1}) and (c) the near infrared region (4000-1400 cm^{-1}). Each of these can contribute different information about the structure of the complex.

1:7:3:1 Far infrared region (400-40 cm^{-1})

This region is mainly associated with the metal-ligand and metal-halogen vibrations. These bands are intense, but the range of each mode is too large to enable assignments to be made with certainty unless a complete study of a range of compounds is undertaken. Fortunately for most commonly encountered metal-halogen species this has already been achieved, and thus by obtaining far infrared spectra and comparing them with published spectra it is usually possible to work out the isomerization (*cis*/*trans*) of the complex.

1:7:3:2 Fingerprint region (1400-400 cm^{-1})

This region contains few bands that are of diagnostic importance. However the region is so sensitive to slight changes in the bonding of any atoms in a molecule (hence fingerprint) that if any coordination has taken place it would be expected to significantly alter bands in the fingerprint region of the spectrum of a ligand, although no information would be deducible about the site of coordination. (See Sec. 3:3:3)

1:7:3:3 Near infrared region (4000-1400 cm^{-1})

Above 1400 cm^{-1} bands present can be assigned with a degree of certainty, making it an important area when attempting to elucidate sites of coordination, especially if those sites give rise to specific bands e.g. C=O,C=N. Unfortunately only one ligand studied in this project has such specific bands associated with potential sites of coordination.

1:7:4 Mass spectrometry

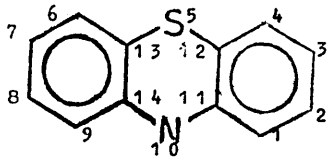
There have been a limited number of applications of mass spectrometry to relatively involatile coordination compounds, including a few studies of platinum(II) compounds. One report [148] observed parent peaks for PtL_2X_2 (L=NH_3, pyridine, $P(C_2H_5)_3$ or $P(C_6H_5)_3$; X=Cl,Br or I). It also proved possible to distiguish between *cis* and *trans* isomers of the phosphine complexes. The application of this technique is not always successful but the ease of obtaining information, together with the usefulness of a relative molecular mass determination, make it an automatic choice for compounds of unknown composition.

1:7:5 ^1H n.m.r. spectroscopy

The technique of nuclear magnetic resonance can provide much direct evidence of the site of coordination on organic ligands. However, changes in the ^1H n.m.r. spectra upon complexation must be interpreted with care as they can be attributed to four factors which are listed below.

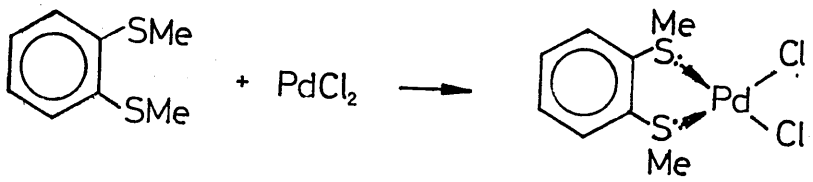
1:7:5:1 Inductive effect

The chemical shift of a particular proton is determined by its magnetic environment, i.e. the shielding caused by the electron density in the region where it is located. If this electron density is altered by coordination of an electropositive diamagnetic metal to an adjacent atom, the inductive withdrawal of electrons would be expected to shift the signal of the proton. If the electron density is reduced the proton signal would be moved downfield upon coordination, and if the effect is only inductive it would be expected to drop off rapidly along an alkyl chain.



Any coordination to the ring sulphur might not be observable for the protons attached to C(4,6), since the signal from these protons are split into a complicated multiplet along with the other six aromatic proton signals and it might prove difficult to confirm ring sulphur coordination by ^1H n.m.r.

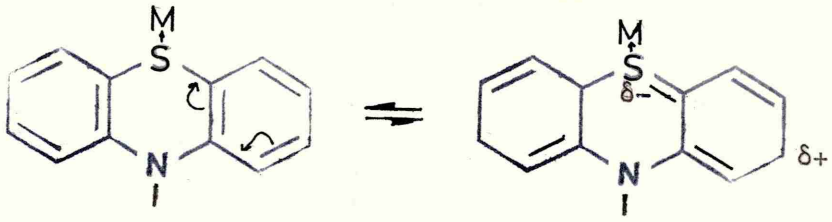
However in the case of thioridazine where the 2 position substituent is $-SCH_3$, the methyl protons on the sulphur would be affected by any coordination to that sulphur, and the singlet signal from those protons would be shifted downfield. This effect is seen for the ligand:-



Upon coordination the $-SCH_3$ singlet shifts from δ 2.38 to δ 2.61 [149]

1:7:5:2 Mesomeric effect

Any coordination to the ring sulphur of phenothiazine might induce a mesomeric shift of electrons:-



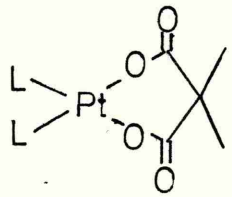
These shifts might alter signals other than those close to the site of coordination; this is particularly relevant for the ^{13}C spectra discussed below.

1:7:5:3 Changes in coupling constants

Any changes in conformation in the N(10) side chain of the Class 2 ligands upon complexation would be expected to be manifested in a change in the coupling constants of the methylene protons. The solution conformation of the propyl side chain in chlorpromazine has been investigated by this method.[150]

1:7:5:4 Interligand effects

Consider a complex:-



It is possible that in some conformations in solution the mobile electrons in the C=O bonds could affect the shielding and hence the resonance of fairly distant atoms in L.

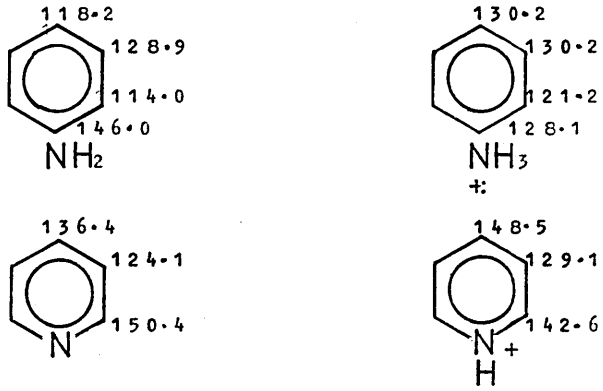
1:7:6 ^{13}C n.m.r. spectroscopy

The chemical shift range for ^{13}C n.m.r. in organic compounds is 0-230 ppm (relative to internal TMS), roughly 20 times the range observed for ^{1}H n.m.r. chemical shifts. Thus any small, subtle changes in the chemical shifts due to alteration of the electron density by through-space effects will not be observable, unlike changes due to inductive and mesomeric electron withdrawal and change in hybridisation, which are commonly observed in ^{13}C n.m.r spectra.

The advantage of ^{13}C n.m.r. is that the spectra of both alkyl and aryl carbon atoms are resolved into widely spaced singlets (assuming proton decoupling has been used) and these signals are much easier to assign to their respective carbon atoms, especially in the aromatic region, than the equivalent signals in ^{1}H n.m.r. spectra.

In the ^{13}C n.m.r. spectra of the system mentioned in Sec. 1:7:5:1 the signal from the $-SCH_3$ carbon atom shifts from δ 17.4 to δ 26.9 i.e. to lower field, as expected for increased carbonium ion character on the carbon adjacent to the site of coordination of an electropositive diamagnetic metal ion. Any coordination by the sulphur of the 2 position substituent in thioridazine would be expected to cause a similar shift in the signal from C(2).

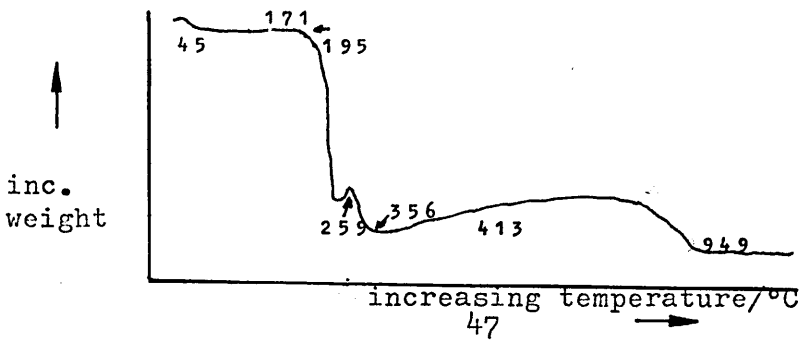
For aromatic systems the expected shifts are not so simple. This can be seen from the change in the ^{13}C signals of the following aromatic systems,[15] on protonation of the heteroatom, and hence the change on electron withdrawal from the heteroatom when it is coordinated to a metal ion.



Thus the signal from the carbon para to the site of electron withdrawal moves downfield, but the signal from the carbons adjacent to the site of electron withdrawal move upfield. Thus for phenothiazines any tendency to induce a positive charge on S(5) during coordination at that atom might produce upfield shifts in the signals from C(12,13) and downfield shifts for the rest of the signals from the aromatic carbons.

1:7:7 Thermal gravimetric analysis

This technique measures the weight loss of a substance during controlled increase in temperature of that substance. When complexes are investigated by this method it is sometimes possible to observe the loss of specific ligands. Thus the bis-(dimethylglyoximato) palladium(II) complex has the following pyrolysis curve:-[151]



After the moisture has been driven off there is a clear horizontal from 45 to 171°C corresponding to the formula $Pd(C_4H_7O_2N_2)_2$, and this decomposes, beginning at 195°C. The complex leaves behind palladium and finely divided carbon which burns from 259 to 356°C. At the same time the palladium oxidises and the oxide then dissociates above 920°C leaving palladium metal.

1:7:8 X-ray crystallography

This technique provides the ultimate arbiter in the elucidation of solid state structures and conformation of metal complexes. The theory of X-ray crystallography has been extensively reviewed [152] together with the experimental techniques and these will not be further considered. Some effects observed in the solid state are due to lattice packing forces rather than any specific chemical interaction. Thus any observations must be treated circumspectly unless a series of related compounds have been studied for comparison. The results of X-ray analysis of a structure are often different from the structure obtained from n.m.r. analysis in solution, because in solution the structure is able to change conformation by rotation about single bonds.

CHAPTER 2

Coordination of metal ions via the ring sulphur

Contents Page

As mentioned in Sec. 1:2:1 any coordination via the ring sulphur would be expected with relatively soft metal ions such as divalent palladium and platinum, or trivalent rhodium and iridium; these are the metal ions that will be discussed in this chapter.

2:1 Complexes of phenothiazine and related Class 1 ligands with divalent palladium and platinum, having a 2:1 ligand:metal ratio.

The ligands used in this part of the project are listed in Table 2:1:1. They are all based on the phenothiazine heterocycle and do not have an exocyclic quaternary nitrogen.

2:1:1 Preparation and properties of the complexes.

All the ligands react according to the scheme:-

$$K_2MX_4 + 2L \rightarrow ML_2X_2 + 2KX \quad (M=Pd,Pt;\ X=Cl,Br,I)$$

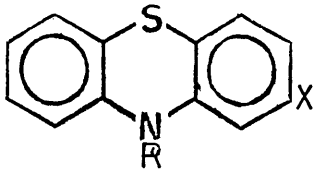
The reaction was carried out using an ethanolic solution of the ligands and an aqueous solution of the metal species. Upon mixing the solutions the ligand was initially precipitated but slowly reacted with the metal species to give a precipitated product. The complexes were only soluble in dimethylformamide (dmf) and any attempt to recrystallise

the complexes from this solvent resulted in contamination by the solvent that was difficult to remove. The complexes decomposed in dimethylsulphoxide (dmso). Table 2:1:2 details the colour, wavelengths of maximum absorption in the visible region and melting points of the complexes. The elemental analyses of the compounds are given in Appendix I.

2:1:2 Electronic spectra

Table 2:1:2 shows the λ max in the visible region of all the palladium complexes (in dmf solution). They are all located around the 500 nm wavelength. The absorptions are intense ($\epsilon > 10^3$ $mol^{-1}dm^{-3}cm^{-1}$) and probably originate from ligand to metal charge transfer, thus masking the d-d transitions within the metal itself. Little information about the stereochemistry of the complex can be deduced from the visible spectra. The fact that the charge transfer bands are found in the visible region is in agreement with the known nature of phenothiazine chemistry, that it is a heterocycle that is easily oxidised, thus enabling the transition to take place in the visible rather than the UV region of the spectrum. The platinum complex absorbs at 430 nm but for reasons explained in Sec. 2:2:2. it is not possible to correlate this with the spectra of the Class 2 complexes. However the electronic spectra of the Class 1 palladium complexes is significant in relation to the equivalent spectra of the Class 2 complexes and both will be discussed more fully in Sec. 2:2:2.

Table 2:1:1



Ligand	R	X
Phenothiazine (ptz)	-H	-H
2-Chlorophenothiazine (cptz)	-H	-Cl
N-Ethylphenothiazine (eptz)	$-CH_2CH_3$	-H
2-Thiomethylphenothiazine (tptz)	-H	$-SCH_3$
N-Dimethylcarbamoylphenothiazine (dptz)	$-CONMe_2$	-H

Table 2:1:2

Complex	mpt/°C	λ max/nm in dmf	colour
$Pd(ptz)_2Cl_2$	280-90	515	blue
$Pd(cptz)_2Cl_2$	275-80	520	blue
$Pd(eptz)_2Cl_2$	260-70	500	blue
$Pd(tptz)_2Cl_2$	275-85	515	blue
$Pd(dptz)_2Cl_2$	265-70	510	mauve
$Pt(ptz)_2Cl_2$	280-90	430	orange
$Pt(ptz)_2Br_2$	280-90	430	orange
$Pt(ptz)_2I_2$	290-95	425	orange

2:1:3 Infrared spectra

2:1:3:1 (4000-400 cm^{-1})

The infrared spectra of the various ligands and their complexes with palladium(II) and platinum(II) are tabulated in Table 2:1:2 As mentioned in Sec. 1:7, this discussion will concentrate on bands above 1300 cm^{-1} with the exception of the out of plane deformation of the aryl hydrogens, whose band occurs at 740 cm^{-1}. The aryl rings also give rise to a doublet at 1580 cm^{-1} and a strong band at 1470 cm^{-1} which arise from C-C stretching.[153] The band at 3350 cm^{-1} is due to N-H stretching.[2] Upon complexation the band at 740 cm^{-1} shifts by no more than 10 cm^{-1}, the C-C stretching bands shift to slightly higher frequency and the doublet becomes asymmetric with either a shoulder or a very much weaker band at the high frequency side. The N-H stretching band shifts to lower frequency by about 40 cm^{-1}.

From the above evidence it seems unlikely that coordination has taken place through the π aromatic system since such complexation alters the aryl hydrogen deformation by more than 10 cm^{-1}.[154] Included in Table 2:1:2 is the IR data for phenothiazine-5-oxide. The C-C stretching modes are seen to alter upon oxidation in the same way as is seen upon complexation. This supports the idea of coordination via the ring sulphur. The position regarding the ν N-H band is more complicated. A shift of similar magnitude and direction (60 cm^{-1}) was cited [155] as evidence of coordination of palladium(II) to a secondary amine. However a similar shift is observed (100 cm^{-1}) upon oxidation of the ring sulphur in going from phenothiazine to phenothiazine-5-oxide. It has been proposed [2] that this is due to the change in the available intermolecular hydrogen

Table 2:1:2

The infrared absorption frequencies (4000-400 cm^{-1}) of Class 1 ligands and their complexes with Pd(II) and Pt(II). All bands medium unless otherwise stated.

w=weak, sh=shoulder, s=strong

Phenothiazine (ptz)

430, 495, 530, 555w, 660, 686w, 718s, 738s, 750sh, 848w, 862w, 888w, 926, 1038, 1122, 1156, 1245w, 1265w, 1285sh, 1305sh, 1315s, 1440s, 1470s, 1570, 1600, 2920w, 3060w, 3350.

$Pt(ptz)_2Cl_2$

450w, 480w, 600w, 745s, 850w, 890w, 940w, 950sh, 1030, 1080w, 1125w, 1135w, 1160, 1235sh, 1250, 1285w, 1310, 1340, 1460sh, 1480s, 1510sh, 1580s, 1600sh, 2920w, 3000w, 3100w, 3200w, 3310.

$Pt(ptz)_2Cl_2$

440, 496, 550w, 600w, 685, 700w, 760s, 866, 880sh, 915, 955w, 1063, 1110, 1160sh, 1170, 1198, 1203sh, 1278sh, 1290s, 1300sh, 1320, 1350, 1460sh, 1480s, 1520sh, 1590s, 1610s, 3000w, 3300.

Phenothiazine-5-oxide

435w, 480, 510, 568, 600w, 644, 750s, 768sh, 860w, 894, 988s, 1030, 1076, 1140w, 1160w, 1230w, 1270, 1370, 1450sh, 1475s, 1530, 1590, 1620, 2930w, 2980, 3060w, 3160w, 3250.

N-Ethylphenothiazine (eptz)

408w, 450, 513w, 536, 575w, 610w, 670w, 733sh, 756s, 804w, 856w, 890, 938w, 966w, 1035, 1055w, 1080w, 1108, 1130, 1140sh, 1160w, 1230sh, 1250, 1280, 1320, 1380, 1450s, 1480sh, 1570, 1590, 2850w, 2940, 2990.

$Pd(eptz)_2Cl_2$

410w, 450, 464, 490s, 595, 680w, 720sh, 756s, 819, 848w, 895, 935, 1045s, 1070w, 1105, 1140sh, 1145, 1155sh, 1175s, 1230sh, 1245s, 1290, 1370s, 1450s, 1480sh, 1580s, 1600sh.

Table 2:1:2. cont.

N-Dimethylcarbamoylphenothiazine (dptz)

460, 530, 630sh, 650, 684, 740sh, 770s, 880w, 952, 1030, 1040sh, 1075w, 1095w, 1130, 1180, 1240sh, 1255s, 1288, 1300sh, 1310w, 1380, 1440sh, 1460s, 1480sh, 1590, 1680s, 2780, 2950.

$Pd(dptz)_2Cl_2$

460, 530w, 645, 720sh, 760s, 865, 935, 1038w, 1060w, 1130, 1165s, 1235s, 1250sh, 1330, 1380, 1440sh, 1460s, 1480sh, 1580, 1680s, 2920w.

bonding between N-H...S and N-H...O=S. With other evidence implicating sulphur bonding as the mode of coordination, it seems reasonable to propose that the shift observed in the N-H stretching band is attributable to a change in the available intermolecular hydrogen bonding between N-H...S and N-H...Cl-Pd-S. All of the changes observed for the $Pt(ptz)_2Cl_2$ complex are also observed for the complexes $Pt(ptz)_2Br_2$ and $Pt(ptz)_2I_2$.

In the case of the ligand N-ethylphenothiazine all the above trends are observed with the exception of the N-H stretching bands. For the ligand N-dimethylcarbamoylphenothiazine, there is an exocyclic tertiary amide that might be a possible site of coordination or interaction with a metal halide system. However, no change is observed in the amide carbonyl band frequency upon complexation and the rest of the trends observed above are seen in this complex, so sulphur bonding is again implicated for this complex.

2:1:3:2 (400-40 cm^{-1})

The far infrared spectra are tabulated in Table 2:1:4. In the spectrum of $Pt(ptz)_2Br_2$ there are two strong bands (Pt-Br str) at 220 and 250 cm^{-1} and two slightly weaker bands (Pt-S str) at 305 and 315 cm^{-1}. From simple group theory it is possible to assign a cis square planar conformation to the metal complex. This result supports the proposed sulphur bonding because the sulphur atom has low lying empty d orbitals available for back donation from the platinum orbitals. In order to maximise the overlap of the sulphur d orbitals with the metal d orbitals a cis square planar conformationis preferred by comparison to

Table 2:1:4

Infrared absorption frequencies (400-40 cm^{-1}) of Class 1 complexes of Pd(II) and Pt(II), in polythene solid dispersion.

Complex	ν M-X	ν M-S
$Pt(ptz)_2Br_2$	220,250(s)	305, 315 (m)
$Pt(ptz)_2Cl_2$	303,327(s)	303, 327 (s)
$Pd(ptz)_2Cl_2$	288,322(s)	288, 322 (s)

m=medium, s=strong.

a trans conformation.

The far infrared spectrum of $Pt(ptz)_2I_2$ shows similar bands (Pt-I str. at 188 and 163 cm^{-1}). The spectra of $Pt(ptz)_2Cl_2$ and $Pd(ptz)_2Cl_2$ are complicated by the overlap of the metal-halogen and metal-sulphur stretching bands and no assignments are possible.

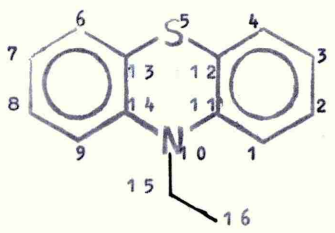
2:1:4 Mass spectra

The mass spectrum of phenothiazine has been well documented.[156] It is one of the few organic compounds to show a triply charged ion (at 66 m/e). The mass spectra of the complexes were identical with that of phenothiazine itself, and no useful information was obtained from them.

2:1:5 Nuclear magnetic resonance spectra

2:1:5:1 ^1H spectra

The ^1H magnetic resonance signals of the ligands and complexes are recorded in Table 2:1:5. The spectrum of phenothiazine is simple, with a singlet at δ 8.6 from the secondary amine proton and a multiplet at δ 6.6-7.1 from the aromatic protons. Neither of these signals is shifted significantly upon complexation and the fact that the signal from the N-H proton is not affected by complexation seems to rule out the possibility of the metal being bonded to the N(10) heteroatom.



N-Ethylphenothiazine

Table 2:1:5

^1H n.m.r. signals for Class 1 ligands and complexes in $^2H_7$ dmf, (δ/ppm).

s=singlet, t=triplet, q=quartet, m=multiplet
coupling given as J in Hz.

Phenothiazine (ptz)

8.6s, 6.6-7.1m

$M(ptz)_2Cl_2$ (M=Pd,Pt)

8.6s, 6.0-7.1m

N-Ethylphenothiazine (eptz)

6.8-7.5m, 3.93q(6.75Hz), 1.32t(6.75Hz)

$Pd(eptz)_2Cl_2$

6.8-7.5m, 3.98q(6.75Hz), 1.35t(6.75Hz)

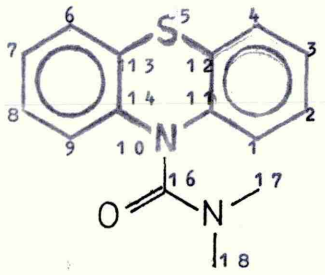
N-Dimethylcarbamoylphenothiazine (dptz)

7.0-7.6m, 2.88s

$Pd(dptz)_2Cl_2$

7.0-7.6m, 2.89s

The spectrum from N-ethylphenothiazine shows as well as the aromatic proton signals, a triplet at δ 1.32 which arises from the C(16) methyl protons and a quartet at δ 3.98 which arises from the C(15) methylene protons. Neither of these signals show any significant change in either chemical shift or coupling constant upon complexation. This effectively rules out any coordination via the N(10) nitrogen. The lack of any observed change in the coupling constant of the side chain protons is not very significant in itself but will be further discussed in relation to the eqivalent signals in the Class 2 complexes.



N-Dimethylcarbamoyl-phenothiazine (dptz)

The spectrum of N-dimethylcarbamoylphenothiazine shows, as well as the aromatic proton signals, a singlet arising from the dimethyl protons of the amide group. These signals are not shifted significantly upon complexation and this rules out any metal ion interaction via the amide nitrogen. In the three ligands discussed, the aromatic proton signals are not shifted upon coordination. Any interaction of the π aromatic protons with a metal ion would be expected to shift the aromatic proton signals by approx 1 ppm.[14]

2:1:5:2 ^{13}C spectra

Chemical shifts and assignments from the ^{13}C spectra of the ligands and complexes are recorded in Table 2:1:6. Unfortunately

Table 2:1:6

^{13}C n.m.r. signals for Class 1 ligands and complexes in $^{2}H_7$ dmf, (δ/ppm).

Phenothiazine (ptz)

142.97,C(11,14); 127.66,C(4,6); 126.54,C(2,8); 122.07,C(3,7); 117.45,C(12,13); 114.86,C(1,9).

$Pd(ptz)_2Cl_2$

142.50,C(11,14); 129.75,C(4,6); 128.87,C(2,8);122.40,C(3,7); 115.81,C(1,9).

N-Ethylphenothiazine (eptz)

145.34,C(11,14); 127.92,C(4,6); 127.48,C(2,8); 124.31,C(12,13); 122.75,C(3,7); 115.88,C(1,9); 41.82,C(15); 19.10,C(16)

$Pd(eptz)_2Cl_2$

128.13,C(4,6); 127.63,C(2,8); 122.94,C(3,7); 117.90,C(12,13); 116.12,C(1,9); 41.98,C(15); 19.28,C(16).

N-Dimethylcarbamoylphenothiazine (dptz)

194.53,C(15); 142.04,C(11,14); 128.25,C(4,6); 128.01,C(2,8); 127.03,C(12,13); 125.28,C(3,7); 120.51,C(1,9); 37.35,C(16,17).

$Pd(dptz)_2Cl_2$

194.57,C(15); 128.66,C(4,6); 128.43,C(2,8); 125.29,C(3,7); 120.67,C(1,9); 37.45,C(16,17).

the solubility of some of the complexes in dmf was insufficient to provide good spectra. N-ethylphenothiazine gives the most complete spectrum for the free ligand and complex. Most of the peaks move downfield by not more than 0.3 ppm upon complexation, the exceptions being the signal from the C(12,13) carbons adjacent to the ring sulphur, which moves upfield by more than 6 ppm. This is exactly the change in chemical shifts expected for increased electron withdrawal via the ring sulphur as explained in Sec 1:7:6. The above observations are also seen in the ^{13}C spectra of the Class 2 complexes and will be further discussed in Sec. 2:2:5:2.

In the other complexes the same trend is seen although the signal from C(12,13) is not observable because of the noise of the spectrum and the low intensity of signals derived from quaternary carbon atoms. The signal from C(11,14) is also difficult to observe for the same reason. However the signal fron C(11,14) is present in the spectra of the complexes of ptz and dptz and is not shifted significantly from its position in the free ligand. This again rules out coordination via the N(10) nitrogen.

The signal from C(15) on dptz occurs at very low field because it is a carbonyl group adjacent to two nitrogens. Upon complexation the signal does not shift significantly and this together with the lack of change in the chemical shift of the signal from C(17,18)(the methyl groups on the amide nitrogen) rules out any coordination via the exocyclic nitrogen. Thus from the n.m.r. spectra of Class 1 complexes it seems possible to assign the site of coordination,in dmf solution, as the ring sulphur in all three ligands.

2:1:6 Thermogravimetric analysis

See Sec. 2:2:7. for a discussion of the pyrolysis curves obtained from Class 1 complexes.

2:1:7 Summary

The Class 1 ligands used this part of the project all react with K_2MCl_4 (M=Pd,Pt) giving 2:1 complexes involving sulphur bonding in cis square planar complexes. All the complexes absorb with a λ max in the visible region of 500 nm. These results will be discussed more fully in Sec. 2:2:9.

2:2 Complexes of phenothiazine drugs (Class 2 ligands) with divalent palladium and platinum, having a 1:1 ligand: metal ratio.

The ligands used in this part of the project are listed in Table 2:2:1. They are all based on the phenothiazine heterocycle with an N(10) substituent consisting of a two or three carbon atom chain terminated at a quaternary nitrogen.

2:2:1 Preparation and properties of the complexes

All the ligands react according to the scheme:-

$$K_2MX_4 + LHCl \rightarrow M(LH)X_3 + KX + KCl \quad (X=Cl,Br;\ M=Pd,Pt)$$

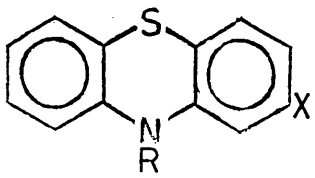
The reaction was carried out in aqueous solution using a salting out technique (see Sec. 4:2:1:2.) to ensure complete precipitation of the product. It was not possible to recrystallise the platinum complexes from dmf. Table 2:2:2 details the colour, λ max in the visible region and melting point of the complexes. It was not possible to measure the visible spectra of the platinum complexes accurately due to the overlap of the UV band from the heterocycle.

2:2:2 Electronic spectra

For the reasons mentioned above this discussion will concentrate on the visible spectra of Pd(II) complexes.

As can be seen from Table 2:2:2 the λ max in the

Table 2:2:1



Ligand	R		X
Chlorpromazine HCl	$-CH_2-CH_2-CH_2-\overset{+}{N}H(CH_3)_2$	Cl^-	-Cl
Promethazine HCl	$-CH_2-CH(CH_3)-\overset{+}{N}H(CH_3)_2$	Cl^-	-H
Thioridazine HCl	$-CH_2-CH_2\,CH(CH_2)_4\,\overset{+}{N}H(CH_3)_2$	Cl^-	$-SCH_3$

Table 2:2:2

Complex	Mpt/°C	λ max/nm	colour
$Pd(cpzH)Cl_3$	250-60	432	red
$Pd(pmzH)Cl_3$	260-70	434	red
$Pd(tdzH)Cl_3$	250-60	435	red
$Pt(cpzH)Cl_3$	300-10	-	yellow
$Pt(pmzH)Cl_3$	290-300	-	yellow
$Pt(tdzH)Cl_3$	300-10	-	yellow

visible spectra of the complexes (in dmf solution) are all located around the 430 nm wavelength. The absorptions are intense (ϵ >10 $M^{-1}cm^{-1}$) and probably arise from charge transfer transitions between the ligand and metal, (see Sec. 2:1:2.). The difference between Class 1 and Class 2 ligands, in the visible spectra of their Pd(II) complexes has already been noted in Table 1:5:3 and Sec. 1:5. The differences noted were that Pd(II)-Class 1 complexes had λ max around 550 nm in aqueous solution and Pd(II)-Class 2 complexes had λ max around 480 nm under the same conditions. This is similar to the difference seen in dmf solution for the same complexes isolated as solids in this work,(i.e. 500 nm and 430 nm respectively).The shift in wavelength is 70 nm in each class so it seems that apart from a solvent induced shift the visible spectra of the complexes isolated in this project are the same as those reported as solution interactions in the literature. Thus all the drugs investigated with Pd(II) in the literature (ca20) complex in the same way despite a wide variety of side chains on the N(10) and C(2) positions, the latter including substituents such as $-SCH_3$, $-SCH_2CH_3$, -CN, $-OCH_3$ all of which might be expected to offer the possibility of coordination to Pd(II).

In table 1:5:3 there are three exceptions to the above generalisation that Class 2 ligands form 1:1 complexes with Pd(II) that have a λ max near 480 nm in aqueous solution. These exceptions are reported by Lee, Puzanowska-Tarasiewicz and Tarasiewicz for the ligands promazine and chlorpromazine. All three authors reported the normal 1:1 complex but also studied the interaction between Pd(II) and the ligand in highly acidic (pH< 2) solution. Under such conditions the

species observed are of 2:1 ligand:metal ratio and have λ max around 550 nm. An explanation of this observation will be given at the end of this chapter after the structure of the Class 2 complexes has been discussed.

2:2:3 Infrared spectra

2:2:3:1 (4000-400 cm^{-1})

The infrared spectra of the various ligands and their complexes with palladium (II) and platinum (II) are tabulated in Table 2:2:3. Typical spectra are displayed in Fig. 2:2:1 and 2:2:2. As mentioned in Sec. 1:7 this discussion will concentrate on bands between 4000 and 1300 cm^{-1} with the exception of the out of plane deformations of the aryl hydrogens. These bands at 700 cm^{-1} do not shift appreciably upon complexation. As mentioned in Sec. 2:1:3:1 the aryl rings also give rise to a strong peak and a doublet at 1470 and 1580 cm^{-1} which arise from C-C stretching vibrations.[2] This implies that the bonding to the heterocycle is similar to that found in the Class 1 complexes i.e. through the ring sulphur. In the Class 2 ligands there is a strong band near 2500 cm^{-1} (see Fig. 2:2:1) due to $\overset{+}{N}$-H...Cl^- stretching.[157] This shifts to higher frequency upon complexation; it also diminishes in breadth and intensity. This indicates that the quaternary nitrogen is involved in some way with the complexation. An alternative explanation is that the amine hydrochloride is hydrated.[157] The presence of water molecules near the amine proton reduces the hydrogen bonding of $\overset{+}{H}$ to its Cl^- counter ion. However no O-H stretching bands are observed in the

Table 2:2:3

The infrared absorption frequencies(4000-400 cm^{-1}) of Class 2 ligands and complexes with Pd(II) and Pt(II); all bands medium unless otherwise stated.

w=weak, sh=shoulder, s=strong

Chlorpromazine HCl (cpzH.Cl)

450, 485, 525, 585, 735sh, 750s, 805s, 880sh, 930, 970, 1040, 1055w, 1100, 1128, 1140w, 1150w, 1160, 1230sh, 1246, 1280, 1320w, 1400sh, 1460s, 1560, 1590, 2420s, 2560sh, 2900sh, 3020w.

$Pd(cpzH)Cl_3$

445, 485, 530w, 550w, 590, 630w, 680w, 700w, 730sh, 755s, 800sh, 820, 864, 890, 930, 970w, 1006w, 1040sh, 1045, 1100, 1130w, 1145, 1170w, 1230sh, 1244, 1260, 1290w, 1310, 1330sh, 1380sh, 1410sh, 1480s, 1570, 1600sh.

Promethazine HCl (pmzH.Cl)

450, 520w, 540w, 602w, 620w, 735sh, 760s, 855, 860, 905w, 932, 1008w, 1035, 1045, 1109sh, 1130, 1170, 1230, 1258, 1272, 1285, 1335, 1450, 1570, 1590, 2400, 2550sh, 2990sh, 3060.

$Pd(pmzH)Cl_3$

440w, 455w, 510w, 545w, 600w, 628w, 730sh, 760s, 860w, 900w, 948w, 994w, 1040w, 1065sh, 1104w, 1160, 1175, 1225, 1250, 1300w, 1340, 1460, 1580, 1600sh, 3040.

Thioridazine HCl (tdzH.Cl)

420w, 440w, 460w, 494, 520, 540w, 570w, 590, 637w, 680w, 756s, 800s, 836, 855,910w, 934, 955, 980, 1040, 1103, 1110sh, 1140, 1150, 1172w, 1192w, 1210, 1235, 1250, 1280, 1325w, 1410sh, 1460s, 1560sh, 1570, 1590sh, 2450s, 2860w, 2920sh, 2940, 3050.

$Pd(tdzH)Cl_3$

485w, 540w, 592, 760s, 810, 860w, 930w, 970, 1040, 1110w, 1130w, 1210sh, 1250s, 1330w, 1410, 1460s, 1580, 1660sh, 3050w.

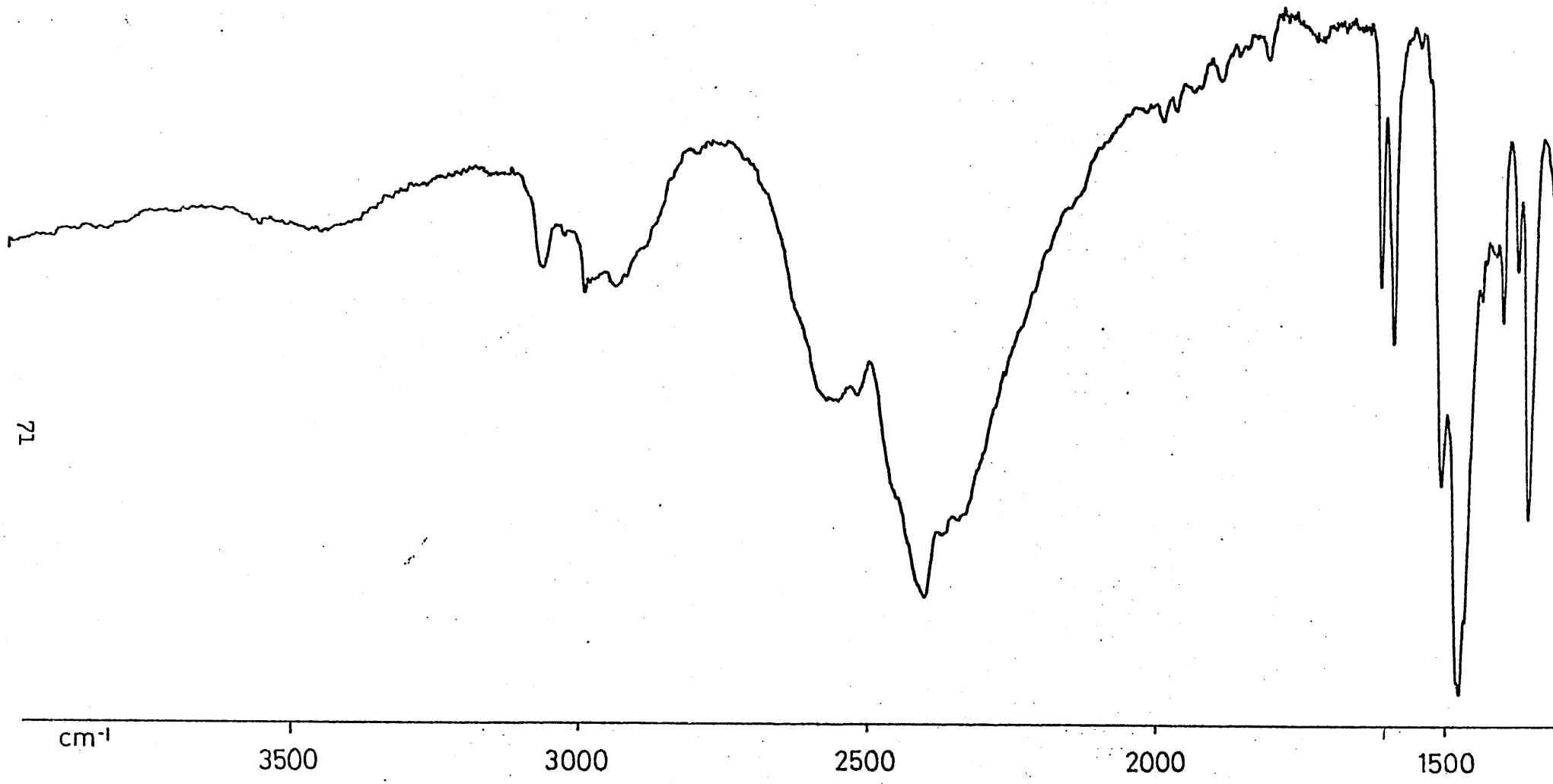


Fig 2:2:1
Infrared spectrum of promethazine hydrochloride (as KBr disc)

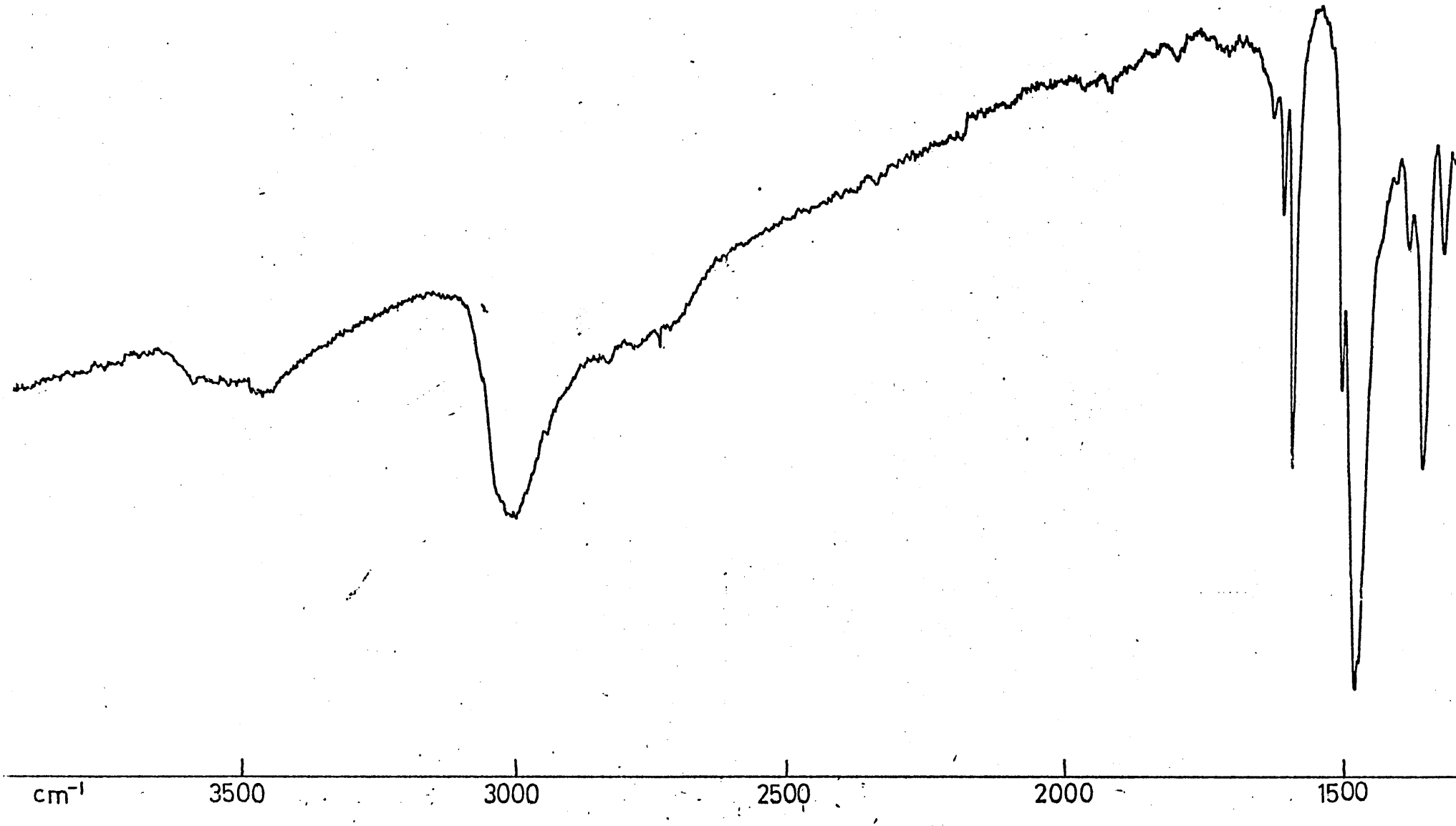


Fig 2:2:2
Infrared spectrum of $Pd(pmzH)Cl_3$ (KBr disc)

region around 3000 cm^{-1} where such a group would be expected to absorb. The shift observed above is seen in both KBr disc and dmf solution.

2:2:3:2 400-40 cm^{-1}

The far infrared spectra of the complexes are tabulated in Table 2:2:4. The spectra of the ligands were obtained and there were no bands present that interfered with the assignment given below. The main area of interest is that between 250 and 400 cm^{-1} where the M-X and M-S stretching bands occur. MX_3^- (M=Pd,Pt) has been investigated before [158] and the assignments given in Table 2:2:4 are based on this previous work. In the case of the MCl_3^- systems it was not possible to assign the metal-ligand stretching band because of the overlap of the M-Cl and M-S bands. The spectra are not significantly affected by the different N(10) and C(2) position substituents.

2:2:4 Mass spectra

The mass spectra of most of the phenothiazine drug types have been investigated by Gilbert.[156] The most abundant peaks were those from the N(10) side chain or a fragment of it. For thioridazine the most abundant peak is at m/e 98 corresponding to the N-methylpiperidine ring. In the mass spectrum of $M(tdzH)Cl_3$ both the peak at m/e 98 and the molecular ion at m/e 370 are absent. The spectra obtained from the complexes are characteristic of phenothiazine itself. This effect is observed for the corresponding complexes of

Table 2:2:4

Infrared absorption bands (400-40 cm^{-1}) of solid dispersions in polythene. Relative intensities are given in parentheses.

MX_3		Metal-ligand stretch	MX_2 asym. str. B_1	MX_2 sym. str. A_1	MX trans to L str. A
M	X				
Pd	Cl	-	348(10)	297(sh)	308(9)
Pd	Br	324(4)	263(sh)	253(8)	230(10)
Pt	Cl	-	327(10)	258(sh)	317(10)
Pt	Br	327(4)	263(sh)	256(7)	230(10)

chlorpromazine and promethazine, but in these the peak due to the side chain is still present but of diminished abundance compared to the ligand, (the molecular ion is still absent). The appearance of a peak at m/e 199 in the mass spectrum of $Pd(tdzH)Cl_3$ is especially strange because there is no peak at this position in the normal decay pattern of thioridazine itself. There is the possibility that phenothiazine is present as an impurity in the drug, although the more likely impurity is 2-thiomethylphenothiazine, but no peak at m/e 245 is observed. It seems likely that decomposition is taking place at the high temperatures needed (> 350°C) to produce spectra. This is supported by the pyrolysis curve of the complex obtained during thermal gravimetric analysis (see Sec 2:2:6). Also on careful observation of the instrument probe it is found that a considerable residue is left after running the mass spectrum of a complex.

2:2:5 Nuclear magnetic resonance spectra

2:2:5:1 ^1H spectra

The ^1H signals from the spectra of the ligands and complexes are recorded in Table 2:2:5. The spectra of $M(pmzH)Cl_3$ (M=Pd, Pt) suggested considerable dissociation in dmf and the spectra of $Pd(tdzH)Cl_3$ was not sufficiently well resolved to enable a full examination of the conformation of the side chain. It was possible to locate the singlets due to the protons on the $-SCH_3$ group and the exocyclic nitrogen $-NCH_3$. The former shifted by only 0.06 ppm and the latter by 0.43 ppm upon complexation. It is thus possible to eliminate the

Table 2:2:5

Proton n.m.r. signals for Class 2 ligands and complexes in $^2H_7$ dmf, (δ/ppm).

s=singlet, t=triplet, d=doublet, q=quartet, m=multiplet. Coupling given as N in Hz (see text)

Chlorpromazine HCl (cpzH.Cl)

6.8-7.6m, 4.16t (14.7Hz), 3.35t (15.05Hz), 2.28m (13.9Hz)

M(cpzH)Cl_3, (M=Pd,Pt)

6.9-7.6m, 4.35t (11.52Hz), 4.02t (16.30Hz), 2.45m (10.96Hz)

Thioridazine HCl (tdzH.Cl)

2.63s, 2.53s.

Pd(tdzH)Cl_3

3.06s, 2.59s.

possibility of coordination via the 2 position substituent on thioridazine, and to postulate the same interaction with Pd(II) and Pt(II) for thioridazine as will be postulated for chlorpromazine in solution.

The spectra of $M(cpzH)Cl_3$ (M=Pd,Pt) were well resolved and the following analysis was possible. The spectrum of the ligand shows multiplets at δ 7.0 due to the aromatic protons, and at δ2.28 due to the protons on C(16), and a singlet at δ 2.73. At δ 4.16 and 3.35 there are what at first sight appear to be triplets. It was possible to assign the spectrum of the side chain from literature values [159] thus:-

$$N(10)\text{-}CH_2(15)\text{-}CH_2(16)\text{-}CH_2(17)\text{-}\overset{+}{N}H(18)\text{-}(CH_3)_2(19,20)$$
$$\delta\ 4.16 \quad \delta\ 2.28 \quad \delta\ 3.35 \qquad \delta\ 2.73$$

On complexation the spectrum of the side chain shows triplets at δ 4.35 and 4.02, a multiplet at δ 2.45 and a singlet at δ 3.02. It was necessary to ascertain whether, upon complexation, the signal from the protons on C(15) had moved upfield to δ 4.02 and the signal from the protons on C(17) downfield to δ 4.35, or whether both the signals from the C(15) and C(17) protons had moved downfield to δ 4.35 and 4.02 respectively.

This was achieved by irradiating the sample with frequencies that fall either side of those observed for the protons on C(15) and C(17); i.e. at δ 0, 1.1, 3.6, 4.8 and 6.1 and observing the separation of the triplet ^{13}C signals from C(15) and C(17). The nearer the irradiation frequency gets to the frequency of the protons on C(15) the smaller will be the separation of the lines of the (15) triplet until, when the frequency of irradiation is exactly that of the

protons the triplet signal coalesces to a singlet. (The same process is applied to the protons on C(17)). In order to obtain maximum accuracy with this method the results are plotted graphically (Fig.2:2:3 and 4) and the results show that C(15) is associated with a signal at δ 4.52 (4.35 observed) and that C(17) is associated with a signal at δ 4.00 (4.05 observed). It is thus possible to assign the proton signals of the complex:-

$$\underset{\delta\ 4.35}{N(10)\text{-}CH_2(15)\text{-}}\underset{\delta\ 2.45}{CH_2(16)\text{-}}\underset{\delta\ 4.02}{CH_2(17)\text{-}}\overset{+}{N}H(18)\text{-}\underset{\delta\ 3.02}{(CH_3)_2(19,20)}$$

Thus all the signals have been shifted downfield upon complexation. The magnitude of the shifts seem to preclude them being due to a change in the charge density on N(18) especially as it is difficult to see how N(18) could be more electropositive in the complex than it is in the hydrochloride salt. A possible explanation of this phenomenon will be presented after a discussion on the conformation of the side chain in solution.

The triplets discussed above, from the protons on C(15) and C(17), are on closer inspection not from a first order process, but rather due to AA′ BB′ coupling. This can best be explained by reference to the Newman projections of the side chain (Fig. 2:2:5)

At room temperature one would expect the side chain to be rapidly rotating about the C-C single bonds, spending equal time in each of the three isomeric states. When rapid internal rotation is occuring the coupling constants assume average values of the constants in the fixed isomeric states.

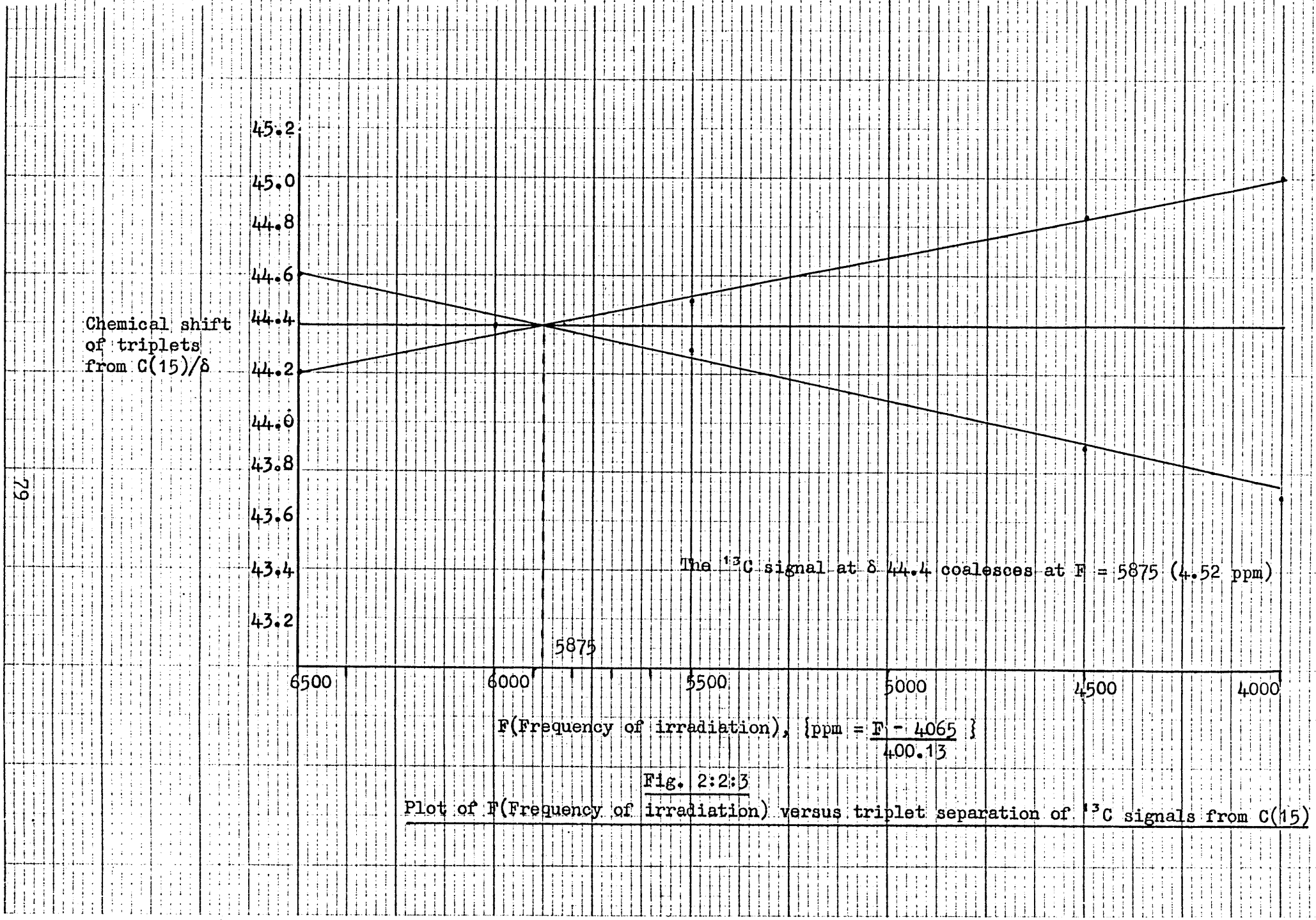


Fig. 2:2:3

Plot of F(Frequency of irradiation) versus triplet separation of ^{13}C signals from C(15)

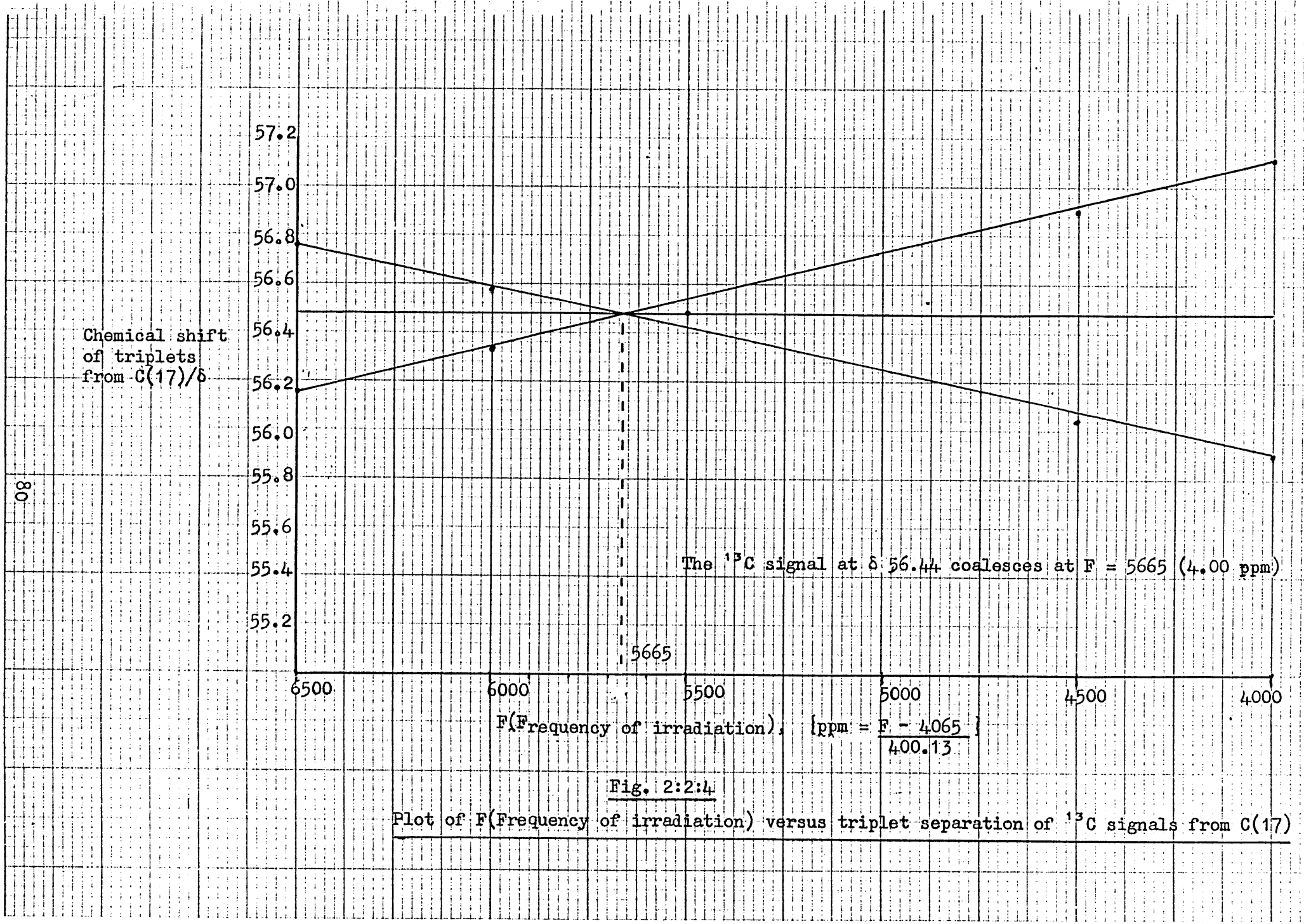
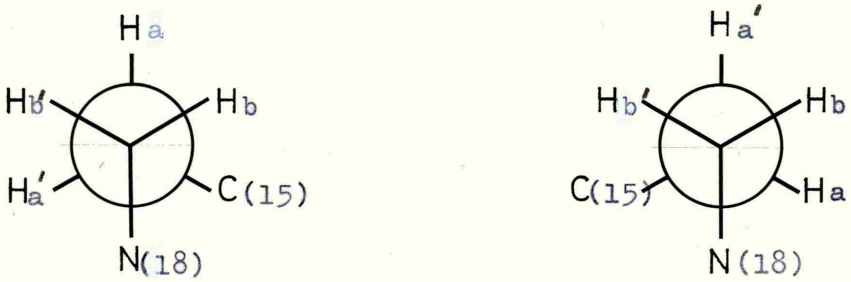


Fig. 2:2:4

Plot of F(Frequency of irradiation) versus triplet separation of ^{13}C signals from C(17)

For the projection along C(16,17) we have either of the gauche conformations:-



or the trans conformation:-

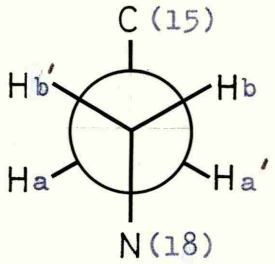


Fig. 2:2:5 Newman projection of chlorpromazine hydrochloride N(10) side chain.

Despite the fact that the chemical shifts of the hydrogen nuclei in each of the two CH_2 groups become equally shielded due to averaging processes associated with the internal rotation, the four nuclei remain magnetically non-equivalent (i.e. AA' BB') since the spin-coupling constants between one of the A hydrogen nuclei and the two B hydrogen nuclei need not be equal.

Because $J_{AB} \neq J_{AB'}$ it is not possible to use coupling constants per se but it is more convenient to formulate the basic equations [150] in terms of the parameter N ($N = \left| J_{AB} + J_{AB'} \right|$) which is simply defined as the separation between the outer lines of the triplet pattern. The observed value of N is then the weighted average of the value of the trans (Nt) and gauche (Ng) conformations :-

$$N_{obs} = ng.Ng + nt.Ng \qquad (1)$$

Ng and Nt are the observed values in piperidine (the $CH_2\,CH_2$ fragment is entirely in the gauche form) and $Bu^t\text{-}CH_2\,CH_2\,NMe_3^+\ I^-$ (the $CH_2\,CH_2$ fragment is entirely in the trans form). These values are [160] :-

Ng = 11.67 Hz Nt = 17.37 Hz

Thus from N_{obs} in Table 2:2:5 it is possible to calculate ng and nt, the populations of the gauche and trans isomers of the $CH_2\,CH_2$ fragments in the side chain of the ligand and complex. These values are tabulated in Table 2:2:6.

Table 2:2:6

ng/nt isomer population ratio in chlorpromazine HCl and $M(cpzH)Cl_3$ (M=Pd,Pt)

Bond	Drug	Complex
C(15)-C(16)	59/41	100/0
C(16)-C(17)	33/67	19/81

Thus in solution there is a considerable change in the conformation of the side chain upon complexation. The C(15)-C(16) isomer population changes from 59(ng),41(nt) to totally gauche. This a surprising result but it seems the side chain is specifically limited to this one conformation, which is the same conformation as is found in the solid state for the complex $Pd(cpzH)Cl_3$. (The N(10)-C(15)-C(16)-C(17) torsion angle is -62.49° in the solid state). However unlike solid state conformations, those seen in solution cannot be due to crystal packing forces and this strong gauche preference must be due to energy gained from the interaction between the MCl_3^- anion and the quaternary nitrogen N(18). This interaction is facilitated in the solid state by the adoption of the scorpion like conformation shown in Fig. 2:2:11. Assuming that in dmf the complex adopts the same scorpion structure this offers a possible explanation of the downfield shifts of the proton signals of the N(10) side chain seen above. In the solid state the side chain is located almost parallel with and above the $PdCl_3S$ plane (Fig. 2:2:13). It has been

shown that a proton located 2.3 Å from Pd in a $PdCP_2Br$ plane has an n.m.r. proton signal shifted by approx. 2ppm from that in the free ligand (Fig. 2:2:6)[161]

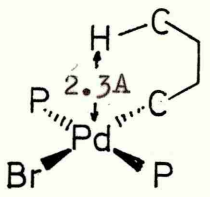


Fig. 2:2:6

Assuming that in $Pd(cpzH)Cl_2$ the distance of the side chain carbon atoms from the palladium atom in solution are similar to those seen in the solid state, it is possible to tabulate these distances versus the change in chemical shift ($\delta\Delta$) of the side chain protons upon complexation. These values are given in Table 2:2:7

Table 2:2:7

Relationship between $\delta\Delta$ (the change in chemical shift upon complexation) and the associated C-Pd distance.

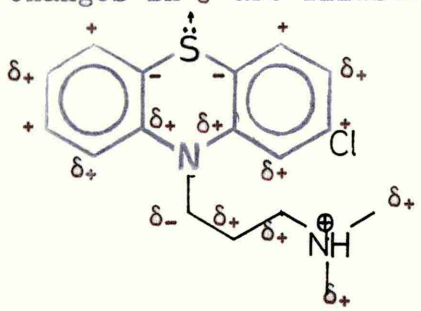
Protons on	distance of C from Pd/ Å	$\delta\Delta$	$\delta\Delta$ /proton
C(15)	5.1	0.19	0.095
C(16)	5.1	0.17	0.085
C(17)	4.1	0.67	0.34
C(19,20)	5.3 (av)	0.29	0.05

The values of $\delta\Delta$ /proton show a linear dependance on the Pd-C distance. This is difficult to explain but it is possibly due to the metal d-electron shielding, though this

gives no basis for the linearity of the effect. In the solid state the interaction between the $PdCl_3^-$ anion and the N(18) cation is one of hydrogen bonding. It is not possible to ascertain from the n.m.r. spectra the type of bonding in dmf solution. However the infrared dmf solution spectra of the complexes all show the presence of $\overset{+}{N}$-H...Cl stretching indicative of hydrogen bonding.

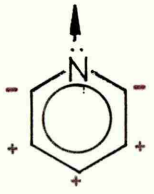
The changes in coupling constants in the N(10) side chain of chlorpromazine HCl upon coordination are in marked contrast to the lack of any such changes in the coupling constants from the N(10) side chain in N-ethyl-phenothiazine upon complexation. This rules out the possiblity that the above changes are due to the presence of the palladium or platinum ion in solution.

The ^{13}C nuclear magnetic resonance signals of chlorpromazine hydrochloride and its complexes with MCl_3^- (M=Pd,Pt) are recorded in Table 2:2:8,together with the change in chemical shift upon complexation, defining $\delta\Delta$ as positive if the shift is from high to low field (i.e. small to large δ value). Using this convention the carbon atoms which have increased carbonium ion character have positive $\delta\Delta$. The largest shift upon complexation is -9 ppm for C(12,13) which is similar to that seen for N-ethylphenothiazine and its $PdCl_3^-$ complex. All the changes in δ are illustrated below:-



changes in the chemical shift upon complexation for $Pd(cpzH)Cl_3$
δ implys a small change.

It is not possible to explain the observed change in $\delta\Delta$ by simple inductive withdrawal of electrons via the ring sulphur. As discussed in Sec. 1:7:6, electron withdrawal because of protonation of a ring heteroatom or substituent leads to a change in the chemical shift similar to those seen here for chlorpromazine on complexation. Using the δ values given in Sec. 1:7:6. we can illustrate the change in δ upon protonation of the nitrogen in pyridine or aniline:-



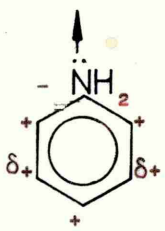
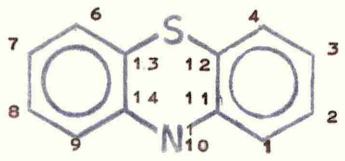


Table 2:2:8

^{13}C n.m.r. signals for cpzH.Cl and $M(cpzH)Cl_3$ in $^2H_7$ dmf (δ /ppm). Change in chemical shift upon coordination = $\delta\Delta$

Carbon atom	Chlorpromazine hydrochloride	$M(cpzH)Cl_3$ M=Pd,Pt	$\delta\Delta$
C(11)	147.14	147.96	+0.82
C(14)	144.61	145.70	+1.09
C(2)	133.62	136.03	+2.41
C(4)	128.71	133.08	+4.37
C(6)	128.51	132.07	+3.56
C(8)	127.90	130.74	+2.84
C(3)	123.83	123.12	-0.71
C(7)	123.06	122.46	-0.60
C(1)	117.22	117.43	+0.21
C(9)	116.63	117.03	+0.40
C(13)	124.76	116.02	-8.74
C(12)	123.59	114.62	-8.97
C(17)	54.97	56.48	+1.51
C(15)	45.11	44.16	-0.95
C(19,20)	42.35	43.59	+1.24
C(16)	22.32	23.23	+0.91

For M=Pt C(4,6) have satellites at 133.6, 132.55 and 132.26, 131.54 respectively, (see text).



Assuming that electron withdrawal via protonation of the nitrogen is analogous to electron withdrawal via metal bonding to the ring sulphur in phenothiazine, the results displayed above for aniline are similar to those observed for the phenothiazine heterocycle in the ligands used in this chapter. The most surprising change in chemical shift is that seen for C(12,13) where the $\delta\Delta$ value is -9 ppm which signifies a lowering of the positive charge on complexation. However exactly the same result for the carbon atoms adjacent to the site of protonation in aniline and pyridine above,

The carbon atoms C(3,7) also have a slightly negative $\delta\Delta$ value. This is not observed in the analogous atoms in aniline and pyridine, however in aniline the meta carbon atoms only show a small positive $\delta\Delta$ value and such a value might be observed in the C(3,7) atoms if it were not for the fact that para to these two atoms is N(10) whose lone pair is possibly affecting the charge density on C(3,7). This idea is supported by the observation that in the palladium complex of thioxanthrene (N(10) replaced by CH_2) C(3,7) show a small positive $\delta\Delta$ value.

Further evidence of the sulphur bonding to $PtCl_3^-$ is obtained from the observation of ^{195}Pt-^{13}C coupling between the metal and the C(4,6) atoms:-

^{195}Pt-$^{13}C(4)$ = 20.6 Hz

^{195}Pt-$^{13}C(6)$ = 14.4 Hz

C(12,13) do not show such satellites but this is possibly because they are low intensity signals (being derived from quaternary carbon atoms) and the satellites being of still lower intensity are lost amongst the noise of the 80 MHz spectrum. It is not possible to observe the coupling on the 400 MHz spectrum because of chemical shift anisotropy which is proportional to B_o^2 (B_o is the field strength)

2:2:6 Thermogravimetric analysis

Both Class 1 and Class 2 complexes show a pyrolysis curve of the type shown in Fig 2:2:7.

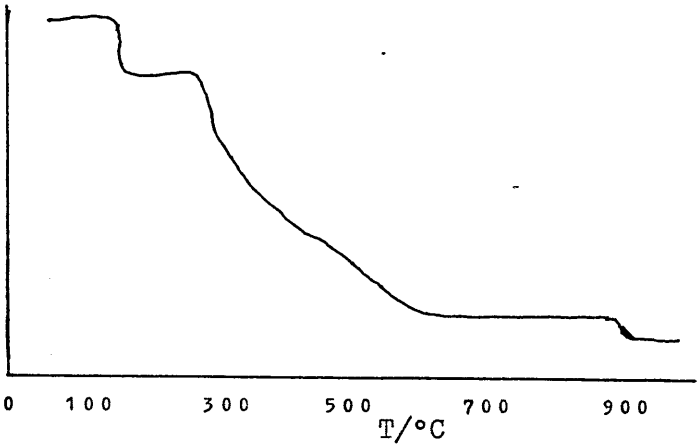


Fig. 2:2:7. Pyrolysis curve for $M(LH)Cl_3$ and ML_2Cl_2. (L=all ligands used in this project, M=Pd,Pt)

As can be seen a stable weight is found at about 200-300°C but it is probable that this comprises of more than one species because it is not possible to correlate the composition of this plateau with the possible permutations of metal, halogen and ligand residue. It is possible to assign the transition at 900°C to the reduction of M oxide to M metal.

2:2:7 X-ray crystallographic analysis

The crystal structure of most of the important phenothiazine drugs have been reported. These include promethazine hydrobromide [162] and chlorpromazine hydrochloride [163]. Both structures are reproduced in Figs 2:2:8 & 9.

The crystal structures of the $PdCl_3^-$ complexes of the above two drugs have both been elucidated as part of this project. There are certain similarities between the two structures which will be discussed first, with the help of Tables 2:2:9 & 10.

2:2:7:1 Structural similarities in $Pd(pmzH)Cl_3$ and $Pd(cpzH)Cl_3$

Both ligands are sulphur bonded to the $PdCl_3^-$ anion (Figs 2:2:10 & 11) such that the resulting $PdCl_3S$ unit is effectively planar and angles around Pd range from 86.2 to 93.4°.

The phenothiazine ring system is both tilted and twisted with respect to the $PdCl_3S$ plane. The Pd-S(5)-N(10) angle is 90.1° in $Pd(pmzH)Cl_3$ and 92.9° in $Pd(cpzH)Cl_3$. The N(10)-S(5)-Pd-Cl(2) torsion angle takes values of 68.5 and 73.4° for the pmz and cpz complexes respectively. (Figs 2:2:12 & 13). Thus palladium is pseudoaxially bonded to the heterocycle, which is opposite to that usually found for ring sulphurs (Sec. 1:2:1). This is possibly because, if the $PdCl_3^-$ anion was attached pseudoequatorially it would not be able to interact with the quaternary nitrogen on the N(10) side chain. Also most of the previous occurrences have involved sulphur as part of a saturated ring where axial coordination

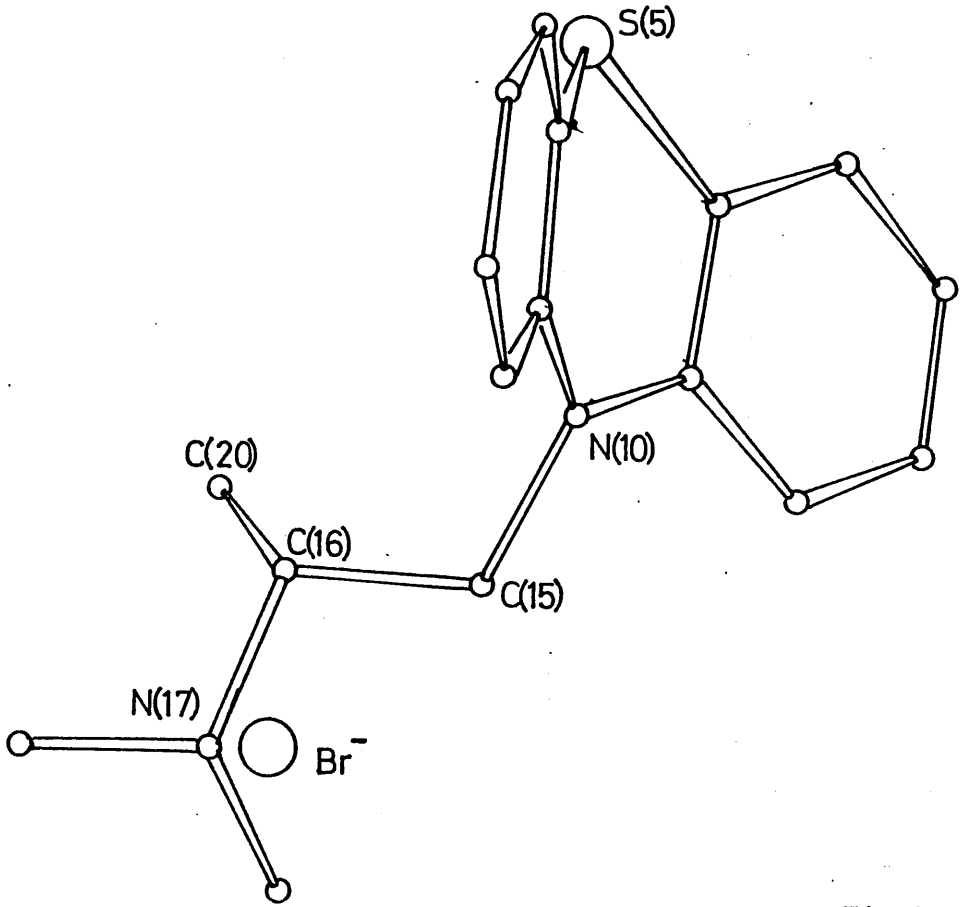


Fig 2:2:8

Molecular structure of promethazine hydrobromide (pmzH.Br)

For clarity all hydrogen atoms have been omitted, the ring carbons are numbered on page 8.

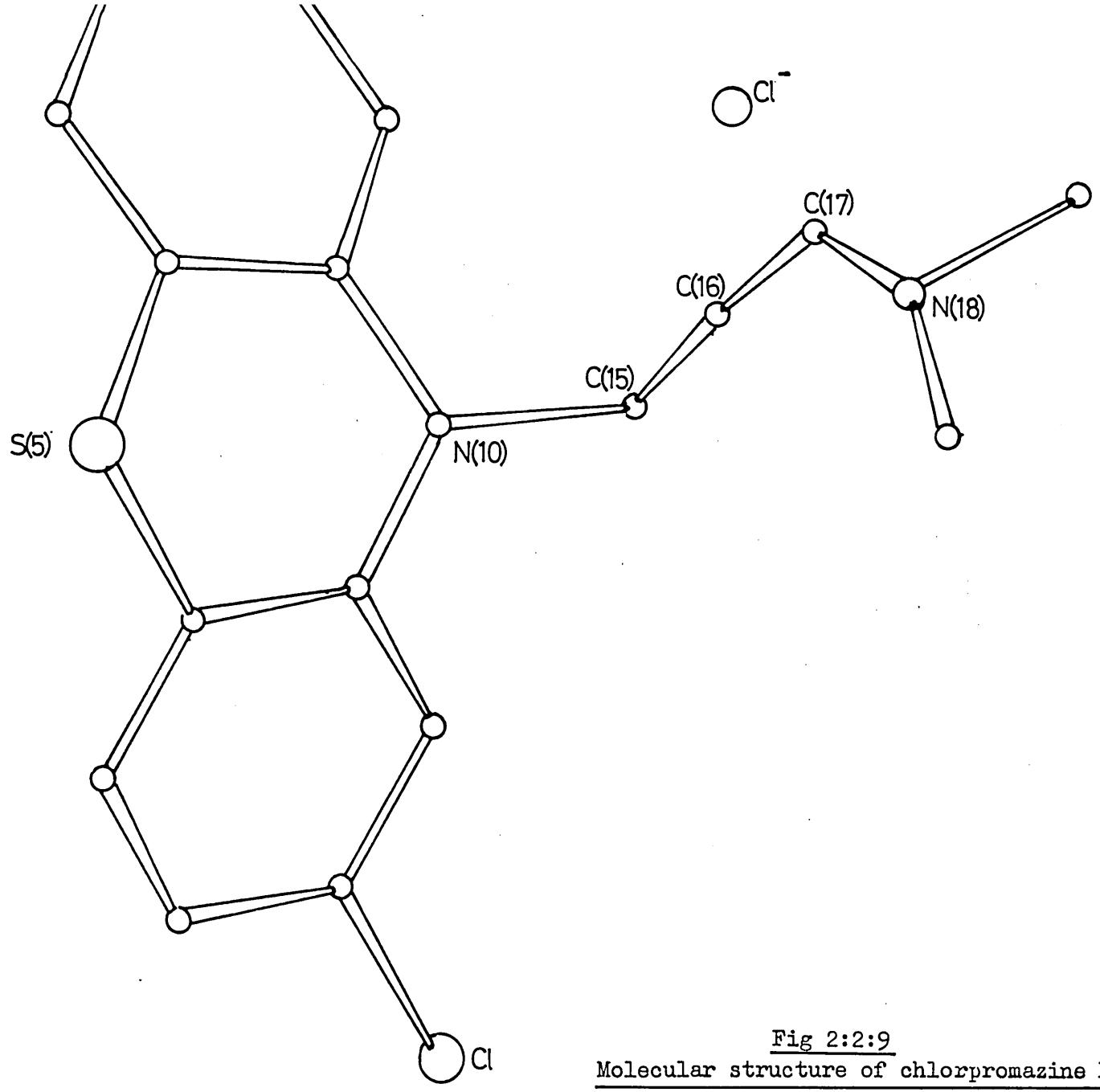


Fig 2:2:9
Molecular structure of chlorpromazine hydrochloride (cpzH.Cl)

Table 2:2:9

Comparison of bond distances (Å) for $Pd(pmzH)Cl_3$ and $Pd(cpzH)Cl_3$

Bond	$Pd(pmzH)Cl_3$	$Pd(cpzH)Cl_3$
Pd-Cl(1)	2.292(3)	2.298(6)
Pd-Cl(2)	2.283(3)	2.295(6)
Pd-Cl(3)	2.328(2)	2.310(4)
Pd-S(5)	2.296(2)	2.307(4)
C(12)-S(5)	1.758(10)	1.707(16)
C(13)-S(5)	1.771(11)	1.818(22)
C(1)-C(11)	1.387(15)	1.401(25)
C(1)-C(2)	1.384(18)	1.430(28)
C(2)-C(3)	1.400(19)	1.400(31)
C(3)-C(4)	1.367(18)	1.394(31)
C(4)-C(12)	1.375(17)	1.419(27)
C(11)-C(12)	1.418(12)	1.411(25)
C(6)-C(7)	1.367(18)	1.390(37)
C(7)-C(8)	1.386(18)	1.375(40)
C(8)-C(9)	1.372(25)	1.367(34)
C(9)-C(14)	1.389(15)	1.417(30)
C(13)-C(14)	1.397(13)	1.352(27)
C(6)-C(13)	1.397(16)	1.389(28)
C(11)-N(10)	1.396(15)	1.436(26)
C(14)-N(10)	1.418(13)	1.396(24)
N(10)-C(15)	1.515(12)	1.469(24)

Table 2:2:10

Comparison of bond angles (°) from $Pd(pmzH)Cl_3$ and $Pd(cpzH)Cl_3$

Bond angle	$Pd(pmzH)Cl_3$	$Pd(cpzH)Cl_3$
Cl(1)-Pd-Cl(2)	173.8(1)	175.5(2)
Cl(1)-Pd-Cl(3)	91.0(1)	88.7(2)
Cl(1)-Pd-S(5)	86.4(1)	86.2(2)
Cl(2)-Pd-Cl(3)	90.6(1)	91.6(2)
Cl(2)-Pd-S(5)	92.2(1)	93.4(2)
Cl(3)-Pd-S(5)	176.2(1)	175.0(2)
Pd-S(5)-C(12)	110.9(3)	112.7(4)
Pd-S(5)-C(13)	106.1(3)	107.0(5)
C(12)-S(5)-C(13)	97.3(5)	96.6(9)
S(5)-C(12)-C(4)	118.9(8)	120.3(14)
S(5)-C(12)-C(11)	119.8(8)	120.6(14)
C(4)-C(12)-C(11)	121.6(10)	119.1(16)
C(3)-C(4)-C(12)	120.7(11)	120.0(23)
C(2)-C(3)-C(4)	119.5(12)	121.1(19)
C(1)-C(2)-C(3)	119.7(11)	119.6(20)
C(2)-C(1)-C(11)	120.0(10)	119.0(18)
N(10)-C(11)-C(12)	119.7(9)	119.4(15)
C(11)-N(10)-C(14)	117.7(7)	117.0(13)
C(1)-C(11)-C(12)	119.7(9)	121.2(17)
C(11)-N(10)-C(15)	117.9(8)	120.6(15)
N(10)-C(14)-C(9)	123.0(8)	122.4(17)
N(10)-C(14)-C(13)	119.5(9)	119.8(18)
C(9)-C(14)-C(13)	119.5(9)	117.5(17)

Table 2:2:10 cont.

C(8)-C(9)-C(14)	120.4(10)	119.5(21)
C(7)-C(8)-C(9)	121.8(13)	121.2(23)
C(6)-C(7)-C(8)	118.8(12)	120.9(24)
C(7)-C(6)-C(13)	119.9(10)	116.4(21)
C(6)-C(13)-S(5)	119.0(8)	114.9(16)
C(6)-C(13)-C(14)	121.4(10)	124.5(20)
S(5)-C(13)-C(14)	119.6(8)	124.5(20)

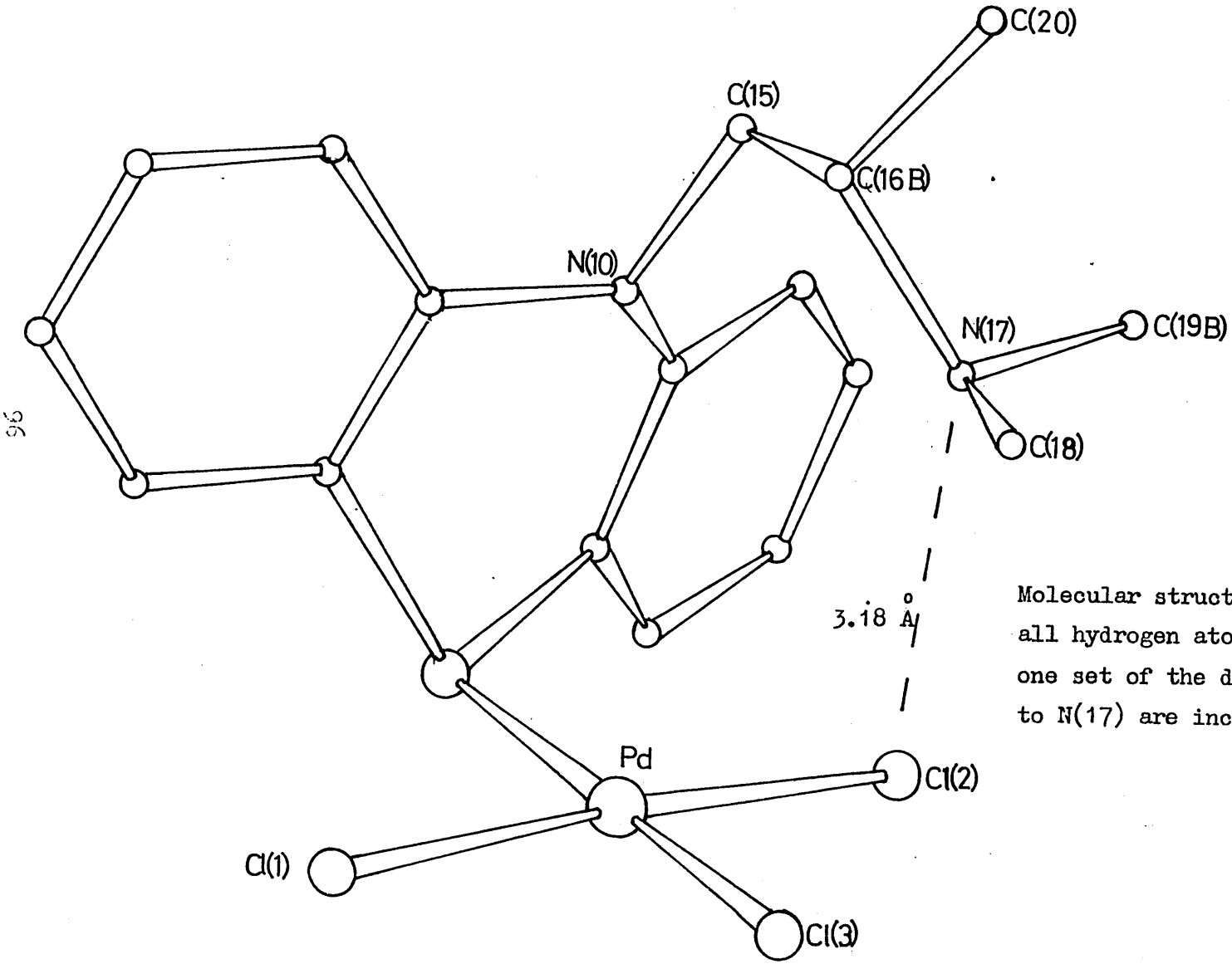


Fig 2:2:10

Molecular structure of $Pd(pmzH)Cl_3$. For clarity all hydrogen atoms have been omitted and only one set of the disordered carbon atoms attached to N(17) are included.

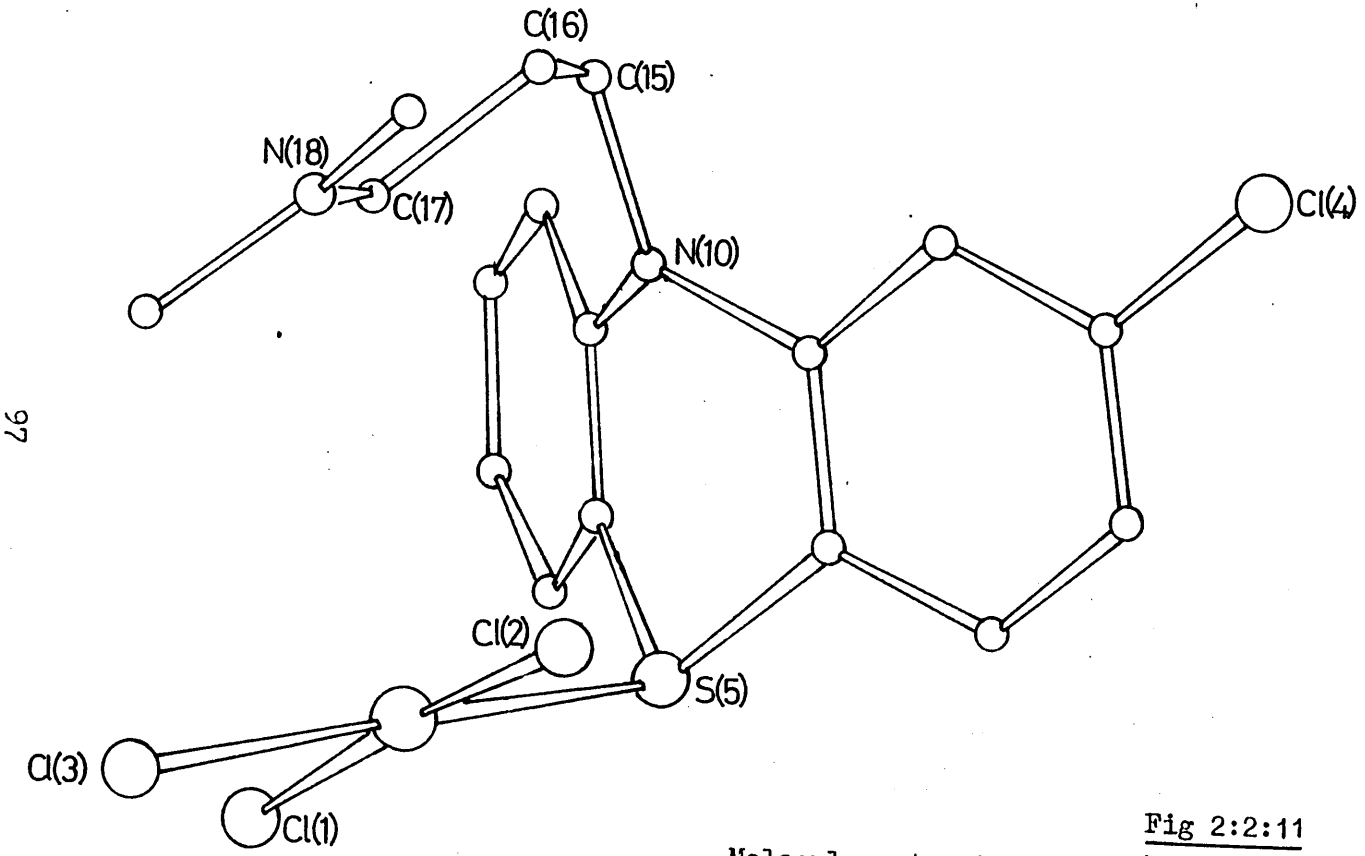


Fig 2:2:11

Molecular structure of $Pd(cpzH)Cl_3$, for clarity all hydrogen atoms have been omitted.

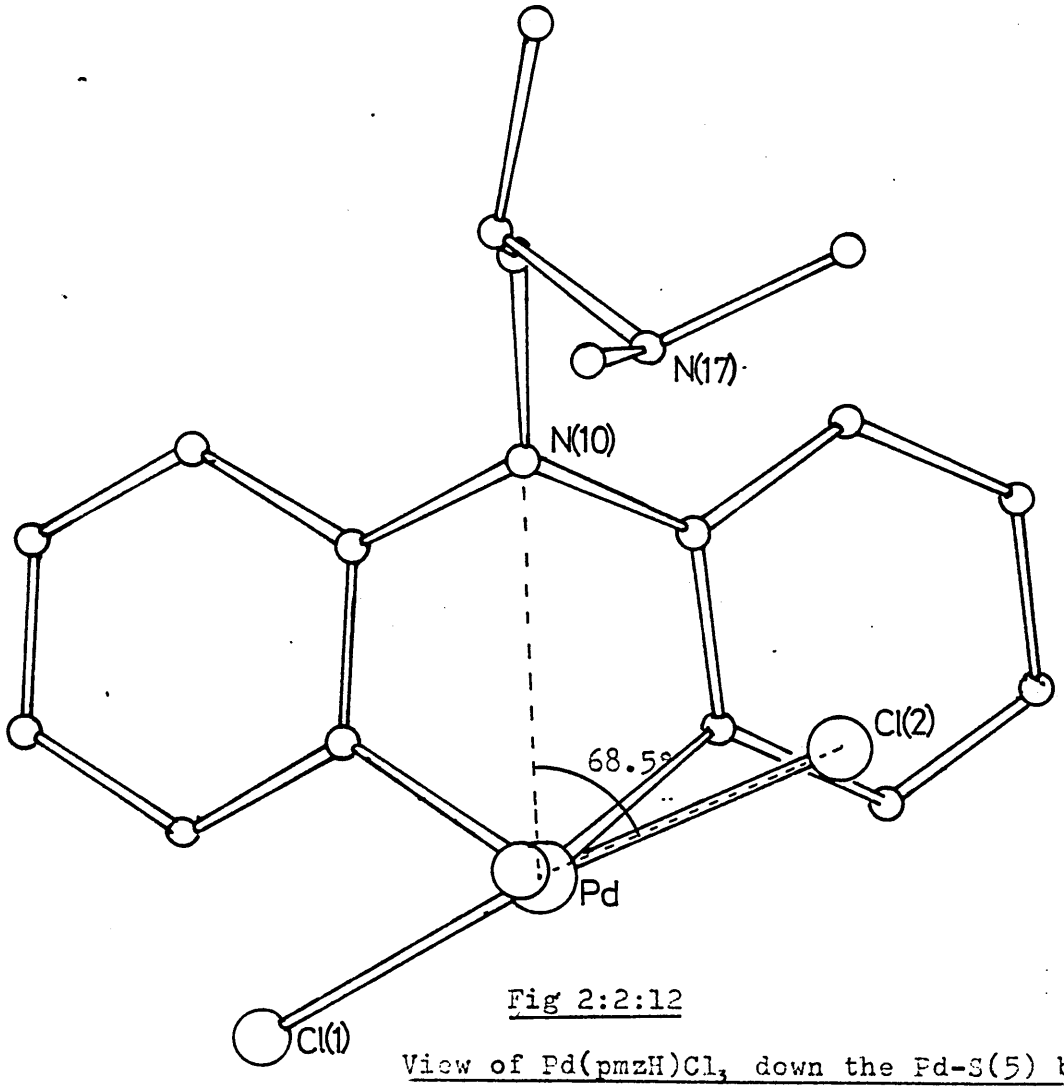


Fig 2:2:12

View of Pd(pmzH)Cl$_2$ down the Pd-S(5) bonds showing the Cl(2)-Pd-S(5)-N(10) torsion angle.

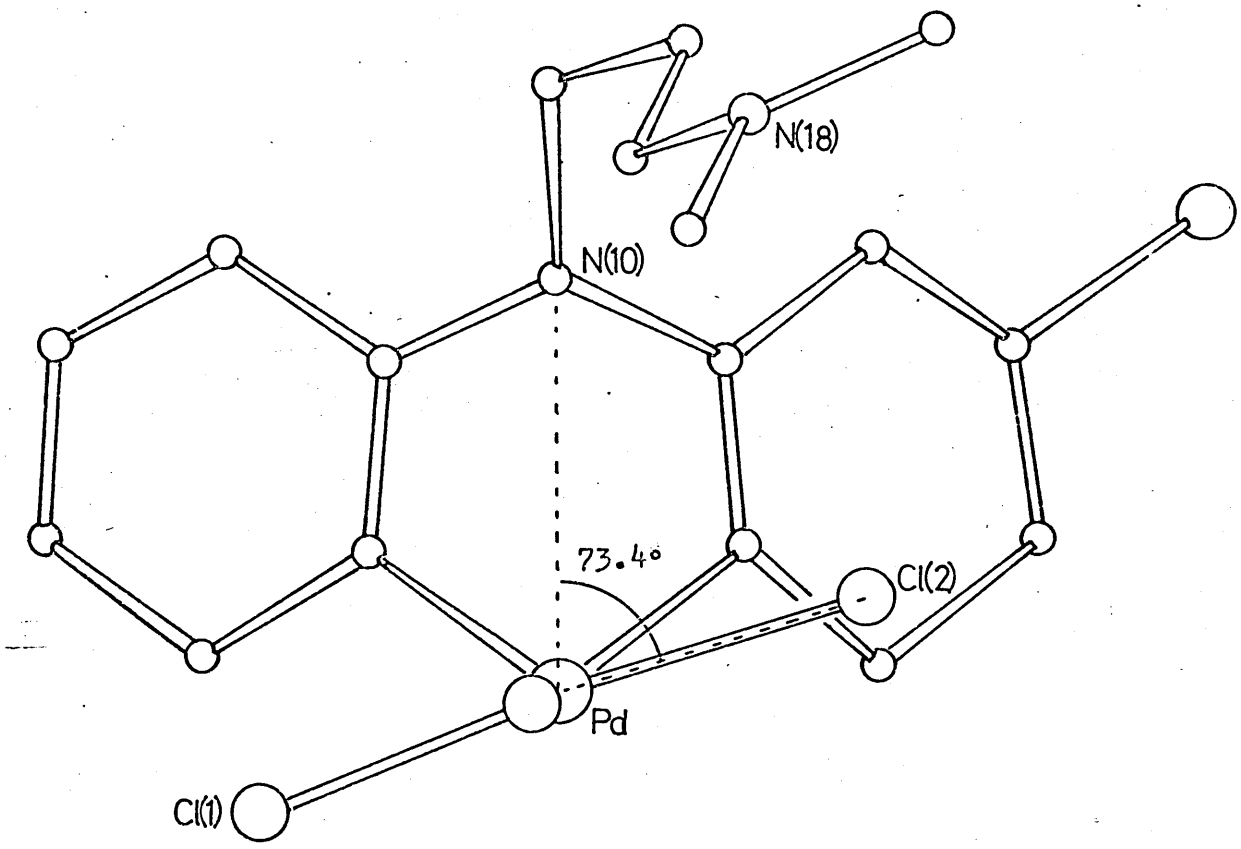


Fig. 2:2:13

View of $Pd(cpzH)Cl_2$ down the Pd-S(5) bond, showing the Cl(2)-Pd-S(5)-N(10) torsion angle.

might have caused interaction between the ring protons and the metal halide system. With the phenothiazine heterocycle this will not occur as there are no protons on C(11) C(12), C(13) or C(14). A recent paper published during the writing of this thesis [164] reports the synthesis and crystal structure of $Pd(psez)_2Cl_2$ (psez= phenoselenazine, i.e. ptz with the sulphur atom replaced with selenium) and in that structure the ring system is axially coordinated to the metal.

This paper also throws light on the twisting of the heterocycle with respect to the metal halide square plane. No such twisting is seen for $Pd(psez)_2Cl_2$ (the N(10) atom lies on the $PdSe_2Cl_2$ plane i.e. there is a mirror plane running through the molecule) and this seems to imply that the twisting is due to facilitation of the intramolecular hydrogen bonding rather than the orientation of the bonding orbitals on the sulphur and palladium.

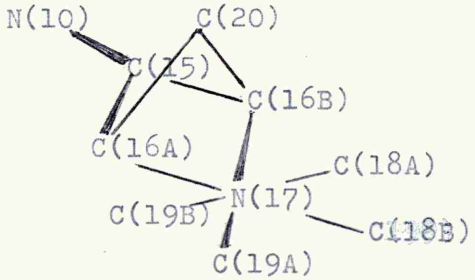
The geometry within the phenothiazine heterocycle is similar to that found in their respective ligands. However the side chain adopts a totally different orientation to that found in the free ligands (Fig. 2:2:8α 9). The side chain bends back over the heterocycle in an unusual scorpion conformation (Fig.2:2:10α 11). In so doing the side chain is able to interact with the $PdCl_3^-$ anion via the hydrogen bonding available through the $NHMe_2$ unit. The two complexes have slightly different hydrogen bonding interactions which will be discussed in separate sections below.

2:2:7:2 Protonated Trichloro 10-(2-diemethylaminopropyl) phenothiazine-S palladium(II).

Those bond distances and angles for $Pd(pmzH)Cl_3$ not given in Table 2:2:9α 10 are given in Table 2:2:11. $Pd(pmzH)Cl_3$ is found to be monomeric in the solid state with no intermolecular interactions observable. The side chain adopts the scorpion conformation discussed above, presumably to maximise the intramolecular hydrogen bonding between Cl(2) attached to palladium and the N-H on the end of the N(10) side chain. The N(17)...Cl(2) distance is 3.17 Å; the limiting contact distance between these two atoms in N-H...Cl is 3.8 Å showing that there is significant hydrogen bonding in the above interaction.

Although not included in the least squares refinement, a peak was located near N(17) consistent with a proton attached to the quaternary nitrogen and directed towards the $PdCl_3^-$ unit.

The ligand has a chiral centre at C(16) but, because of the difficulties of separating optical isomers, it is supplied as a 50/50 racemic mixture. The considerable disorder of atoms C(16), C(18) and C(19) was attributed to this, half the atoms are present as one enantiomer and half as the other (Fig. 2:2:14).



Atoms labelled A belong to one enantiomer, those labelled B to the other. N(10),C(15) N(17) and C(20) are common to both enantiomers.

Fig. 2:2:14 Disorder in $Pd(pmzH)Cl_3$

Table 2:2:11

Bond distances (Å) and angles (°) for $Pd(pmzH)Cl_3$ not given in Table 2:2:9 ∝ 10*

C(15)-C(16)	1.35
C(16)-C(20)	1.63
C(16)-N(17)	1.50
N(17)-C(18)	1.52
N(17)-C(19)	1.53
Pd-Cl(2)...N(17)	3.17
N(10)-C(15)-C(16)	114.3
C(15)-C(16)-N(17)	113.4
C(15)-C(16)-C(20)	104.4
N(17)-C(16)-C(20)	106.5
C(16)-N(17)-C(18)	112.1
C(16)-N(17)-C(19)	116.0
C(18)-N(17)-C(19)	108.9

* C(16), C(18) and C(19) are disordered (see text) so all distances and angles are average values.

The disordered atoms were given occupancy factors of 0.50 and common temperature factors were applied to the disordered pairs.

The C(14)-N(10)-C(15)-C(16B) torsion angle is 141.8° (62.2° for pmzHBr) reflect the change in conformation upon complexation.

2:2:7:3 Protonated Trichloro 2-chloro-10-(3-dimethyl aminopropyl)phenothiazine-S palladium (II)

Those bond distances and angles for $Pd(cpzH)Cl_3$ not given in Table 2:2:9α10 are given in Table 2:2:12. The N(10) side chain on chlorpromazine has no chiral centre and is a simple propyl chain. It responds to complexation in the same way as the promethazine side chain, with the C(14)-N(10)-C(15)-C(16) torsion angle of 140.4° being comparable to the value of 141.8° found in the $Pd(pmzH)Cl_3$ complex.

In the drug the N(10)-C(15)-C(16)-C(17) torsion angle is 179.0° and upon complexation this changes to 62.5° i.e. from trans to gauche conformation. In contrast the C(15)-C(16)-C(17)-N(18) torsion angle changes on complexation from 69.2° to 179.6° i.e. from a gauche to trans conformation. These changes lead to the quaternary nitrogen being slightly further away from the palladium atom than in $Pd(pmzH)Cl_3$ and the N(18)...Cl(2) distance of 3.74 Å in the $Pd(cpzH)Cl_3$ complex seems to reflect a medium strength hydrogen bond (but see below).

Unlike $Pd(pmzH)Cl_3$, which is monomeric, $Pd(cpzH)Cl_3$ exists as a centrosymmetric dimer held together by

Table 2:2:12

Bond distances (Å) and angles (°) for $Pd(cpzH)Cl_3$ not given in Table 2:2:9 10.

C(15)-C(16)	1.557(27)
C(16)-C(17)	1.528(26)
C(17)-N(18)	1.421(26)
N(18)-C(19)	1.476(30)
N(18)-C(20)	1.388(41)
Cl(2)...N(18)	3.74
Cl(1′)..N(18)	3.54
N(10)-C(15)-C(16)	112.3(18)
C(15)-C(16)-C(17)	110.6(16)
C(16)-C(17)-N(18)	114.5(18)
C(17)-N(18)-C(19)	115.3(20)
C(17)-N(18)-C(20)	126.7(20)
C(19)-N(18)-C(20)	117.6(18)

Table S:S:12

Bond distances (Å) and angles (°) for Pd(cpmH)Cl$_2$ not given in Table S:S:9 1c.

Cl(1)...N(18)	3.34
Cl(2)...N(18)	3.34
N(16)-C(20)	1.388(41)
N(18)-C(19)	1.496(30)
C(17)-N(18)	1.431(26)
C(16)-C(17)	1.528(26)
C(15)-C(16)	1.557(27)
N(10)-C(15)-C(16)	112.3(18)
C(15)-C(16)-C(17)	110.6(16)
C(16)-C(17)-N(18)	114.5(18)
C(17)-N(18)-C(19)	115.3(20)
C(17)-N(18)-C(20)	125.7(20)
C(19)-N(18)-C(20)	117.6(18)

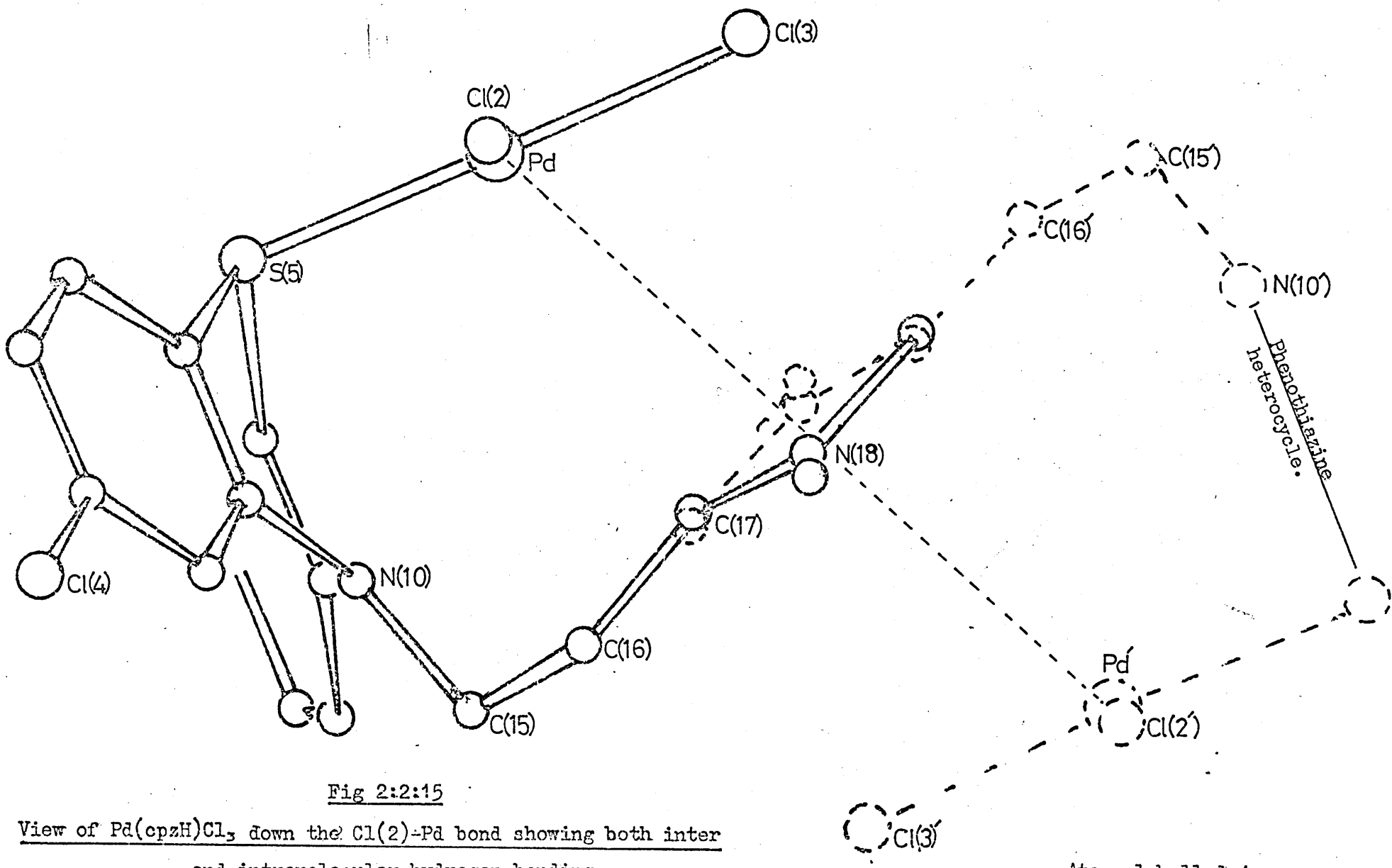
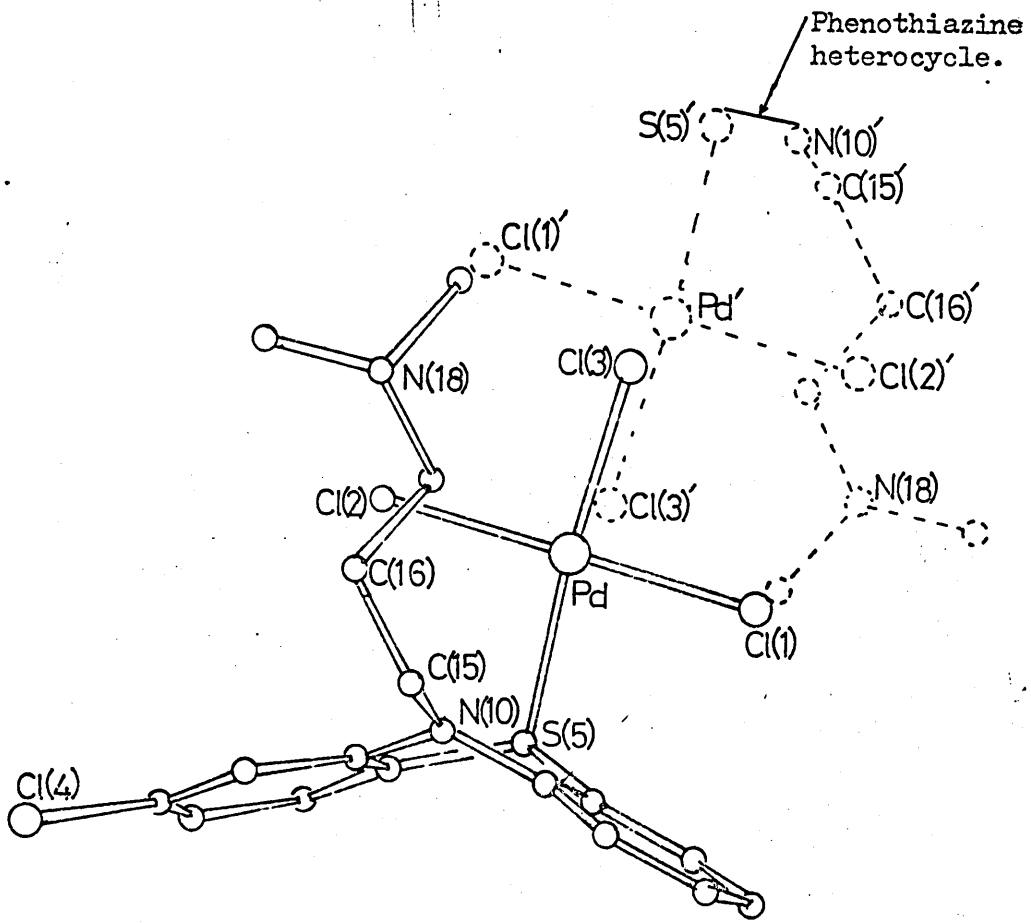


Fig 2:2:15

View of $Pd(cpzH)Cl_2$ down the Cl(2)-Pd bond showing both inter and intramolecular hydrogen bonding.

Atoms labelled ' are symmetry related.



Atoms labelled ' are symmetry related.

Fig 2:2:16

View of $Pd(cpzH)Cl_3$ perpindicular to the $PdCl_3$ plane, showing atoms involved in inter and intramolecular hydrogen bonding.

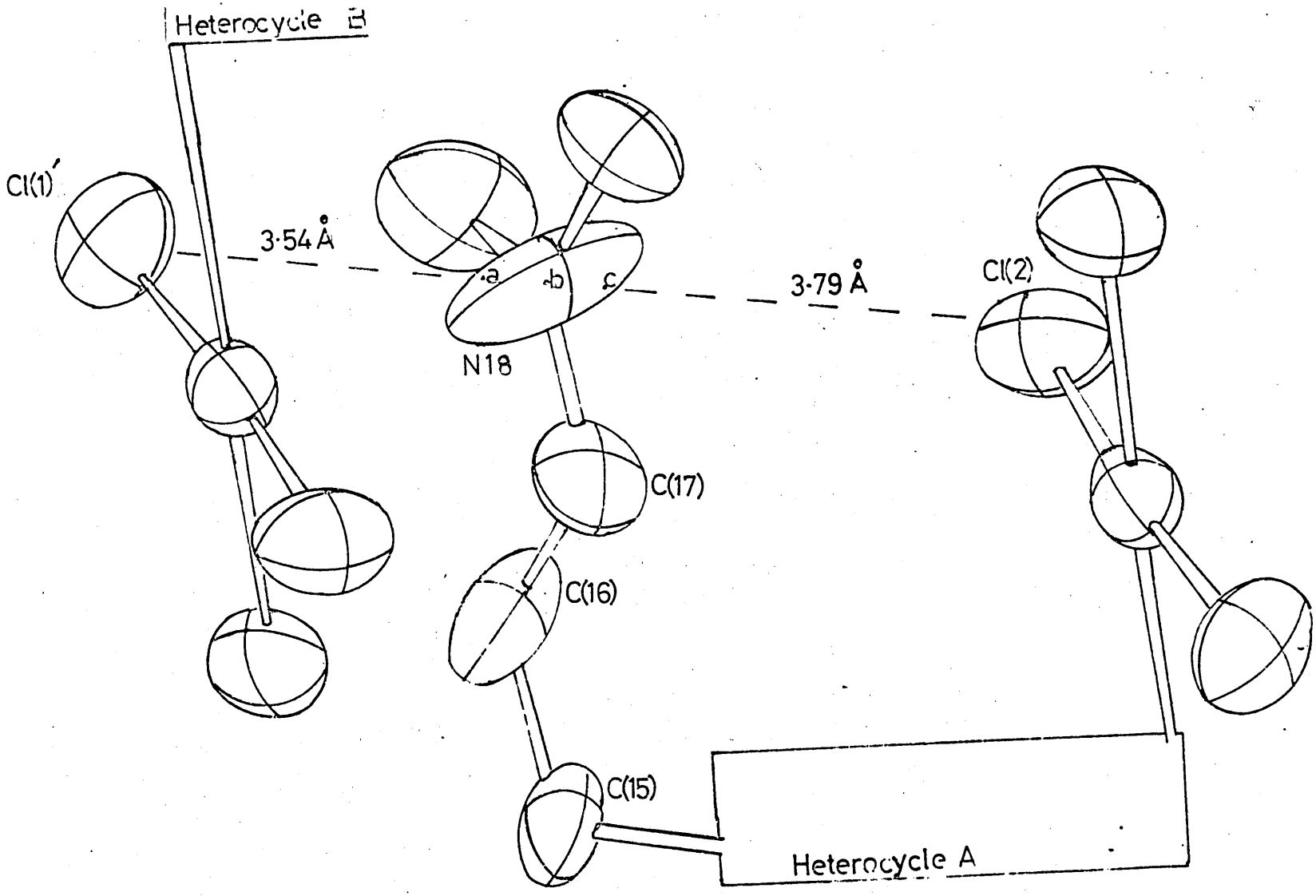


Fig 2:2:17
View of $Pd(cpzH)Cl_2$ showing thermal ellipsoids of selected atoms.

intermolecular N(18)...Cl(1′) hydrogen bonds of length 3.54 Å. This is illustrated in Figs 2:2:15,16 and 17 where it can be seen that the N(18) nitrogen atom lies almost in the line joining Cl(1′) to Cl(2) while N(18′) lies in the line joining Cl(1) to Cl(2′). (′) indicates a symmetry related atom. These nitrogen atoms are not midway between the two chlorine atoms and the intermolecular distance of 3.54 Å indicates that the intermolecular interaction is the stronger of the two hydrogen bonding interactions. At first sight the C(17), N(18), C(19,20) unit appears to be effectively planar (the sum of the C-N-C angles being 359.6°). However in view both of the spectroscopic evidence for protonation occurring at N(18) and also the high vibrational parameter associated with the N(18), C(19) and C(20) atoms shown in Fig. 2:2:17, it seems more probable that this apparent planarity is attributable to disorder of the NMe_2 fragment. It seems likely that N(18) is involved in either inter or intra molecular hydrogen bonding, with the position located by X-ray analysis representing an average of the two possible locations. This is supported by the fact that if N(18) is indeed protonated C(17), N(18), C(19) and C(20) would be expected to adopt a pyramidal arrangement with the proton pointing either towards Cl(2) or Cl(1′) depending on whether the interaction is intra or inter-molecular. If the nitrogen is in a pyramidal arrangement then the actual position of N(18) in either of the two average locations can be calculated to be shifted along the line joining Cl(2) to Cl(1′) by 0.5 Å to give a tetrahedral arrangement of the atoms attached to N(18). These two positions are marked on the thermal ellipsoid of N(18) by A and C. This reduces

the intermolecular hydrogen distance Cl(1′)...N(18) to 3.04 Å and the intramolecular hydrogen distance Cl(2)...N(18) to 3.24 Å which both represent strong hydrogen bonds, and are comparable to the value of 3.17 Å found in the promethazine complex.

2:2:8 Cancer studies

The complexes $PtLCl_3$ (L=pmzH and cpzH) were submitted to the National Cancer Institute, Bethesda, Maryland, USA. They were injected, as saline suspensions, into mice with the L1210 lymphoid leukaemia tumour. The dose used was in the range 3-200 mg/kg body weight/injection. The treatment was evaluated on the basis of median survival time.

$Pt(pmzH)Cl_3$ showed no anticancer activity but $Pt(cpzH)Cl_3$ showed presumptive activity in the preliminary screening and was used in a longer term trial. The results of this showed an increase of 136% in survival time of treated mice over controls; this is considered by the Institute to show anticancer activity. However the ligand chlorpromazine hydrochloride has been found to show only inconsistent activity against L1210 but the doses used were lower than those used for the complex.[165] The level of anticancer activity of the complex does not make further investigation worthwhile.

2:2:9 Summary and conclusions

It has been possible to fulfil objectives 1 to 3 and 5 discussed in Sec. 1:6.

2:2:9:1

The non-drugs have been shown to form Class 1 complexes ML_2Cl_2 and the drugs have been shown to form Class 2 complexes $M(LH)Cl_3$ where M is either divalent palladium or platinum and the ligand. By the use of chlorine analysis it was possible to confirm the presence of a third (unexpected) chlorine in the Class 2 complexes. It has not been possible to reproduce the work of Cimpu or Gowda discussed in Sec.1:5:3.

2:2:9:2

By using techniques outlined in Sec. 1:7 together with a knowledge of the formulae proposed above it has been possible to elucidate the solid state structure of both the Class 1 and Class 2 complexes of Pd(II) and Pt(II).

The Class 2 complexes involve sulphur bonding to the metal, evidence for this being primarily from the X-ray analysis. Supporting evidence for this comes from infrared data showing a change in the C-C ν aromatic modes. The complexes are square planar; the main evidence for this again comes from the X-ray work but is supported by the far infrared data. The N(10) side chain bends back over the heterocycle allowing the exocyclic quaternary nitrogen to interact via hydrogen bonding with the $PdCl_3^-$ anion.

The Class 1 complexes are also S bonded to the metal; the evidence is indirect but is in agreement with that seen for Class 2 complexes i.e. the infrared C-C ν aromatic modes change upon complexation and the far infrared spectra show the complex to be cis square planar, which is the expected conformation if sulphur-metal bonding was present.

2:2:9:3

It has been possible, using the above data, to postulate and confirm similar structures to explain the solution chemistry of the drugs with divalent palladium and platinum.

Both the Class 1 and Class 2 complexes are soluble in dmf and the ^{1}H and ^{13}C n.m.r. confirm S bonding in solution. The Class 2 complexes have the side chain in similar conformation to that seen in the solid state.

The electronic spectra showed quite a clear distinction between Class 1 and Class 2 ligands, their λ max in the visible region being around 500nm (dmf), {550nm water} and 430nm (dmf), {480nm water} respectively. This is found for all Class 2 complexes in the literature, even for drugs with 2-position substituents that might be expected to coordinate to divalent palladium or platinum e.g. $-SCH_3$, -C=N and $-OCH_3$. This is indirect evidence for the non-interaction of 2-position substituents; direct evidence is obtained for thioridazine where the C(2) ^{13}C n.m.r. signal is not shifted significantly upon complexation.

There have been three reports[101-103] of 2:1 complexes absorbing at 550nm with Class 2 ligands rather

than Class 1. These studies have all been conducted in highly acidic (pH< 2) aqueous solutions of the drugs and Pd(II). In the present project it was found that when $Pd(pmzH)Cl_3$ was dissolved intrifluoroacetic acid a solution with a λ max of 560nm was obtained, a shift of 130nm from that seen in dmf. However when $Pd(ptz)_2Cl_2$ was dissolved in trifluoroacetic acid the solution obtained had the same λ max as seen in dmf (515nm). Thus the acidic nature of a solvent affects the electronic spectra of Class 2,but not Class 1 complexes. It is possible that at pH 2 the protonation of the N(10) nitrogen prevents the exocyclic nitrogen remaining in place near the $PdCl_3^-$ anion. The side chain would presumably extend away from the heterocycle to separate the positive charges by approx 5.5 Å rather than by 4 Å in the in the solid state structure. The removal of the exocyclic nitrogen from the vicinity of the $PdCl_3^-$ anion would possibly allow another drug molecule to coordinate to the palladium ion. (The species observed in the literature have 2:1 L:M ratios.)

2:2:9:4

From a biological point of view (despite Pd(II) and Pt(II) not having major biological significance) the observation that the drug conformation, both in the solid state and in solution, changes significantly upon complexation is very interesting. Much research (some of which has been outlined in Sec 1:1) has been conducted into the significance of the solid state, solution or theoretical conformation of the drugs in determing their pharmacological properties. It is

known that the drugs are in the protonated form when they interact with the receptor site. It is also known that the ring sulphur is crucial to drug activity. Thus a receptor needs to be able to interact via both hydrogen bonding and electron donation with the drug molecule. It is therefore possible that the $PdCl_3^-$ anion provides a useful model of a potential receptor site. That is not to say that $PdCl_3^-$ gives an exact model of receptor shape or size but that using this model it is possible to show that the drug may interact with the receptor site in a way that can never be predicted from theoretical, solid state or[166] solution studies of the drug itself. Also the conformation adopted by the drug on complexation is very similar to the conformation proposed by Barbe [9] shown in Fig. 1:1:3.

It might be worthwhile to synthesise a drug molecule that has a structure similar to that found for the drug when complexed with Pd(II), and to see if such a drug was more specific to one receptor site rather than having a wide variety of pharmacological actions.

2:3 Complexes of phenothiazines with trivalent rhodium and iridium.

2:3:1 Class 1 complexes.

The ligand phenothiazine reacts with trivalent rhodium and iridium thus:-

$$MCl_3 + 3(ptz) \longrightarrow M(ptz)_3Cl_3 \quad ; \quad (M=Rh,Ir)$$

The complex $Rh(ptz)_3Cl_3$ is red and $Ir(ptz)_3Cl_3$ purple. The reaction was carried out using ethanolic solutions of both ligand and metal chloride. The complexes were soluble in dmf, nitromethane and ethanol. The infrared spectra of the complexes show identical features to those seen in Sec. 2:1:3:1 for the equivalent Pd(II) and Pt(II) complexes; this seems to imply the metal is sulphur bonded as expected from its soft character. The stoichiometry is that expected for the metal species in question.[167] This aspect of the project was not carried further because of the failure of the work with the Class 2 ligands described below.

2:3:2 Class 2 complexes

This part of the project concentrated on cpzH.Cl as a typical Class 2 ligand. The ligand and metal chloride were reacted in aqueous solution in a wide variety of mole ratios and a wide variety of techniques were employed to separate and purify the product. However each synthesis yielded a red(M=Rh) or brown

(M=Ir) complex which gave a different elemental analysis for each synthetic attempt. The infrared spectra of the complexes show identical features to those seen in Sec. 2:2:3 for the equivalent Pd(II) and Pt(II) complexes; this seems to imply the metal is both sulphur bonded to the heterocycle and interacting via hydrogen bonding via the exocyclic quaternary nitrogen. The poor reproducibility of the elemental analysis precluded any further meaningful investigation of these complexes.

CHAPTER 3

Interactions of phenothiazine drugs with biologically significant first row transition metal ions.

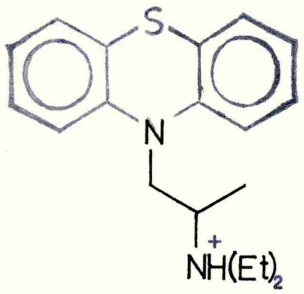
Contents

3:1 Introduction

This part of the project arose from interest in *in vivo* metal ion-drug interactions discussed in Sec. 1:3. It was decided to concentrate the investigation on the divalent ions of Mn, Fe, Co, Ni, Cu, Zn and Fe(III). Where possible the experimental conditions used have been kept as close as practicable to those found in the body i.e. no elevated temperatures (except to dry products), no extremes of pH and the use of metal halide salts. Even with these criteria these preliminary studies cannot give more than a general indication of possible reactions since in the body most metal ions are bound to proteins rather than in the free form.

3:2 Ligands

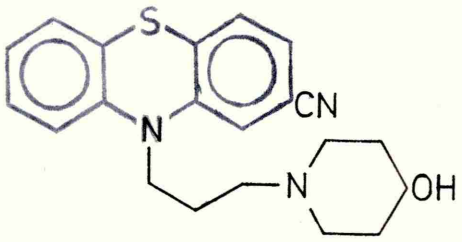
It has not proved possible to isolate any complexes involving the above metal ions and any Class 1 ligands. This aspect will be discussed later, but this chapter will concentrate on the results with Class 2 ligands, specifically chlorpromazine hydrochloride. Also investigated has been ethopropazine hydrochloride:-



Protonated ethopropazine (epzH)

The results of these studies are applicable to all phenothiazine drugs.

There have been reports of a reaction between $NiCl_2\,6H_2O$ and pericyazine involving precipitation of a fine solid product.[168]



pericyazine (pcyz)

Pericyazine is unusual in that it is a solid without having its exocyclic nitrogen quaternised (it is not water soluble)

3:3 Complexes of Class 2 (drug) ligands with divalent cobalt, nickel and copper.

3:3:1 Physical properties

The complexes prepared in this part of the project are listed in Table 3:3:1. They all have a 2:1 ligand:metal ratio. They are all very hygroscopic and sparingly soluble in most common solvents. It was not possible to recrystallise the complexes from any of these solvents. The cobalt and nickel complexes were both an intense blue colour in the solid state while the copper complexes were dark red. The copper complexes were prepared under nitrogen using degassed solvent to prevent the formation of drug cation radicals.

3:3:2 Electronic spectra

The spectra discussed in this section were run as diffuse

Table 3:3:1

Complexes of divalent cobalt, nickel and copper with Class 2 ligands.

Complex	mpt/°C	λmax/nm	colour
$(cpzH)_2.CoCl_4$	110	695	turquoise
$(pcyzH)_2.CoCl_4$	115	690	turquoise
$(cpzH)_2.NiCl_4$	110	653	blue
$(pcyzH)_2.NiCl_4$	120	646	blue
$(cpzH)_2.CuCl_4$	120	*	dark red
$(epzH)_2.CuCl_4$	120	*	dark red

* see text.

reflectance spectra because of the poor solubility of the complexes in any common solvents; while this had the advantage of eliminating any solvent effects the spectra are of poor quality due to the noise inherent in the technique.

The wavelength of maximum absorption, in the visible region, for the complexes are given in Table 3:3:1. Tetrahedral cobalt(II) complexes often exhibit an intense blue colour ($\epsilon \simeq 600$ $dm^3 mol^{-1} cm^{-1}$) and as such they are readily distinguishable from pink octahedral cobalt(II) complexes ($\epsilon \simeq 10$ $dm^3 mol^{-1} cm^{-1}$). The tetrahedral $CoCl_4^{2-}$ has a band at 690nm [169] and a band pattern very similar to that seen in $(LH)_2.CoCl_4$ (Fig. 3:3:1). It seems likely that the cobalt species present in the complexes is $CoCl_4^{2-}$ especially as this gives a sensible explanation of the stoichiometry of the complexes. Tetrahedral nickel(II) complexes are also an intense blue colour (λ max=660nm, $\epsilon \simeq 600 dm^3 mol^{-1} cm^{-1}$).[169] The spectrum of $NiCl_4^{2-}$ is very similar to that displayed in Fig. 3:3:2 of $(LH)_2.NiCl_4$ and like $CoCl_4^{2-}$ it seems sensible to propose the presense of $NiCl_4^{2-}$ in $(LH)_2.NiCl_4$. It was not possible to obtain reproducible spectra from the copper complexes.

3:3:3 Infrared spectra (4000-400 cm^{-1})

As in Sec. 2:2:3 this discussion will concentrate on bands above 1300 cm^{-1}. Indeed the only band in the ligand spectra seen to alter upon reaction is that at 2500 cm^{-1}, due to $\overset{+}{N}$-H...Cl stretching, which shifts to 2700 cm^{-1} and diminishes in intensity. This change is identical to that observed in

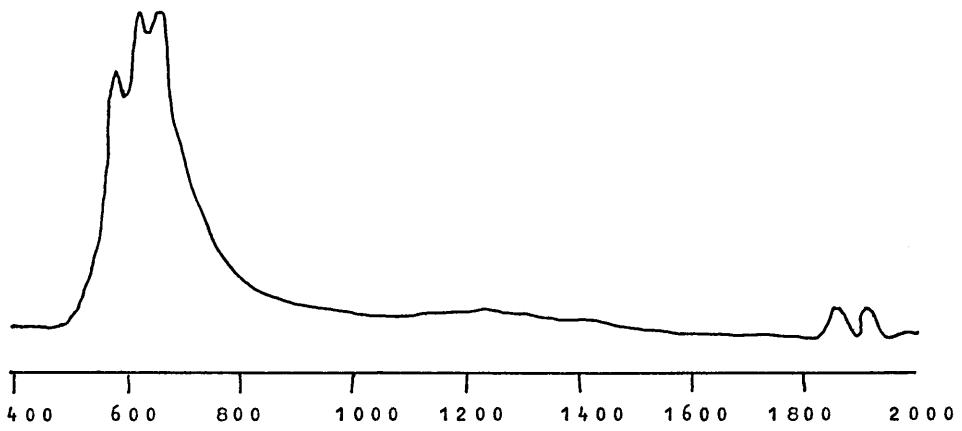


Fig. 3:3:1 wavelength/nm

Electronic spectrum of $(LH)_2 .CoCl_4$ (L=cpz,pcyz)

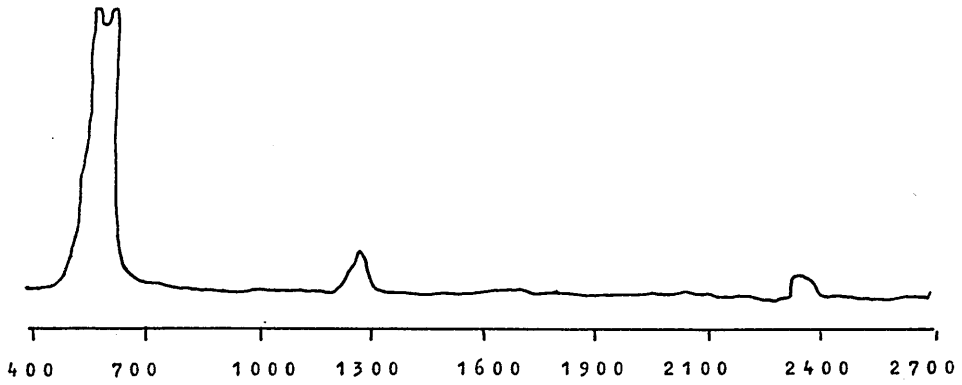


Fig 3:3:2 wavelength/nm

Electronic spectrum of $(LH)_2 ,NiCl_4$ (L=cpz,pcyz)

the palladium(II) and platium(II) complexes discussed in Sec. 2:2:3, where the quaternary nitrogen is involved with hydrogen bonding to a MCl_3^- anion. However unlike those complexes no alteration is seen in the bands at 1580 and 1600 cm^{-1}, due to C-C aromatic stretching, or in the finger-print region generally. This implies that although there is an interaction between the quaternary nitrogen and the metal species, no actual coordination to the ring hetero-cycle has occured.

These results are found for all three metal ions reacting with drugs supplied as their hydrochloride salts. Pericyazine is supplied as a solid without its exocyclic nitrogen being quaternised. Its reaction with $NiCl_2$ has been reported as producing a precipitate [168] however no solid product was isolated and characterised in that report. When the work was repeated in this project it was found that the precipitate was totally inorganic. The conditions used were an ethanolic solution of $NiCl_2\,6H_2O$ and pericyazine. When the supernatent liquor was reduced in volume a bright blue solution was obtained and from this a blue solid isolated. The infrared spectrum of this compound $(pcyzH)_2.NiCl_4$ was found to be very different from that of the drug. However when pericyazine hydrochloride was obtained and its spectrum recorded it was found to be identical to the spectrum of $(pcyzH)_2.NiCl_4$ except in the region 2500-2700cm^{-1} where the difference is the same as that seen in the drugs complexed with Pd(II) and Pt(II). The reaction seems to involve the protonation of pericyazine and the formation of an insoluble nickel species:-

$$2NiCl_2\,6H_2O + 2pcyz \longrightarrow Ni?? + (pcyzH)_2.NiCl_4 + xH_2O$$

3:3:4 Thermogravimetric analysis

These compounds show similar pyrolysis curves to those seen in Sec. 2:2:6 for the Pd(II) and Pt(II) complexes. The major difference is that the residue remains as the metal oxide rather than being reduced to the metal at above 900°C. As before it was not possible to deduce the formulae of the stable species formed between 400 and 500°C.

3:3:5 Summary

The data presented in Sec 3:3:2-4 fit in well with the proposed formula $(LH)_2.MCl_4$. The molar conductivity of the compounds is in the range 15-17 $x10^{-3}$ Sm^2 mol^{-1} and as such agrees with the proposed 2:1 electrolyte composition of the complexes.

The magnetic moment of $(cpzH)_2.NiCl_4$ is 3.53 B.M. ($(Et_4N)_2.NiCl_4$, 3.8 B.M. [169]) indicating a tetrahedral nickel environment. For $(cpzH)_2.CoCl_4$ the value is 4.51 B.M. (Cs_2CoCl_4, 4.6 B.M. [169]) also indicating a tetrahedral metal environment.

The infrared data show quite clearly that the complex does not contain a metal bond to the ring heterocycle but does involve a hydrogen bonding interaction between the complex metal chloride MCl_4^{2-} and the protonated exocyclic nitrogen on the end of the N(10) side chain. This, especially for the copper compounds, is important because the drugs have frequently been proposed as chelates[44-47] with Cu(II); the bidentate bonding being through the two

nitrogen atoms despite the fact that the ring nitrogen is a very weak base. Evidence for this bonding has usually come from the change in the infrared spectrum of the drugs upon complexation; however the drugs have often been used as the free base and the comparison of the spectra before and after complexation has merely shown the effect of protonation of the exocyclic nitrogen rather than any actual coordinate bonding. An attempt was made to reproduce the results of the above papers but on each occasion the products obtained were always those outlined in this section. The results presented here agree with the tendency of many metal thiocyanates to form salts with phenothiazine drugs as discussed in Sec. 1:5:2.

It is possible that Huang [44] and Harris [47] produced a species of cation radical as their work was not carried out under nitrogen:-

$$2CuCl_2 + cpzHCl \longrightarrow (\dot{c}pzH).CuCl_4 + CuCl$$

Evidence for this comes from the observed e.s.r. spectrum of the complex being very similar to that of cpzH cation radical. Also Huang found that chlorpromazine-5-oxide (incapable of forming the cation radical, thus a monovalent cation) gave a complex of the type $(cpzHS{=}O)CuCl_3$.

It was not possible to induce coordinate bonding by increasing the pH and deprotonating the exocyclic nitrogen (leaving the lone pair available for coordination) because this precipitated the metal hydroxides from solution.

3:4 Reaction of phenothiazines with iron(III)chloride.

3:4:1 Phenothiazine

As there have been no literature reports of the reaction of phenothiazine with Fe(III)chloride, this was briefly investigated.

The reaction of $FeCl_3$ with phenothiazine was carried out in ethanolic solution in a 1:1 mole ratio. A blue/green product was obtained; its mass spectra gave a molecular ion of m/e 418. In order to assess the purity of the product it was analysed by TLC using 75% ethyl acetate, 25% 40/60 pet.spirit. as the elutant. The chromatogram is shown in Fig. 3:3:3.

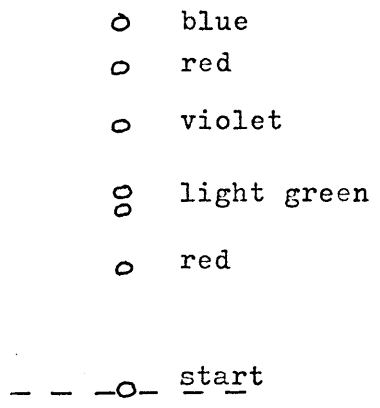
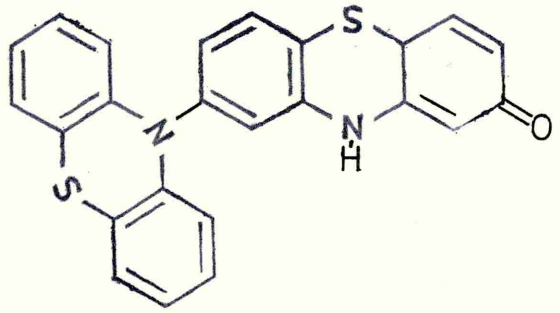


Fig. 3:3:3

TLC of product from the reaction of ptz and $FeCl_3$

The chromatogram shows that the product is a complex mixture. This chromatogram and the mass spectra are characteristic of

the products formed in the oxidation of phenothiazine.[170] These products include phenothiazine-5-oxide, 3-H-phenothiazine-3-one, phenothiazine-5,5-dioxide and a dimer:-

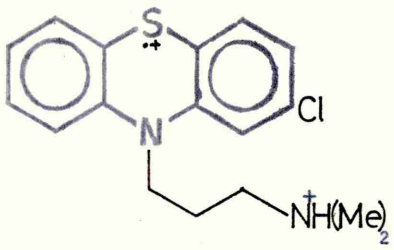


It is this dimer that is responsible for the molecular ion in the mass spectrum. There was no evidence to suggest that any of the iron(III)chloride had coordinated to the phenothiazine. Since it is well known that the above oxidation products are obtained via a free radical mechanism the inference is that a similar mechanism applies for the ligand-metal reaction. Hence the reaction was repeated in the presense of a molar equivalent of 1,3-ditertbutyl-2-hydroxy-5-methylbenzene to act as a radical scavenger. This successfully prevented oxidation of the phenothiazine but again no product was obtained from the reaction of $FeCl_3$ with phenothiazine.

3:4:2 Chlorpromazine hydrochloride.

One of the earliest reports [41] of in vitro metal ion-phenothiazine drug interaction was between $FeCl_3$ and chlorpromazine hydrochloride. The report emphasised that the product was a complex and not an oxidation product. On attempting to reproduce this work the only observed reaction

was the production of a rose red colour (λ max 525nm) which is characteristic of the cation radical:-



protonated chlorpromazine cation radical

No other product was isolated despite a range of pH values and solvents being used.

3:5 Reactions of phenothiazines with divalent manganese iron and zinc

No reaction was observed with these metal ions despite a wide range of pH values and solvents being used.

3:6 Conclusion

It has not been possible to fully realise all the objectives 1:6:4-6 in this part of the project. The solid complexes obtained from the first row transition metal ions Co(II),Ni(II) and Cu(II) showed no evidence of coordinate bonding. It was not possible to obtain single crystals suitable for X-ray analysis but the infrared evidence is conclusive in this respect. Thus the interaction observed between the complex anions and the protonated drugs is one of hydrogen bonding. Although hydrogen bonding is important in biological systems it is unlikely that in a complex system such as the body such a non-specific interaction would be significant in the

mechanism of action of the drugs, especially as the metals in the body are not free but bound to proteins. It did not seem worthwhile to submit these compounds for screening for biological activity or anticancer activity.

Needless to say Class 1 ligands showed no reactivity towards divalent cobalt nickel or copper because of the absence of a quaternary exocyclic nitrogen. The lack of reactivity of the ring sulphur to metals, other than soft ones discussed in Chapter 2., is in accord with the lack of such reactivity for aryl thioethers generally as discussed in Sec. 1:2:1. This is presumably due to the aryl rings withdrawing σ electron density from the sulphur and making it a weaker base than the equivalent alkyl thioether where the alkyl groups are able to donate σ electron density to the sulphur. This effect is seen in alkyl and aryl phosphines e.g. PEt_3 will coordinate to $NiCl_2$ as a square planar complex but PPh_3 will coordinate as a tetrahedral complex. The crystal field splitting in a square planar complex has a larger energy gap than a tetrahedral complex implying the square planar arrangement is a stronger complex and thus PEt_3 is a stronger σ donor than PPh_3 (σ donation being the important criterion first row transition metal ions). Likewise it must be assumed that phenothiazine has such weak σ electron donating properties that no coordination is seen for hard first row transition metal ions, despite the fact that phenothiazine has a low ionization potential (4.36 eV) and is known to be a powerful electron donor.[2]

When the phenothiazine nucleus is substituted in the 2 and 7 positions by electron donating groups then coordination via the ring sulphur is observed e.g. the

ligand 2,7-dimethylphenothiazine forms complexes with Hg(II), Cu(II) and Ni(II)[171] presumably because the methyl groups are able to donate σ electron density making the sulphur a strong enough electron donor to interact with the hard metal ions mentioned. It is possible that if a drug was synthesised with the 2 position substituent as an alkyl group, the drug would be able to coordinate with first row transition metal ions.

The reaction of iron(III)chloride is typical of that of a metal oxidising agent as discussed in Sec. 1:5:1, and it seems that Floderer was mistaken in thinking that[41] the interaction was one of coordination between $FeCl_3$ and chlorpromazine hydrochloride.

Manganese(II)chloride has been extensively studied in its interactions with chlorpromazine since the drug inhibits the action of the enzymes in oxidative phosphorylation, enzymes which are activated by Mn(II). Manganese(II)chloride showed no action on the drugs, except when the medium was rendered alkaline and then back titrated with acids under aerobic conditions when Mn(III) was formed. Despite having a short lifetime this was able to oxidise the drug to its cation radical.[35] The results obtained in this project are in agreement with these observations.

Iron and zinc are the two most abundant heavy metals in the body and their *in vivo* interaction with phenothiazine drugs has been discussed in Sec. 1:3. Despite the observed *in vivo* interactions no reaction was observed for the drugs with $FeCl_2$ or $ZnCl_2$ *in vitro* under the conditions used in this project. This is perhaps surprising for although, for the reasons given above, no sulphur bonding would be expected,

the exocyclic nitrogen either protonated or as the free base would be expected to offer acceptable reactivity towards $FeCl_2$ or $ZnCl_2$ especially as together with $MnCl_2$ salts of the type $R_4N.MCl_4$ are known for M=Mn,Fe and Zn [172-174]

From this part of the work there is no evidence of involvement of phenothiazine drug-metal ion interaction in either the mechanism of action or their side reactions or metabolism.

Contents

Contents

4:1 Ligands

All the ligands used in this project are listed in Table 4:1. The drugs were supplied as their hydrochloride salts (except pericyazine) by May and Baker Ltd and Sandoz Ltd. All are light sensitive both in the solid state and in solution, and hence were always stored in dark bottles and kept in cupboards. The drugs are known to promote allergic reactions and were handled without skin contact. The drugs were used without further purification. When needed the free base was obtained by the literature method [175] which involved increasing the pH of an aqueous solution of the drug hydrochloride, thus precipitating the free base which was then extracted into diethyl ether. The solvent volume was reduced on a rotary evaporator and the free base isolated as a brown oil.

Two of the ligands were synthesised by routes not previously reported and are detailed below. All other ligands were used as supplied by Aldrich Ltd.

4:1:1 N-Ethylphenothiazine (eptz)

Potassium hydroxide (0.4 mol, 22.4g) was added to dmso (200 cm^3) with stirring (5 min). Phenothiazine (ex Aldrich, 0.1 mol, 20g) was then added to the mixture with stirring (45 min) followed by the addition of iodoethane (0.2 mol, 31.2g) (over 15 min) with cooling and stirring. Water (200 cm^3) was added and the mixture extracted with diethylether (3x100 cm^3).

Table 4:1

Ligands used in this project, together with their Chemical Abstracts Registry Number where applicable.

Phenothiazine	(92-84-2)
2-Chlorophenothiazine	(93-39-7)
N-Ethylphenothiazine	(1637-16-7)
2-Thiomethylphenothiazine	(7643-08-5)
N-Dimethylcarbamoylphenothiazine	———
Promethazine hydrochloride	(58-33-3)
Chlorpromazine hydrochloride	(69-09-0)
Thioridazine hydrochloride	(130-61-0)
Ethopropazine hydrochloride	(1094-08-2)
Pericyazine	(2622-26-6)

Each extract was washed with water ($3x50cm^3$). The ether solution was dried over solid $CaCl_2$ and the solvent removed under reduced pressure.

Yield 13.5g (58.9%) Mpt 101-3°C lit. 103-4°C [176]

Calculated for $C_{14}H_{13}NS$	%C,73.97; H,5.76; N,6.16
Found for eptz	%C.73.79; H,5.65; N,6.24

4:1:2 N-Dimethylcarbamoylphenothiazine (dptz)

Phenothiazine-10-carbamoylchloride (ex Aldrich) (0.1 mol,26g) was weighed into a 250 cm^3 round bottomed flask. A glass phial of pure dimethylamine (0.4 mol,18g) was cooled in liquid N_2, carefully opened and added to the flask. A liquid N_2 condensor was fitted to the top of the flask. The mixture was allowed to reflux at room temperature for four hours. The unreacted dimethylamine was allowed to boil off. The product was recrystallised from ethyl acetate/hexane. Mpt 97°C.

Calculated for $C_{15}H_{15}N_2OS$	%C,66.39; H,5.57; N,10.33
Found for dptz	%C,66.64; H,5.36; N,10.31

This compound was treated with $LiAlH_4$ in an attempt to reduce the amide to an amine. The product was found to be phenothiazine and it was subsequently established that this deamination also occurs for the equivalent primary amide with $LiAlH_4$.

4:2 Complexes

All the complexes were filtered through a grade 3 sintered crucible and dried at 100°C under vacuum.

4:2:1 Complexes of divalent palladium and platinum

The metals were usually used as their K_2MCl_4 salt, where the bromide or iodide was needed this was obtained by using 1 mmole of the above salt with 10 mmole of KBr or KI, in the reaction mixture.

4:2:1:1 Complexes with Class 1 ligands

All the Class 1 ligands are water insoluble (they have no exocyclic nitrogen) and were reacted in ethanolic solution. Upon mixing this with an aqueous solution of potassium tetrahalo metal(II) salt, a green (L=ptz) or pink (L=dptz or eptz) precipitate was formed. After 5 minutes this precipitate turned blue (M=Pd) or red (M=Pt), the original precipitate being the water insoluble ligand and the later precipitate being the product. The precipitate was washed with acetone to remove any unreacted ligand and dried as above.

An attempt was made to recrystallise the complexes from dmf and dmso. No product was recoverable from dmso and it was subsequently established that the complexes were decomposing in dmso. The recovered product from dmf was contaminated with dmf that could not be removed either by drying under vacuum for 48 hours or by thorough washing with various solvents. The contamination was confirmed by observation of the amide carbonyl band at 1700 cm^{-1} in the IR spectrum of the complex. A sample of the complex $Pt(ptz)Cl_2$ was heated to 130°C in the TGA apparatus. A small mass loss was observed between 120-125°C and the residue remaining was examined as a KBr disk where it was found that the carbonyl band was no longer present in the IR spectrum.

4:2:1:2 Complexes with Class 2 ligands

All the Class 2 ligands are water soluble except pericyazine, which was reacted in ethanolic solution, the rest in aqueous solution. Upon mixing this solution with an aqueous solution of potassium tetrahalometal(II) salt, a red (M=Pd) or yellow (M=Pt) colour was observed and almost instantly a precipitate was formed of the same colour. Complete precipitation was rarely obtained without the addition to the solution of an equal volume of a saturated NaCl solution to give a common ion effect. This gave complete precipitation with a clear supernatant which was decanted off and the precipitate washed by decantation and then filtered and washed until the filtrate was free from chloride (tested with $AgNO_3$) The complexes were dried as above. Two of the complexes ($PdLCl_3$, L=pmzH and cpzH) were recrystallised from dmf. In order to obtain crystals suitable for X-ray analysis the dmf solutions were left for a period of up to 1 month in a darkened laboratory cupboard under ambient summer conditions.

4:2:2 Complexes of trivalent rhodium and iridium

4:2:2:1 Complexes with Class 1 ligands

For phenothiazine the ligand and the metal salts ($RhCl_3$ and $IrCl_3$) were dissolved in ethanol. Upon mixing a red (M=Rh) or purple (M=Ir) solution was obtained and upon reduction of the volume a similarly coloured product was obtained. This was dried as in Sec. 4:2.

4:2:2:2 Complexes with Class 2 ligands

For Class 2 ligands the metal salts and ligands were reacted in aqueous solution and precipitation of the red (M=Rh) or brown (M=Ir) product was assisted by saturated NaCl solution as in Sec. 4:2:1:2. Various ligand:metal ratios from 1:1 to 4:1 were used, but the same product was apparently obtained in each case. However no consistent analytical data could be obtained. The complexes were dried as in Sec. 4:2. An attempt was made to recrystallise the products from dmf without success.

4:2:3 Complexes of divalent cobalt, nickel and copper

These metals were used as hydrated dichlorides in ethanolic solution (under N_2 for Cu). Under the conditions used the Class 1 ligands showed no reaction with these metals. The Class 2 ligands were used in ethanolic solutions (under N_2 for Cu) and on mixing with the metal salt solution, a blue (M=Ni,Co) and brown (M=Cu) coloured solution was obtained. The precipitation of the product was induced by the addition of an excess of 40/60 pet. spirit. The supernatant was decanted off and the precipitate washed by decantation with ethanol and diethylether and dried as in Sec. 4:2.

4:3 Analytical methods

4:3:1 Metal analysis

Metal analysis was usually carried out as part of the TGA procedure, details of which are given in Sec. 4:4:7. Metal

salts were used to determine the character of the final residue obtained during pyrolysis. Thus $PdCl_2$ was examined by TGA and found to give a final stable product (at 900°C) of palladium metal whereas $NiCl_2 6H_2O$ gave nickel oxide as the final stable product. These investigations also showed the value of the technique in obtaining the metal composition of the complexes. The accuracy of the technique was sufficient to give the the %metal content to within 1% of the calculated value.

4:3:2 Chlorine analysis

Chlorine analysis was needed to determine the presence or absence of the third chlorine atom in the Class 2 complexes of palladium and platinum. The sample was combusted in an oxygen flask [177] and the combustion products absorbed in NaOH (0.05M). This was acidified with HNO_3 (0.1M) to bromophenol blue. A five-fold excess of ethanol was then added and the chloride titrated against $Hg(NO_3)_2$, (0.02M), using diphenylcarbazone indicator. By performing the combustion in a 250 cm^3 Erlenmeyer flask it was possible to complete the titration without needing to transfer the analyte to another flask.

4:3:3 Elemental analysis

C,H and N analysis was carried out by Dr F.B. Strauss of Oxford, and by the Analytical Dept. of May and Baker Ltd.

4:4 Instrumental methods

4:4:1 Conductance measurements

The conductance of solutions of the complexes in nitromethane (10^{-3} mol dm^{-3}) was measured at 25°C using a Lock Type MCB conductivity bridge. A solution of KCl in water (0.5 mol dm^{-3}) was used to determine the cell constant. The molar conductance of the solution was calculated from the following equation:-

$$\Lambda m = \Lambda . c . v \ Sm^2 \ mol^{-1}$$

Where Λ is the measured conductance, c is the cell constant, and v is the volume in m^3 containing one mole of solute. Nitromethane was dried over ahhydrous $CaCl_2$ and fractioned before use, the fraction distilling at 101 °C being collected.

4:4:2 Electronic spectra

Diffuse reflectance spectra for all the complexes of first row transition metal ions were recorded over the ranges 400-850 nm and 750-2500 nm using Unicam SP800B and Beckman DK2A instruments equipped with standard diffuse reflectance attachments. Magnesium oxide was used as a reference.

The rest of the complexes were only soluble in dmf and this solvent was used in obtaining spectra in the visible region. A Pye-Unicam SP800 instument was used; the solubility of the complexes usually determined the strength of the solution, but in general, the concentration was in the range 10^{-4} – 10^{-2} M.

4:4:3 Infrared spectra

4:4:3:1 4000-400 cm^{-1}

The infrared spectra of all the ligands and their complexes were recorded over the above range as KBr disks at 2% conc. A Pye Unicam SP 1200 spectrophotometer was used and was calibrated at 1600 cm^{-1} with polystyrene.

4:4:3:2 400-40 cm^{-1}

The far infrared spectra of the ligands and their complexes were recorded over the above range using a Beckmann R.I.I.C FS 720 Interferometer. The instrument was evacuated to a pressure of 0.05 mm Hg in order to remove water vapour.

Output from the interferometer was in the form of punched tape and these data were computed to a resolution of 5 cm^{-1} using an IBM 1130 computer.

The samples were prepared as pressed polyethlyene disks (20 mg polyethylene to 6mg sample)

4:4:4 Magnetic susceptibility measurements

Magnetic susceptibility of the complexes were measured by the Gouy Method, using a Newport Instruments Type A 4 inch electro-magnet. The sample was suspended from one arm of a Stanton Instruments Type MC5 balance. The tube was calibrated using mercury(II)tetrathiocyanato cobalt(II). Corrections for the diamagnetism of the ligands were made using Pascals constants.[178]

4:4:5 Mass spectra

Mass spectra were run on an MS 30 Instrument at 70 eV with a probe temperature of 300 °C.

4:4:6 Nuclear magnetic resonance

All spectra were recorded in $^{2}H_{7}$ dmf solution. ^{13}C and ^{1}H spectra of the Class 1 ligands and complexes were recorded at May and Baker Ltd on a CFT 20 Instument at 80 MHz. The Class 2 ligands and complexes were recorded at Sheffield University on a Brucker WH 400 Instrument at 400 MHz.

4:4:7 Thermal gravimetric analysis

The thermal properties of the complexes were investigated using a Du Pont Instruments 950 TGA coupled to a Du Pont Model 900 Console.

The sample was contained in a small platinum boat, suspended from a silica rod which forms one arm of a sensitive microbalance. The balance was tared electrically with the empty boat in position, and the chart recorder pen adjusted to read zero mg. The sample was carefully added to the boat until the chart recorder pen showed a weight between 6-12 mg.

Care was taken to ensure the addition of the sample did not disturb the sample boat. A silica combustion tube was then placed over the sample and over this an electric furnace. A pump was connected to give an air supply over the sample of 250 cm^{3} / min. The heating rate on the recorder was set at 15°C/min and the furnace actuated.

4:4:8 X-ray crystallographic methods

The general methods of structure solution and refinement used in this project are well documented elsewhere [152] and will not be given,

4:4:8:1 Space group determination

Space group information was initially determined by examination of oscillation, Weissenberg and precession photographs for symmetry and systematic absences. The oscillation, Weissenberg and precession photographs were taken using conventional methods and Cu-Kα and Mo-Kα radiations.

4:4:8:2 Data collection

All data were obtained with Mo-Kα radiation (λ=0.71069 Å) with a Stöe Stadi-2 two circle diffractometer. This instrument uses a graphite monochromator, a Phillips PW 1964/20/30 scintillation counter as detector, and a PDF8/f control unit. Data were collected using the background-ω scan-background technique. In both cases Lorentz and polarisation corrections have been made but not absorption. The data were processed on paper tape, which was subsequently converted into card via an IBM 1130 computer. It was then processed with the SHELX system of computer programs. [179] Computation was carried out using an IBM 370/135 and 145 computers at Sheffield City Polytechnic.

4:4:8:3 Crystal Data

$Pd(pmzH)Cl_3$

$C_{17}H_{21}Cl_3N_2PdS$, M= 498.21, Monoclinic, space group $P2_1$, a=11.381(5), b=9.791(4), c=9.098(4)Å, ß=100.85(5)°, U=995.76Å^3, λ =0.710 69Å, D_m= 1.67, Z=2, D_c=1.69 Mg m^{-3}, μ(Mo-Kα)=1.32 mm^{-1}, F(000)=500.

$Pd(cpzH)Cl_3$

$C_{17}H_{20}Cl_4N_2PdS$, M= 532.6, Monoclinic, space group C2/c, a=29.757(9), b=9.487(4), c=16.184(6)Å, ß=116.5(1)°, U=4088.2Å^3, λ =0.710 69Å, D_m=1.71, Z=8, D_c=1.73 Mg m^{-3}, μ(Mo-Kα)=2.30 mm^{-1}, F(000)=2000.

4:4:8:4 Structure determination and refinement

$Pd(pmzH)Cl_3$

A crystal of approximate dimensions 0.47x0.32x0.08 mm was mounted with the b axis coincident with the ω axis of a Stöe Stadi 2 two circle diffractometer. Of the 1 790 unique reflections collected, 1 524 had $I \geq 3.0\,\sigma(I)$ and were used in the subsequent structure analysis.

While systematic absences do not distinguish between space groups $P2_1$ and $P2_1/m$, in the centrosymmetric space group Z = 2 requires the molecules to possess mirror symmetry. Subsequent analysis confirmed $P2_1$ to be the correct space group, with the two molecules occupying general positions. Interpretation of a three-dimensional Patterson map readily afforded the x and z coordinates of the palladium atom.

Successive difference electron-density maps revealed the remaining atoms and showed the N(10) side chain to be disordered as discussed in Sec.2:2:8. Only the hydrogen atoms of the C_6 rings could be satisfactorily located and were included in positions calculated from the geometry of the molecule (C-H 1.08 Å). A common isotropic thermal parameter was applied to the located hydrogen atoms and refined to a final value of U=0.085(85) Å^2. Scattering factors were calculated [180] using an analytical approximation and the weighting scheme adopted was $w = 0.2622/\{\sigma^2(F_o) + 0.0044(F_o)^2\}$. Full matrix refinement with isotropic thermal parameters for the disordered carbon atoms and with anisotropic thermal parameters for all other non-hydrogen atoms gave the final R=0.036 and R′=0.039. Final atomic parameters are given in Appendix II. Lists of structure factors are given in Appendix III and thermal parameters are given in Appendix IV.

Pd(cpzH)Cl_3

A crystal of approximate dimensions 0.37x0.32x0.15 mm was mounted with the b axis coincident with the ω axis of a Stöe Stadi 2 two circle diffractometer. Of the 3 122 unique reflections collected, 1 277 had $I \geq 3.0\,\sigma(I)$ and were used in the subsequent structure analysis.

While the systematically absent reflections are consistent with the space groups Cc and C2/c, subsequent analysis confirms the centrosymmetric space group to be correct with the asymmetric unit containing one Pd(cpzH)Cl_3 molecule. The palladium position was determined from the three dimensional Patterson function and the remaining atoms

were located from succesive difference electron density maps. Only the hydrogen atoms of the C_6 rings could be satisfactorily located and were included in positions calculated from the geometry of the molecule (C-H 1.08 Å). A common isotropic temperature factor was applied to the located hydrogen atoms and refined to a final value of U = 0.069(20) Å^2. Scattering factors were calculated [180] using an analytical approximation and the weighting scheme adopted was $w = 1.000/\{\sigma^2(F_o) + 0.0044(F_o)^2\}$. Full matrix refinement with anisotropic temperature factors for all non-hydrogen atoms gave the final R=0.056 and R'=0.060. Final atomic parameters are given in Appendix II. Lists of structure factors are given in Appendix III and thermal parameters are given in Appendix IV.

Appendix I

Compounds with acceptable C,H and N analysis, calculated values given in parentheses.

Compound	Formula	% Carbon	% Hydrogen	% Nitrogen
$Pd(ptz)_2Cl_2$	$C_{24}H_{18}Cl_2N_2PdS_2$	49.82(50.06)	3.23(3.15)	4.90(4.86)
$Pd(eptz)_2Cl_2$	$C_{28}H_{26}Cl_2N_2PdS_2$	52.59(53.22)	4.06(4.15)	4.29(4.43)
$Pd(dptz)_2Cl_2$	$C_{30}H_{28}Cl_2N_4O_2PdS_2$	50.18(50.18)	4.03(3.93)	7.76(7.80)
$Pd(cpzH)Cl_3$	$C_{17}H_{20}Cl_4N_2PdS$	38.26(38.34)	3.76(3.78)	5.21(5.26)
$Pd(pmzH)Br_3$	$C_{17}H_{21}Br_3N_2PdS$	32.49(32.33)	3.54(3.35)	4.34(4.44)
$Pd(pmzH)Cl_3$	$C_{17}H_{21}Cl_3N_2PdS$	41.07(41.00)	4.22(4.25)	5.50(5.62)
$Pd(pmzH)I_3$	$C_{17}H_{21}I_3N_2PdS$	26.15(26.43)	2.90(2.74)	3.23(3.63)
$Pd(tdzH)Cl_3$	$C_{21}H_{27}Cl_3N_2PdS_2$	43.20(43.16)	4.80(4.66)	4.71(4.80)
$Pt(ptz)_2Br_2$	$C_{24}H_{18}Br_2N_2PtS_2$	37.96(38.26)	2.53(2.41)	3.64(3.72)
$Pt(ptz)_2Cl_2$	$C_{24}H_{18}Cl_2N_2PtS_2$	43.26(43.38)	2.61(2.73)	4.60(3.72)
$Pt(cpzH)Cl_3$	$C_{17}H_{20}Cl_4N_2PtS$	32.79(32.85)	3.44(3.25)	4.39(4.50)
$Pt(pmzH)Cl_3$	$C_{17}H_{21}Cl_3N_2PtS$	34.74(34.80)	3.82(3.61)	4.57(4.77)
$Pt(tdzH)Cl_3$	$C_{21}H_{27}Cl_3N_2PtS$	37.25(37.48)	3.74(4.04)	4.13(4.16)
$(cpzH)_2CoCl_4$	$C_{34}H_{40}Cl_6CoN_4S_2$	48.71(48.59)	5.12(4.80)	6.27(6.67)
$(pcyzH)CoCl_4$	$C_{42}H_{46}Cl_4CoN_6O_2S_2$	54.30(54.14)	5.56(4.98)	9.18(9.02)
$(cpzH)_2NiCl_4$	$C_{34}H_{40}Cl_6N_4NiS_2$	50.11(48.60)	5.13(4.80)	6.85(6.67)
$(pcyzH)_2NiCl_4$	$C_{42}H_{46}Cl_4N_6NiO_2S_2$	53.92(54.16)	5.62(4.98)	9.06(9.02)
$(cpzH)_2CuCl_4$	$C_{34}H_{40}Cl_6CuN_4S_2$	48.19(48.32)	5.13(4.77)	6.23(6.63)
$(epzH)_2CuCl_4$	$C_{38}H_{50}Cl_4CuN_4S_2$	54.67(54.84)	6.31(6.05)	6.67(6.73)

Appendix II

Final atomic parameters

$Pd(pmzH)Cl_3$

Final atomic paremeters (x 10^5 for Pd; x 10^4 for other atoms).

Estimated standard deviations for non-hydrogen atoms in parenthese.

	x	y	z
Pd	24447(5)	25000	42418(6)
Cl(1)	2890(2)	4338(3)	2885(3)
Cl(2)	2175(3)	555(3)	5522(3)
Cl(3)	821(2)	1940(4)	2374(2)
S(5)	4001(2)	3200(3)	6072(2)
C(1)	3126(9)	1795(13)	9863(10)
H(1)	2502	2026	10588
C(2)	3911(11)	711(15)	10221(13)
H(2)	3864	79	11181
C(3)	4762(11)	439(15)	9330(13)
H(3)	5380	-401	9603
C(4)	4806(9)	1247(15)	8117(13)
H(4)	5471	1051	7439
C(6)	4095(9)	5889(13)	6221(11)
H(6)	4753	5911	5512
C(7)	3764(10)	7244(14)	6663(13)
H(7)	4145	8163	6292
C(8)	2929(10)	7316(15)	7589(13)

$Pd(pmzH)Cl_3$ cont.

H(8)	2680	8305	7960
C(9)	2411(9)	6167(12)	8048(11)
H(9)	1735	6263	8732
C(11)	3117(6)	2594(16)	8602(8)
C(12)	4008(7)	2302(14)	7747(9)
C(13)	3579(7)	4810(12)	6689(10)
C(14)	2751(7)	4879(10)	7643(9)
N(10)	2306(6)	3653(9)	8164(8)
C(15)	1182(8)	3736(12)	8821(11)
C(16A)	121(16)	3480(34)	7829(21)
C(16B)	329(12)	2487(32)	8394(15)
N(17)	181(6)	2086(10)	6909(11)
C(18A)	-735(20)	2081(27)	5654(25)
C(18B)	-323(30)	3287(44)	5686(36)
C(19A)	131(23)	872(34)	8038(29)
C(19B)	-488(36)	858(52)	6264(44)
C(20)	-949(11)	3251(26)	8674(17)

$Pd(cpzH)Cl_3$

Final atomic parameters (x 10^5 for Pd; x 10^4 for other atoms).

Estimated standard deviations for non-hydrogen atoms in parentheses.

	x	y	z
Pd	35921(4)	37616(16)	-513(9)
Cl(1)	3557(2)	5722(5)	752(4)
Cl(2)	3668(2)	1902(7)	-887(3)
Cl(3)	2864(2)	4516(7)	-1288(3)
Cl(4)	4920(3)	-3044(8)	1138(5)
S(5)	4316(2)	3186(5)	1251(3)
C(1)	4356(5)	-1041(21)	1405(9)
H(1)	4145	-1875	1523
C(2)	4763(6)	-1366(24)	1193(11)
C(3)	5030(6)	-270(23)	1036(11)
H(3)	5344	-517	896
C(4)	4899(6)	1135(25)	1058(10)
H(4)	5107	1966	928
C(6)	4262(7)	4181(22)	2776(13)
H(6)	4447	5098	2677
C(7)	4126(7)	4101(32)	3492(15)
H(7)	4199	4984	3955
C(8)	3898(7)	2914(31)	3616(12)
H(8)	3801	2872	4184
C(9)	3793(6)	1784(24)	3035(12)
H(9)	3621	851	3151

$Pd(cpzH)Cl_3$ cont.

C(11)	4235(6)	374(18)	1452(10)
C(12)	4491(6)	1472(16)	1251(8)
C(13)	4147(6)	3018(21)	2195(11)
C(14)	3913(5)	1847(19)	2281(11)
N(10)	3835(5)	710(16)	1685(10)
C(15)	3460(5)	358(21)	1602(13)
C(16)	3151(6)	-874(21)	590(15)
C(17)	2852(6)	341(21)	-32(13)
N(18)	2555(9)	-36(25)	-971(14)
C(19)	2249(8)	1114(27)	-1575(13)
C(20)	2568(12)	-1306(36)	-1386(16)

Appendix III

Tables of observed and calculated structure factors.

$Pd(pmzH)Cl_2$

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR PD(PROMETHAZINE)CL3 PAGE 1

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
2	0	0	89	96	2	3	0	22	22	9	6	0	11	11	6	0	1	81	78	-5	2	1	13	13
3	0	0	46	48	3	3	0	26	25	10	6	0	20	19	7	0	1	24	25	-4	2	1	45	45
4	0	0	78	81	4	3	0	52	48	2	7	0	17	17	8	0	1	17	17	-3	2	1	56	53
5	0	0	10	12	5	3	0	52	51	3	7	0	40	38	10	0	1	25	26	-7	2	1	84	82
6	0	0	52	90	6	3	0	31	30	5	7	0	22	24	11	0	1	28	28	-1	2	1	61	57
7	0	0	14	13	7	3	0	41	41	6	7	0	14	15	12	0	1	15	16	0	2	1	54	58
8	0	0	45	44	9	3	0	23	24	7	7	0	10	11	-13	1	1	21	21	1	2	1	28	24
11	0	0	14	14	10	3	0	18	18	9	7	0	24	23	-12	1	1	8	8	2	2	1	28	25
12	0	0	18	18	11	3	0	28	28	10	7	0	12	10	-11	1	1	11	11	3	2	1	29	29
13	0	0	14	14	12	3	0	16	17	2	8	0	31	31	-10	1	1	11	12	4	2	1	35	35
2	1	0	39	40	1	4	0	23	23	4	8	0	29	30	-9	1	1	26	25	5	2	1	48	47
3	1	0	51	50	2	4	0	65	65	5	8	0	10	9	-7	1	1	64	64	6	2	1	38	37
4	1	0	21	21	3	4	0	38	36	6	8	0	16	16	-6	1	1	20	19	7	2	1	30	31
5	1	0	71	73	4	4	0	50	50	8	8	0	23	22	-5	1	1	30	30	8	2	1	10	11
6	1	0	24	24	5	4	0	52	51	9	8	0	12	12	-4	1	1	46	44	9	2	1	14	14
7	1	0	51	50	6	4	0	38	37	1	9	0	27	26	-3	1	1	87	86	10	2	1	21	22
8	1	0	24	24	7	4	0	15	14	3	9	0	32	31	-2	1	1	83	80	11	2	1	26	26
9	1	0	20	19	8	4	0	26	25	5	9	0	22	23	-1	1	1	87	86	12	2	1	15	16
10	1	0	15	13	10	4	0	26	26	7	9	0	16	16	0	1	1	76	74	13	3	1	19	20
11	1	0	11	11	11	4	0	16	16	8	9	0	15	14	1	1	1	53	51	12	3	1	12	12
12	1	0	16	17	12	4	0	13	13	2	10	0	30	30	2	1	1	81	79	11	3	1	19	18
13	1	0	22	22	1	5	0	79	77	4	10	0	27	26	3	1	1	60	57	10	3	1	15	15
1	2	0	32	33	2	5	0	26	24	6	10	0	14	13	4	1	1	37	36	9	3	1	41	41
2	2	0	37	36	3	5	0	73	72	3	11	0	21	21	5	1	1	20	20	8	3	1	16	17
3	2	0	30	31	4	5	0	23	21	5	11	0	14	15	6	1	1	21	22	7	3	1	69	67
4	2	0	29	32	5	5	0	55	54	12	0	1	13	13	10	1	1	25	25	6	3	1	41	41
5	2	0	11	11	6	5	0	13	14	11	0	1	9	7	11	1	1	21	22	5	3	1	46	47
6	2	0	58	58	7	5	0	24	23	8	0	1	49	51	12	1	1	12	15	4	3	1	12	12
7	2	0	24	23	9	5	0	26	26	6	0	1	38	39	13	2	1	7	6	3	3	1	50	51
8	2	0	29	29	11	5	0	17	16	5	0	1	30	27	12	2	1	16	18	2	3	1	23	25
9	2	0	9	7	1	6	0	22	22	4	0	1	16	14	11	2	1	16	16	1	3	1	60	58
10	2	0	16	15	2	6	0	57	57	3	0	1	31	29	10	2	1	19	20	0	3	1	53	54
11	2	0	15	15	4	6	0	53	53	2	0	1	156	152	9	2	1	22	22	1	3	1	45	43
12	2	0	24	26	6	6	0	23	23	3	0	1	23	26	8	2	1	67	71	2	3	1	18	19
13	2	0	12	13	7	6	0	13	13	4	0	1	96	94	7	2	1	19	20	4	3	1	41	41
1	3	0	31	33	8	6	0	16	16	5	0	1	78	75	6	2	1	57	57	5	3	1	41	39

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR PD(PROMETHAZINE)CL3 PAGE 2

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
6	3	1	28	28	-5	5	1	41	41	-9	7	1	21	19	2	9	1	14	13	9	0	2	41	41
7	3	1	18	18	-4	5	1	20	19	-8	7	1	10	8	3	9	1	20	21	10	0	2	10	9
8	3	1	18	18	-3	5	1	68	64	-7	7	1	15	15	6	9	1	10	11	-11	0	2	27	29
9	3	1	20	21	-1	5	1	56	57	-6	7	1	16	15	7	9	1	14	15	-13	1	2	14	14
10	3	1	24	24	0	5	1	42	45	-5	7	1	40	40	8	9	1	17	16	-11	1	2	18	17
11	3	1	15	16	1	5	1	69	67	-4	7	1	23	24	-6	10	1	14	15	-10	1	2	16	15
12	3	1	14	15	2	5	1	52	49	-3	7	1	35	35	-4	10	1	26	26	-9	1	2	41	40
12	4	1	21	21	3	5	1	70	71	-2	7	1	23	21	-3	10	1	14	14	-8	1	2	27	27
11	4	1	12	11	4	5	1	34	33	0	7	1	26	28	-2	10	1	21	22	-7	1	2	35	35
10	4	1	27	27	5	5	1	47	44	1	7	1	30	31	0	10	1	19	20	-6	1	2	30	28
9	4	1	12	13	6	5	1	27	27	2	7	1	32	30	2	10	1	25	29	-5	1	2	25	23
8	4	1	45	46	7	5	1	31	30	3	7	1	38	37	3	10	1	16	16	-4	1	2	31	32
7	4	1	17	17	8	5	1	30	29	4	7	1	13	12	4	10	1	19	17	-3	1	2	95	91
6	4	1	51	50	9	5	1	28	27	5	7	1	10	9	5	10	1	12	11	-2	1	2	97	99
5	4	1	44	45	10	5	1	15	17	7	7	1	16	15	6	10	1	16	17	-1	1	2	47	47
4	4	1	71	67	11	5	1	12	11	8	7	1	21	20	3	11	1	14	14	0	1	2	70	75
3	4	1	18	16	-10	6	1	18	19	-9	7	1	18	18	1	11	1	20	20	1	1	2	113	112
2	4	1	90	66	-9	6	1	10	8	-10	7	1	9	9	3	11	1	16	17	2	1	2	76	74
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1	4	1	47	47	-5	6	1	19	19	-5	8	1	12	11	-12	0	2	14	14	5	1	2	30	30
2	4	1	42	42	-4	6	1	46	45	-4	8	1	39	39	-10	0	2	31	30	6	1	2	29	30
3	4	1	39	38	-3	6	1	26	26	-2	8	1	20	19	-9	0	2	22	22	7	1	2	16	15
4	4	1	28	29	-2	6	1	42	40	1	8	1	16	15	-8	0	2	33	34	8	1	2	25	27
5	4	1	40	38	-1	6	1	24	24	2	8	1	26	26	-6	0	2	10	8	10	1	2	29	29
6	4	1	27	26	0	6	1	37	39	7	8	1	15	14	-5	0	2	25	22	11	1	2	9	7
7	4	1	33	34	1	6	1	36	34	8	8	1	13	14	-3	0	2	62	60	12	1	2	17	14
8	4	1	23	22	2	6	1	60	60	9	8	1	12	12	-2	0	2	79	80	-13	2	2	10	10
9	4	1	28	30	3	6	1	39	38	-6	9	1	8	8	-1	0	2	64	64	-12	2	2	11	12
10	4	1	20	20	4	6	1	45	44	-7	9	1	16	15	0	0	2	24	26	-11	2	2	19	20
11	4	1	20	21	5	6	1	16	14	-5	9	1	31	30	1	0	2	36	35	-10	2	2	34	34
-11	5	1	20	20	6	6	1	25	23	-4	9	1	15	15	3	0	2	139	132	-9	2	2	28	28
-10	5	1	9	8	7	6	1	22	21	-3	9	1	27	27	4	0	2	42	41	-8	2	2	42	43
-9	5	1	20	20	8	6	1	24	24	-2	9	1	22	21	5	0	2	86	86	-7	2	2	35	38
-7	5	1	23	23	9	6	1	21	21	-1	9	1	21	20	6	0	2	38	37	-6	2	2	34	33
-6	5	1	17	17	10	6	1	19	18	1	9	1	22	21	7	0	2	25	25	-5	2	2	48	45

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR PDIPROMETHAZINEJCL3 PAGE 3

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
-4	2	2	52	50	9	3	2	16	18	-1	5	2	28	29	-6	7	2	30	32	-1	9	2	18	17
-3	2	2	66	63	10	3	2	22	21	0	5	2	45	48	-5	7	2	35	35	0	9	2	29	30
-2	2	2	77	81	12	3	2	9	11	1	5	2	43	44	-4	7	2	26	25	1	9	2	14	15
-1	2	2	71	76	-12	4	2	19	18	2	5	2	48	47	-3	7	2	21	20	2	9	2	22	22
0	2	2	15	16	-11	4	2	11	11	3	5	2	41	39	-2	7	2	17	18	4	9	2	11	12
1	2	2	61	58	-10	4	2	21	21	4	5	2	47	45	-1	7	2	15	15	6	9	2	16	16
2	2	2	74	74	-9	4	2	21	21	5	5	2	26	25	0	7	2	48	51	-6	10	2	13	13
3	2	2	68	66	-8	4	2	22	23	6	5	2	41	40	1	7	2	28	28	-4	10	2	14	13
4	2	2	34	31	-7	4	2	25	25	7	5	2	23	23	2	7	2	35	35	-1	10	2	14	15
5	2	2	25	26	-6	4	2	29	28	8	5	2	35	35	3	7	2	22	22	0	10	2	16	18
6	2	2	10	10	-5	4	2	35	32	9	5	2	21	21	4	7	2	10	8	1	10	2	20	21
7	2	2	9	10	-4	4	2	48	47	10	5	2	18	17	6	7	2	25	23	2	10	2	14	16
9	2	2	21	22	-3	4	2	17	19	11	5	2	7	4	7	7	2	13	13	3	10	2	14	16
11	2	2	18	20	-2	4	2	38	38	-10	6	2	19	17	8	7	2	21	20	5	10	2	16	16
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-10	3	2	31	30	3	4	2	60	56	-4	6	2	25	24	-5	8	2	35	34	-11	0	3	25	25
-9	3	2	32	32	4	4	2	35	34	-3	6	2	25	24	-4	8	2	26	24	-10	0	3	19	19
-8	3	2	30	30	5	4	2	38	37	-2	6	2	17	17	-3	8	2	23	21	-9	0	3	35	33
-7	3	2	42	43	6	4	2	24	24	-1	6	2	33	33	-2	8	2	14	13	-8	0	3	14	15
-6	3	2	54	54	7	4	2	34	33	0	6	2	20	22	-1	8	2	27	28	-7	0	3	12	12
-5	3	2	39	38	8	4	2	24	23	1	6	2	55	54	0	8	2	14	15	-6	0	3	26	26
-4	3	2	59	58	9	4	2	24	24	2	6	2	40	38	1	8	2	44	44	-5	0	3	60	59
-3	3	2	65	63	10	4	2	11	12	3	6	2	40	37	2	8	2	13	13	-4	0	3	39	38
-2	3	2	90	90	11	4	2	15	17	4	6	2	22	22	3	8	2	20	19	-3	0	3	43	45
-1	3	2	70	69	-12	5	2	7	8	5	6	2	33	31	5	8	2	13	14	-2	0	3	25	25
0	3	2	45	48	-11	5	2	16	16	6	6	2	17	17	7	8	2	20	19	-1	0	3	10	9
1	3	2	32	33	-9	5	2	13	13	7	6	2	37	35	-8	9	2	10	11	0	0	3	10	13
2	3	2	48	50	-7	5	2	15	16	8	6	2	21	20	-7	9	2	12	13	1	0	3	71	68
3	3	2	62	56	-6	5	2	22	22	9	6	2	18	19	-6	9	2	20	20	2	0	3	16	14
4	3	2	25	28	-5	5	2	27	27	-10	7	2	8	9	-5	9	2	21	21	3	0	3	111	108
5	3	2	27	26	-4	5	2	19	20	-9	7	2	16	15	-4	9	2	22	23	4	0	3	27	25
6	3	2	11	13	-3	5	2	21	20	-8	7	2	19	18	-3	9	2	15	14	5	0	3	35	35
8	3	2	17	16	-2	5	2	29	28	-7	7	2	24	25	-2	9	2	14	14	7	0	3	43	39

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR PDIPROMETHAZINEJCL3 PAGE 4

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
9	0	3	52	52	-1	2	3	78	79	-12	4	3	14	13	5	5	3	23	24	6	7	3	32	32
11	0	3	24	24	0	2	3	21	20	-11	4	3	12	12	6	5	3	43	44	7	7	3	17	18
-12	1	3	14	14	1	2	3	69	69	-10	4	3	11	9	7	5	3	14	16	8	7	3	15	14
-11	1	3	12	12	2	2	3	35	35	-9	4	3	28	26	8	5	3	28	28	-9	8	3	11	12
-10	1	3	34	35	3	2	3	65	70	-8	4	3	11	11	9	5	3	8	6	-8	8	3	10	7
-9	1	3	29	29	4	2	3	17	16	-7	4	3	46	47	10	5	3	15	17	-7	8	3	34	34
-8	1	3	35	35	5	2	3	33	32	-6	4	3	28	27	-10	6	3	9	10	-6	8	3	14	13
-7	1	3	22	23	6	2	3	8	9	-5	4	3	40	38	-9	6	3	17	16	-5	8	3	36	35
-6	1	3	18	18	7	2	3	25	24	-4	4	3	16	15	-7	6	3	36	35	-4	8	3	12	12
-5	1	3	43	41	8	2	3	19	19	-3	4	3	51	51	-6	6	3	15	15	-3	8	3	35	35
-4	1	3	70	69	9	2	3	25	25	-2	4	3	41	41	-5	6	3	25	23	-1	8	3	50	53
-3	1	3	32	32	11	2	3	13	12	-1	4	3	64	65	-4	6	3	15	14	0	8	3	17	18
-2	1	3	54	52	-12	3	3	12	12	0	4	3	19	19	-3	6	3	19	17	1	8	3	40	41
-1	1	3	41	42	-11	3	3	14	13	1	4	3	59	57	-1	6	3	36	37	3	8	3	22	21
2	1	3	65	65	-10	3	3	27	28	2	4	3	13	12	0	6	3	13	14	4	8	3	9	7
3	1	3	19	18	-9	3	3	21	20	3	4	3	35	34	1	6	3	33	33	5	8	3	27	26
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6	1	3	23	24	-6	3	3	45	44	7	4	3	29	29	5	6	3	30	30	-7	9	3	9	8
7	1	3	15	16	-5	3	3	22	22	8	4	3	12	11	6	6	3	15	14	-6	9	3	23	23
8	1	3	45	44	-4	3	3	82	83	9	4	3	13	13	7	6	3	34	34	-4	9	3	19	20
9	1	3	8	9	-3	3	3	34	34	10	4	3	9	9	8	6	3	15	15	-2	9	3	24	26
10	1	3	31	30	-2	3	3	98	100	11	4	3	14	14	9	6	3	16	16	0	9	3	30	31
12	1	3	14	13	-1	3	3	51	47	-11	5	3	14	14	-10	7	3	10	10	2	9	3	20	20
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-11	2	3	18	21	2	3	3	57	57	-7	5	3	15	15	-6	7	3	41	40	6	9	3	21	21
-10	2	3	19	19	3	3	3	26	26	-6	5	3	36	35	-5	7	3	16	17	-6	10	3	9	6
-9	2	3	37	38	4	3	3	45	44	-5	5	3	29	29	-4	7	3	27	27	-5	10	3	12	11
-8	2	3	25	27	5	3	3	23	24	-4	5	3	17	16	-2	7	3	39	38	-1	10	3	14	15
-7	2	3	31	32	6	3	3	25	25	-2	5	3	25	27	0	7	3	48	52	1	10	3	15	15
-6	2	3	13	15	7	3	3	14	14	0	5	3	35	37	1	7	3	25	26	5	10	3	17	17
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-4	2	3	22	21	9	3	3	10	10	-2	5	3	25	26	3	7	3	22	21	-13	0	4	12	14
-3	2	3	95	97	10	3	3	16	16	3	5	3	10	8	4	7	3	18	17	-12	0	4	8	8
-2	2	3	25	25	11	3	3	8	9	4	5	3	18	18	5	7	3	14	12	-11	0	4	44	42

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR (PROMETHAZINE)CL3 PAGE 5

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
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-7	0	4	31	31	-10	2	4	11	11	5	3	4	20	19	0	5	4	26	27	0	7	4	32	32
-6	0	4	9	7	-9	2	4	24	24	6	3	4	34	32	2	5	4	17	18	1	7	4	16	17
-5	0	4	55	58	-8	2	4	9	9	7	3	4	14	13	3	5	4	25	23	2	7	4	23	23
-3	0	4	25	26	-7	2	4	29	30	8	3	4	25	25	4	5	4	34	34	3	7	4	22	22
-2	0	4	20	19	-6	2	4	11	10	9	3	4	18	17	5	5	4	10	10	4	7	4	37	36
-1	0	4	29	29	-5	2	4	66	68	10	3	4	9	8	6	5	4	23	24	5	7	4	24	25
2	0	4	18	17	-4	2	4	43	41	11	3	4	8	5	7	5	4	9	9	6	7	4	31	31
4	0	4	14	12	-3	2	4	64	65	-11	4	4	20	19	8	5	4	12	12	7	7	4	8	9
6	0	4	12	13	-2	2	4	22	22	-10	4	4	8	8	9	5	4	10	11	8	7	4	9	7
7	0	4	20	19	-1	2	4	59	58	-9	4	4	37	37	-10	6	4	13	14	-9	8	4	16	17
8	0	4	27	28	0	2	4	37	38	-7	4	4	37	38	-9	6	4	30	31	-7	8	4	24	25
9	0	4	22	21	1	2	4	78	83	-6	4	4	42	42	-8	6	4	14	13	-3	8	4	28	28
10	0	4	5	7	2	2	4	44	45	-5	4	4	42	43	-7	6	4	37	37	-2	8	4	14	14
11	0	4	9	8	3	2	4	57	58	-3	4	4	38	37	-5	6	4	21	20	-1	8	4	40	40
-12	1	4	27	27	4	2	4	16	16	-2	4	4	17	17	-4	6	4	17	18	0	8	4	14	13
-10	1	4	41	42	5	2	4	35	34	-1	4	4	52	54	-3	6	4	31	32	1	8	4	21	22
-9	1	4	11	11	6	2	4	26	26	0	4	4	36	37	-2	6	4	12	13	2	8	4	10	9
-8	1	4	23	23	7	2	4	31	33	1	4	4	51	51	-1	6	4	35	35	3	8	4	25	24
-6	1	4	41	41	8	2	4	21	21	2	4	4	14	14	0	6	4	17	17	4	8	4	17	17
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-4	1	4	71	70	11	2	4	7	7	4	4	4	25	26	2	6	4	12	12	6	8	4	11	9
-3	1	4	46	45	-12	3	4	17	17	5	4	4	36	34	3	6	4	26	25	7	8	4	11	11
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6	1	4	30	30	-2	3	4	49	50	-8	5	4	40	39	-8	7	4	32	32	-3	10	4	12	12
7	1	4	26	26	-1	3	4	39	39	-7	5	4	10	10	-6	7	4	30	29	-2	10	4	10	10
8	1	4	28	28	0	3	4	69	73	-6	5	4	24	24	-5	7	4	10	11	-1	10	4	15	14
9	1	4	21	21	1	3	4	42	44	-4	5	4	25	24	-4	7	4	20	20	1	10	4	9	7
10	1	4	13	13	2	3	4	73	74	-3	5	4	15	14	-3	7	4	21	21	4	10	4	10	9
-12	2	4	8	6	3	3	4	32	31	-2	5	4	27	28	-2	7	4	51	52	-12	0	5	14	14

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR (PROMETHAZINE)CL3 PAGE 6

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
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-9	0	5	18	18	-11	2	5	21	22	3	3	5	30	30	-4	5	5	30	31	3	7	5	25	25
-8	0	5	23	22	-10	2	5	8	7	4	3	5	35	35	-3	5	5	33	34	4	7	5	22	23
-7	0	5	44	43	-9	2	5	14	14	5	3	5	26	27	-2	5	5	33	33	5	7	5	17	17
-6	0	5	42	42	-8	2	5	14	12	6	3	5	22	22	-1	5	5	21	22	6	7	5	8	6
-5	0	5	60	61	-7	2	5	27	28	7	3	5	30	29	0	5	5	19	19	7	8	5	8	9
-4	0	5	40	41	-6	2	5	22	23	8	3	5	11	12	1	5	5	15	16	-5	8	5	12	11
-3	0	5	12	10	-5	2	5	49	51	9	3	5	12	13	4	5	5	17	15	-4	8	5	21	22
-2	0	5	25	25	-4	2	5	27	28	10	3	5	7	8	5	5	5	16	15	-3	8	5	24	25
-1	0	5	32	33	-3	2	5	33	34	-11	4	5	18	19	7	5	5	12	11	-2	8	5	20	20
0	0	5	60	62	-2	2	5	22	23	-10	4	5	17	16	-9	6	5	25	24	-1	8	5	21	21
1	0	5	48	50	-1	2	5	39	39	-9	4	5	21	22	-8	6	5	19	20	0	8	5	17	17
2	0	5	23	22	0	2	5	56	56	-8	4	5	17	18	-7	6	5	23	22	1	8	5	13	15
6	0	5	42	42	1	2	5	51	54	-7	4	5	21	20	-6	6	5	18	18	2	8	5	21	23
7	0	5	9	11	2	2	5	51	51	-6	4	5	16	15	-5	6	5	28	29	3	8	5	17	18
8	0	5	22	21	3	2	5	29	30	-5	4	5	18	18	-4	6	5	28	29	4	8	5	29	30
9	0	5	8	8	4	2	5	20	21	-4	4	5	25	25	-3	6	5	37	37	5	8	5	13	13
12	1	5	28	28	5	2	5	35	36	-3	4	5	27	28	-2	6	5	23	24	6	8	5	15	16
-11	1	5	9	10	6	2	5	32	36	-2	4	5	33	33	-1	6	5	26	28	-6	9	5	9	9
-10	1	5	17	17	7	2	5	14	13	-1	4	5	36	37	0	6	5	12	11	-5	9	5	11	11
-8	1	5	24	23	8	2	5	21	22	0	4	5	28	28	1	6	5	16	17	-4	9	5	18	18
-7	1	5	31	30	9	2	5	10	11	1	4	5	15	15	2	6	5	17	17	-3	9	5	20	21
-6	1	5	57	57	10	2	5	11	10	2	4	5	30	30	3	6	5	14	14	-1	9	5	12	13
-5	1	5	45	47	12	3	5	19	20	3	4	5	18	18	4	6	5	19	18	0	9	5	12	12
-4	1	5	47	48	-11	3	5	8	8	4	4	5	13	13	5	6	5	11	11	1	9	5	11	12
-3	1	5	22	21	-10	3	5	17	16	5	4	5	27	27	6	6	5	10	11	2	9	5	14	14
-2	1	5	25	28	-8	3	5	15	14	6	4	5	26	25	-9	7	5	13	14	3	9	5	20	19
-1	1	5	29	31	-7	3	5	26	28	7	4	5	9	10	-8	7	5	20	19	4	9	5	12	12
0	1	5	56	56	-6	3	5	30	30	8	4	5	14	14	-6	7	5	13	12	-4	10	5	13	14
1	1	5	55	58	-5	3	5	24	23	9	4	5	11	11	-5	7	5	20	20	-3	10	5	15	14
2	1	5	36	36	-4	3	5	35	36	-11	5	5	17	16	-4	7	5	31	31	-2	10	5	10	11
4	1	5	14	13	-3	3	5	22	21	-10	5	5	22	22	-3	7	5	24	26	-1	10	5	9	10
5	1	5	18	17	-2	3	5	26	30	-9	5	5	21	21	-2	7	5	34	35	0	10	5	8	8
6	1	5	17	15	-1	3	5	42	43	-8	5	5	22	22	-1	7	5	13	14	1	10	5	9	6
7	1	5	34	33	0	3	5	44	44	-7	5	5	23	23	0	7	5	23	23	0	11	5	9	9
9	1	5	11	12	1	3	5	51	53	-6	5	5	24	23	1	7	5	18	18	-12	0	6	14	12

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR PDIPROMETHAZINEJCL3 PAGE 7

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
-11	0	6	8	7	-10	2	6	10	12	8	3	6	8	6	-8	6	6	15	16	-7	0	7	9	4
-10	0	6	15	15	-9	2	6	15	16	9	3	6	16	15	-7	6	6	10	11	-6	0	7	32	32
-8	0	6	40	39	-8	2	6	22	22	-11	4	6	14	14	-6	6	6	24	23	-5	0	7	16	16
-7	0	6	24	24	-7	2	6	29	30	-10	4	6	20	21	-5	6	6	15	16	-4	0	7	32	31
-6	0	6	57	58	-6	2	6	28	28	-9	4	6	13	12	-4	6	6	35	34	-3	0	7	16	17
-5	0	6	19	20	-5	2	6	18	19	-8	4	6	24	22	-3	6	6	14	15	-2	0	7	68	71
-4	0	6	32	31	-3	2	6	9	9	-7	4	6	19	19	-2	6	6	30	31	0	0	7	40	38
-3	0	6	20	20	-2	2	6	31	33	-6	4	6	40	39	-1	6	6	10	9	1	0	7	14	12
-2	0	6	59	62	-1	2	6	16	16	-5	4	6	13	14	0	6	6	21	21	2	0	7	25	25
-1	0	6	32	31	0	2	6	44	44	-4	4	6	38	39	1	6	6	13	14	4	0	7	37	36
0	0	6	53	53	1	2	6	26	25	-3	4	6	27	29	2	6	6	33	32	5	0	7	10	10
1	0	6	16	16	2	2	6	24	24	-2	4	6	32	34	4	6	6	20	21	6	0	7	10	10
4	0	6	27	27	3	2	6	9	8	-1	4	6	22	22	6	6	6	8	7	-11	1	7	11	12
5	0	6	12	12	4	2	6	30	31	0	4	6	34	34	8	7	6	9	9	-10	1	7	12	12
6	0	6	32	32	6	2	6	42	43	2	4	6	33	34	-6	7	6	8	7	-9	1	7	31	30
-12	1	6	13	13	7	2	6	9	10	3	4	6	20	20	-5	7	6	17	17	-7	1	7	31	31
-11	1	6	14	12	8	2	6	16	17	4	4	6	33	34	-4	7	6	12	12	-5	1	7	17	18
-10	1	6	10	8	-12	3	6	15	17	5	4	6	12	11	-3	7	6	23	23	-4	1	7	16	18
-9	1	6	24	24	-11	3	6	15	15	6	4	6	22	21	-1	7	6	12	12	-3	1	7	48	48
-8	1	6	21	22	-10	3	6	9	9	8	4	6	12	13	0	7	6	9	9	-2	1	7	14	13
-7	1	6	50	51	-9	3	6	16	16	-10	5	6	11	12	1	7	6	24	25	-1	1	7	56	57
-6	1	6	23	22	-8	3	6	24	23	-9	5	6	24	23	3	7	6	27	28	0	1	7	16	17
-5	1	6	25	26	-7	3	6	25	26	-8	5	6	17	17	5	7	6	12	12	1	1	7	22	23
-4	1	6	21	21	-6	3	6	29	30	-7	5	6	27	27	-5	8	6	9	9	3	1	7	36	35
-3	1	6	23	25	-5	3	6	20	20	-6	5	6	16	16	-4	8	6	14	15	4	1	7	18	16
-2	1	6	21	22	-4	3	6	8	7	-5	5	6	43	43	-3	8	6	10	10	5	1	7	28	26
-1	1	6	63	63	-3	3	6	10	10	-4	5	6	14	15	-2	8	6	11	13	6	1	7	13	12
0	1	6	27	27	-2	3	6	28	28	-3	5	6	40	41	0	8	6	11	11	7	1	7	8	7
1	1	6	25	27	-1	3	6	38	40	-2	5	6	18	19	2	8	6	25	25	-10	2	7	19	20
2	1	6	25	26	0	3	6	8	8	-1	5	6	27	29	3	8	6	9	9	-9	2	7	10	9
3	1	6	16	16	1	3	6	27	26	-1	5	6	31	30	4	8	6	19	20	-8	2	7	27	27
5	1	6	36	36	2	3	6	10	11	2	5	6	9	7	-5	9	6	12	13	-6	2	7	17	18
6	1	6	13	13	3	3	6	28	29	3	5	6	32	32	-3	9	6	15	15	-5	2	7	11	10
7	1	6	25	26	4	3	6	14	15	4	5	6	11	9	-1	9	6	9	9	-4	2	7	20	21
-12	2	6	11	12	5	3	6	40	40	5	5	6	14	14	-10	0	7	15	17	-3	2	7	11	13
-11	2	6	11	11	7	3	6	27	28	7	5	6	10	9	-8	0	7	42	42	-2	2	7	37	38

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR PDIPROMETHAZINEJCL3 PAGE 8

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
0	2	7	28	27	3	4	7	24	24	-4	0	8	44	42	-2	2	8	23	24	5	4	8	10	12
1	2	7	10	10	4	4	7	24	25	-3	0	8	23	23	0	2	8	8	7	6	4	8	8	7
2	2	7	16	15	5	4	7	9	9	-2	0	8	26	27	1	2	8	8	8	-8	5	8	11	11
4	2	7	34	34	6	4	7	11	11	-1	0	8	22	22	2	2	8	13	13	-7	5	8	17	17
5	2	7	13	13	-9	5	7	14	16	0	0	8	18	17	3	2	8	17	16	-6	5	8	16	16
6	2	7	13	14	-7	5	7	22	21	1	0	8	24	23	4	2	8	10	12	-5	5	8	21	22
7	2	7	7	5	-6	5	7	15	16	2	0	8	27	27	5	2	8	12	13	-4	5	8	12	11
8	2	7	10	11	-5	5	7	36	35	3	0	8	32	32	6	2	8	7	10	-3	5	8	18	19
11	3	7	16	15	-3	5	7	32	33	4	0	8	29	28	-10	3	8	10	8	-2	5	8	17	18
10	3	7	11	10	-1	5	7	34	35	5	0	8	18	18	-9	3	8	26	26	-1	5	8	19	19
9	3	7	27	27	0	5	7	15	15	7	0	8	14	15	-8	3	8	17	16	0	5	8	22	22
8	3	7	9	9	1	5	7	31	32	10	1	8	6	7	-7	3	8	23	23	1	5	8	26	26
7	3	7	19	18	2	5	7	9	6	9	1	8	29	27	-6	3	8	15	14	2	5	8	17	19
5	3	7	14	14	3	5	7	28	27	8	1	8	11	9	-5	3	8	22	22	3	5	8	13	14
4	3	7	16	17	5	5	7	12	12	7	1	8	16	14	-4	3	8	15	15	4	5	8	12	11
3	3	7	26	26	6	5	7	7	6	6	1	8	6	6	-3	3	8	32	33	5	6	8	14	14
2	3	7	11	11	6	6	7	24	25	5	1	8	28	28	-2	3	8	12	13	6	6	8	16	16
1	3	7	27	28	4	6	7	31	32	4	1	8	21	19	-1	3	8	18	18	3	6	8	8	8
0	3	7	12	12	2	6	7	26	26	3	1	8	36	36	1	3	8	11	11	2	6	8	12	12
1	3	7	11	10	0	6	7	29	29	2	1	8	20	19	2	3	8	15	16	1	6	8	16	16
2	3	7	16	17	1	6	7	12	10	1	1	8	15	17	3	3	8	11	10	0	6	8	20	20
3	3	7	28	28	2	6	7	29	28	0	1	8	9	10	4	3	8	12	12	1	6	8	18	18
4	3	7	16	16	4	6	7	16	15	1	1	8	16	16	5	3	8	9	10	5	7	8	18	18
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7	3	7	10	11	5	7	7	24	24	3	1	8	24	23	8	4	8	21	20	1	7	8	13	12
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5	4	7	9	7	3	7	7	16	16	9	2	8	10	10	3	4	8	13	13	1	0	9	14	12
4	4	7	34	34	4	8	7	17	17	6	2	8	26	26	2	4	8	19	19	0	0	9	13	12
3	4	7	16	17	0	8	7	12	12	7	2	8	13	13	1	4	8	20	20	1	0	9	30	30
2	4	7	29	29	2	8	7	15	16	6	2	8	20	20	0	4	8	16	16	2	0	9	11	13
0	4	7	25	26	10	0	8	25	24	5	2	8	8	8	1	4	8	16	17	3	0	9	27	25
1	4	7	8	7	8	0	8	25	25	4	2	8	35	35	2	4	8	17	17	5	0	9	8	8
2	4	7	26	26	6	0	8	10	8	3	2	8	15	16	3	4	8	15	14	9	1	9	14	14

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR PD(PROMETHAZINE)CL3 PAGE 9

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
-8	1	9	11	8	-3	2	9	23	22	4	3	9	9	8	-1	5	9	12	11	2	1	10	18	18
-7	1	9	10	9	-1	2	9	14	14	-8	4	9	9	11	0	5	9	21	20	-5	2	10	26	27
-6	1	9	16	15	0	2	9	15	15	-7	4	9	13	14	2	5	9	14	15	-3	2	10	19	19
-5	1	9	15	14	1	2	9	19	20	-6	4	9	14	14	-7	0	10	15	14	-1	2	10	16	16
-4	1	9	25	24	2	2	9	11	11	-5	4	9	16	17	-6	0	10	9	7	0	2	10	8	7
-3	1	9	5	10	3	2	9	17	16	-4	4	9	11	13	-5	0	10	28	28	1	2	10	22	21
-2	1	9	19	19	-8	3	9	16	16	-3	4	9	25	25	-4	0	10	9	6	-6	3	10	22	22
-1	1	9	10	10	-7	3	9	11	10	-2	4	9	16	17	-3	0	10	8	8	-4	3	10	21	22
0	1	9	16	16	-6	3	9	19	20	-1	4	9	28	28	-1	0	10	10	9	-2	3	10	18	18
1	1	9	12	12	-5	3	9	17	17	0	4	9	15	15	1	0	10	21	21	-1	3	10	9	9
2	1	9	33	31	-4	3	9	21	22	1	4	9	17	18	-7	1	10	7	5	0	3	10	20	19
3	1	9	14	14	-3	3	9	18	17	3	4	9	15	15	-6	1	10	23	22	-5	4	10	14	16
-8	2	9	9	9	-2	3	9	20	20	-6	5	9	11	10	-4	1	10	22	21	-4	4	10	9	8
-7	2	9	13	13	0	3	9	17	17	-5	5	9	9	10	-3	1	10	7	4	-3	4	10	17	17
-6	2	9	17	15	1	3	9	15	15	-4	5	9	10	11	-2	1	10	10	9	-2	4	10	7	7
-5	2	9	24	23	2	3	9	14	15	-3	5	9	11	10	0	1	10	20	18	-1	4	10	16	14
-4	2	9	15	14	3	3	9	10	7	-2	5	9	19	21	1	1	10	10	7					

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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 2KN5 L.S. REFINEMENT PAGE 1

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
8	0	0	387	400	3	5	0	272	270	12	2	1	240	247	19	5	1	106	-105	-14	0	2	190	199
10	0	0	162	-170	5	5	0	99	97	14	2	1	57	59	23	5	1	49	55	-12	0	2	89	-93
12	0	0	72	-72	7	5	0	181	-180	16	2	1	102	-107	-24	6	1	45	-46	-10	0	2	98	-111
14	0	0	438	454	11	5	0	191	199	24	2	1	41	-37	-20	6	1	77	82	-6	0	2	239	258
16	0	0	84	76	17	5	0	107	107	26	2	1	80	78	-16	6	1	81	-92	6	0	2	456	463
18	0	0	128	-127	21	5	0	79	-75	-27	3	1	40	-37	-12	6	1	113	117	8	0	2	374	392
22	0	0	63	59	8	8	0	51	45	-23	3	1	64	60	-10	6	1	161	-153	10	0	2	376	-387
24	0	0	70	-69	10	8	0	70	-69	-19	3	1	50	-52	-8	6	1	142	-136	12	0	2	130	-122
26	0	0	105	100	12	8	0	42	-44	-15	3	1	77	78	-6	6	1	157	145	14	0	2	254	264
1	1	0	197	-196	7	5	0	60	59	-13	3	1	102	-95	-2	6	1	186	-175	18	0	2	81	-78
3	1	0	154	162	-21	1	1	90	-90	-11	3	1	129	115	2	6	1	202	191	20	0	2	104	104
5	1	0	118	122	-19	1	1	67	-64	-9	3	1	149	142	4	6	1	105	-102	22	0	2	169	164
7	1	0	172	-175	-17	1	1	130	132	-5	3	1	99	-98	6	6	1	175	-161	24	0	2	101	-103
21	1	0	72	66	-13	1	1	266	-279	3	3	1	101	88	8	6	1	102	102	26	0	2	82	-76
25	1	0	81	-80	-9	1	1	160	144	9	3	1	66	-65	10	6	1	63	59	28	0	2	77	70
29	1	0	54	48	-7	1	1	277	-265	13	3	1	90	91	12	6	1	81	82	-31	1	2	53	-50
31	1	0	33	-28	-5	1	1	437	-430	15	3	1	67	-67	16	6	1	106	107	-29	1	2	48	48
2	2	0	263	-271	7	1	1	162	-142	-24	4	1	46	38	20	6	1	61	-66	-25	1	2	51	-47
4	2	0	106	95	9	1	1	145	-148	-14	4	1	74	-76	22	6	1	43	41	-23	1	2	56	-55
6	2	0	79	-70	11	1	1	113	121	-12	4	1	112	107	-23	7	1	60	-66	-21	1	2	95	101
16	2	0	91	-96	13	1	1	190	204	-10	4	1	120	118	-9	7	1	153	-159	-17	1	2	158	-167
34	2	0	36	-25	15	1	1	94	-97	-6	4	1	67	87	5	7	1	168	-166	-15	1	2	117	125
7	3	0	83	-90	19	1	1	61	56	4	4	1	165	156	9	7	1	64	67	-11	1	2	114	-114
13	3	0	184	-188	23	1	1	79	-70	-23	5	1	63	-68	17	7	1	37	36	-9	1	2	255	235
15	3	0	83	-96	27	1	1	69	68	-17	5	1	64	-68	19	7	1	56	-60	-7	1	2	478	428
21	3	0	52	-51	-30	2	1	44	55	-13	5	1	78	74	-19	9	1	31	-31	-5	1	2	116	-87
29	3	0	36	-35	-26	2	1	84	-86	-11	5	1	141	142	-15	9	1	38	42	3	1	2	348	-320
6	4	0	226	222	-20	2	1	120	-123	-9	5	1	154	-147	-5	9	1	46	43	5	1	2	218	-205
8	4	0	110	-109	-18	2	1	58	-54	-5	5	1	148	139	5	9	1	68	68	7	1	2	251	242
8	4	0	105	-104	-16	2	1	124	133	-3	5	1	109	-94	-12	10	1	44	-53	9	1	2	112	115
10	4	0	197	196	-12	2	1	136	-137	3	5	1	172	162	-10	10	1	46	45	11	1	2	238	-253
12	4	0	72	70	-4	2	1	185	-172	5	5	1	227	-217	-8	10	1	77	83	13	1	2	57	65
14	4	0	121	-127	-2	2	1	291	272	9	5	1	132	129	6	10	1	73	78	15	1	2	57	55
16	4	0	116	126	2	2	1	145	-149	11	5	1	75	-75	-32	0	2	52	-54	19	1	2	48	-43
22	4	0	67	-66	8	2	1	233	-226	13	5	1	116	-117	-26	0	2	52	-38	21	1	2	67	64
24	4	0	81	78	10	2	1	65	-67	17	5	1	62	60	-18	0	2	276	-280	25	1	2	57	-50

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 2KN5 L.S. REFINEMENT PAGE 2

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
-20	2	2	77	77	14	4	2	99	-106	-7	6	2	55	53	22	2	3	81	-79	5	5	3	151	-140
-8	2	2	114	-108	18	4	2	77	81	3	6	2	74	-68	24	2	3	61	-59	9	5	3	109	110
-6	2	2	290	278	20	4	2	66	-66	-23	1	3	48	39	-27	3	3	78	-82	13	5	3	90	-95
-2	2	2	190	-164	22	4	2	65	-66	-21	1	3	53	-58	-23	3	3	91	97	19	5	3	69	-60
6	2	2	271	-260	-21	5	2	80	-80	-19	1	3	76	-76	-19	3	3	100	-110	-24	6	3	56	-53
8	2	2	123	118	-15	5	2	93	-90	-17	1	3	129	121	-17	3	3	126	140	-20	6	3	48	54
14	2	2	49	-49	-13	5	2	66	-64	-13	1	3	74	-78	-15	3	3	64	69	-16	6	3	73	-77
25	3	2	50	52	-11	5	2	164	149	-9	1	3	159	135	-13	3	3	133	-132	-12	6	3	118	112
-21	3	2	67	-63	-7	5	2	182	-170	-7	1	3	298	-281	-11	3	3	75	-73	-10	6	3	100	-93
-19	3	2	66	-74	-1	5	2	150	-135	-5	1	3	287	-266	-9	3	3	216	209	-8	6	3	74	-70
-17	3	2	103	116	3	5	2	235	225	-3	1	3	241	222	-5	3	3	169	-158	-6	6	3	78	72
-13	3	2	109	-112	5	5	2	128	118	1	1	3	325	-313	-3	3	3	303	268	-2	6	3	161	-148
-11	3	2	110	111	7	5	2	125	-124	5	1	3	208	199	1	3	3	146	-134	2	6	3	160	156
-9	3	2	90	-76	11	5	2	112	120	7	1	3	138	-154	5	3	3	112	116	4	6	3	124	-127
-7	3	2	184	-185	13	5	2	60	-56	9	1	3	272	-294	9	3	3	71	-66	6	6	3	91	-98
-3	3	2	190	193	15	5	2	70	-67	15	1	3	90	-97	11	3	3	155	162	8	6	3	83	80
1	3	2	247	-227	17	5	2	134	138	19	1	3	89	92	15	3	3	80	-86	12	6	3	124	-127
7	3	2	118	-111	19	5	2	78	79	23	1	3	85	-77	19	3	3	76	76	16	6	3	107	108
11	3	2	122	123	-10	6	2	76	66	-30	2	3	84	85	-18	4	3	83	94	20	6	3	43	-39
15	3	2	117	-116	-6	6	2	124	-121	-24	2	3	74	70	-14	4	3	99	-97	-17	7	3	51	-47
19	3	2	50	-42	4	6	2	120	115	-22	2	3	49	54	-12	4	3	68	64	-13	7	3	88	88
28	4	2	45	-49	-19	7	2	52	-50	-20	2	3	189	-201	-4	4	3	334	305	-11	7	3	65	62
-24	4	2	70	70	-15	7	2	55	64	-16	2	3	162	200	-2	4	3	114	112	-9	7	3	107	-107
-22	4	2	72	-68	-11	7	2	59	-60	-14	2	3	114	-120	0	4	3	170	-146	-3	7	3	76	-75
-18	4	2	145	154	-7	7	2	77	74	-12	2	3	123	-132	6	4	3	104	98	-1	7	3	107	-98
-14	4	2	154	-157	3	7	2	102	-104	-10	2	3	141	137	10	4	3	142	145	5	7	3	85	83
-12	4	2	60	61	9	7	2	53	-58	-8	2	3	184	172	12	4	3	66	66	7	7	3	55	-61
-10	4	2	238	223	-22	8	2	41	45	-6	2	3	435	-416	20	4	3	43	40	13	7	3	58	-63
-8	4	2	122	-126	-14	8	2	57	63	-4	2	3	155	-154	22	4	3	42	38	17	7	3	48	47
-6	4	2	80	-72	-10	8	2	71	-69	-2	2	3	274	262	24	4	3	40	39	19	7	3	36	-39
-4	4	2	265	255	-8	8	2	68	69	2	2	3	232	-231	-17	5	3	55	-53	-1	9	3	74	72
-2	4	2	211	-202	0	8	2	96	90	6	2	3	224	207	-15	5	3	75	-65	-12	10	3	48	-53
4	4	2	205	203	4	8	2	54	-59	8	2	3	229	-224	-6	5	3	113	-113	-8	10	3	43	45
6	4	2	234	-223	18	8	2	52	-50	10	2	3	67	-77	-7	5	3	81	77	-2	10	3	51	51
8	4	2	112	-113	-15	9	2	41	40	16	2	3	54	-53	-5	5	3	80	77	6	10	3	47	54
10	4	2	87	97	-11	9	2	52	-57	20	2	3	59	62	-1	5	3	164	-158	-32	0	4	55	-53

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 2KN5 L.S. REFINEMENT PAGE 3

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
-24	0	4	68	-66	-6	2	4	106	105	18	4	4	59	67	4	8	4	61	-60	6	2	5	252	254
-22	0	4	101	102	16	2	4	82	88	20	4	4	40	-37	6	8	4	50	48	8	2	5	185	-207
-18	0	4	182	-183	-31	3	4	49	46	22	4	4	41	-41	10	8	4	58	-60	10	2	5	76	-77
-16	0	4	102	-101	-25	3	4	85	87	-29	5	4	42	-45	14	8	4	76	80	12	2	5	102	106
-12	0	4	166	-176	-23	3	4	49	-56	-25	5	4	52	44	-15	9	4	52	54	16	2	5	109	-106
-10	0	4	135	-152	-21	3	4	92	-97	-15	5	4	99	-99	-11	9	4	49	-49	-20	2	5	77	80
-6	0	4	86	87	-19	3	4	59	62	-13	5	4	80	-83	-1	9	4	74	66	22	2	5	39	-38
-4	0	4	413	-406	-17	3	4	156	167	-7	5	4	107	-102	-1	11	4	39	-42	-27	3	5	74	-76
-2	0	4	138	-153	-15	3	4	72	-85	-3	5	4	69	66	-33	1	5	45	-38	-23	3	5	55	63
0	0	4	360	-351	-11	3	4	311	288	-1	5	4	204	-182	-27	1	5	52	-47	-21	3	5	87	-98
2	0	4	233	-234	-7	3	4	141	-131	1	5	4	135	-139	-23	1	5	105	114	-19	3	5	72	-73
4	0	4	388	-392	-3	3	4	275	252	7	5	4	64	-65	-19	1	5	75	-78	-17	3	5	90	99
6	0	4	185	181	-1	3	4	95	-80	15	5	4	88	-86	-15	1	5	72	71	-13	3	5	174	-187
8	0	4	103	107	3	3	4	203	201	-12	6	4	78	-74	-11	1	5	104	107	-11	3	5	84	-79
10	0	4	181	-183	7	3	4	126	-119	-8	6	4	61	55	-9	1	5	205	217	-9	3	5	206	205
18	0	4	130	-121	11	3	4	131	137	2	6	4	105	-108	-5	1	5	79	-65	-7	3	5	131	-125
22	0	4	92	86	17	3	4	95	106	10	6	4	59	-56	-3	1	5	144	137	-5	3	5	212	-210
-21	1	4	110	105	21	3	4	53	-50	-25	7	4	39	-41	1	1	5	165	-165	-3	3	5	156	145
-15	1	4	64	-79	23	3	4	44	-42	-21	7	4	50	51	3	1	5	68	70	-1	3	5	126	119
-17	1	4	56	-54	-28	4	4	55	-56	-15	7	4	73	79	5	1	5	169	207	1	3	5	225	-206
-15	1	4	60	60	-22	4	4	82	-82	-11	7	4	71	-68	9	1	5	70	-81	5	3	5	218	213
-13	1	4	115	116	-20	4	4	52	-52	-9	7	4	61	59	15	1	5	105	-101	9	3	5	149	-155
-5	1	4	214	-195	-16	4	4	119	122	-7	7	4	75	70	19	1	5	54	50	13	3	5	92	95
-7	1	4	408	376	-14	4	4	137	-141	-1	7	4	139	129	-30	2	5	43	40	17	3	5	47	-43
-5	1	4	84	-89	-12	4	4	72	71	3	7	4	76	-74	-24	2	5	174	173	19	3	5	74	77
-3	1	4	182	-172	-10	4	4	55	57	7	7	4	77	79	-22	2	5	104	107	23	3	5	49	-44
-1	1	4	52	79	-8	4	4	178	-168	11	7	4	47	-45	-20	2	5	175	-186	-26	4	5	40	-38
1	1	4	307	287	-6	4	4	130	-124	13	7	4	59	60	-16	2	5	236	238	-24	4	5	46	-45
3	1	4	73	51	-4	4	4	232	218	-22	8	4	46	44	-14	2	5	89	-94	-20	4	5	55	-51
5	1	4	155	-152	-2	4	4	107	91	-18	8	4	60	-64	-12	2	5	217	-225	-12	4	5	90	-86
7	1	4	188	206	0	4	4	180	-172	-14	8	4	115	119	-10	2	5	318	310	-6	4	5	94	-91
11	1	4	117	-122	4	4	4	188	184	-12	8	4	53	-54	-8	2	5	311	293	6	4	5	67	-63
15	1	4	88	93	6	4	4	123	-125	-10	8	4	64	-60	-6	2	5	342	-322	8	4	5	84	-91
19	1	4	64	-68	8	4	4	122	-132	-8	8	4	80	76	-2	2	5	275	260	10	4	5	96	101
21	1	4	92	92	10	4	4	91	100	-6	8	4	124	-112	2	2	5	311	-301	22	4	5	48	-50
-24	2	4	54	-54	14	4	4	114	-124	0	8	4	128	120	4	2	5	185	196	-19	5	5	62	68

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 2KN5 L.S. REFINEMENT PAGE 4

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
-13	5	5	65	67	-12	C	6	183	-192	-15	3	6	171	-178	7	5	6	59	-59	-1	1	7	129	126
-11	5	5	58	-55	-10	C	6	208	-215	-11	3	6	243	234	21	5	6	46	-43	1	1	7	108	-105
-9	5	5	86	-83	-8	C	6	184	188	-7	3	6	179	-185	-6	6	6	52	46	5	1	7	112	121
-5	5	5	101	98	-2	C	6	78	-66	-5	3	6	85	82	-21	7	6	42	41	11	1	7	57	56
1	5	5	67	63	C	C	6	139	131	-3	3	6	237	218	-15	7	6	73	78	13	1	7	81	80
5	5	5	53	56	2	C	6	147	-151	-1	3	6	245	215	-11	7	6	81	75	15	1	7	49	-48
15	5	5	67	65	4	C	6	329	-332	3	3	6	196	198	-7	7	6	78	67	-30	2	7	45	50
-20	6	5	44	-42	8	C	6	83	-83	5	3	6	65	65	-5	7	6	65	59	-28	2	7	68	-72
-16	6	5	80	-88	14	C	6	86	87	7	3	6	112	-120	-3	7	6	75	-77	-26	2	7	118	-112
-14	6	5	77	74	16	C	6	72	-81	11	3	6	97	90	-1	7	6	100	93	-24	2	7	72	78
-12	6	5	102	93	18	C	6	116	-106	13	3	6	80	-79	7	7	6	89	98	-22	2	7	78	83
-7	6	5	66	60	-29	1	6	41	44	17	3	6	77	75	-22	8	6	49	51	-20	2	7	55	-63
-2	6	5	120	-109	-25	1	6	103	-101	19	3	6	42	36	-18	8	6	99	-102	-16	2	7	165	182
2	6	5	93	95	-23	1	6	61	61	-26	4	6	45	49	-14	8	6	77	80	-14	2	7	74	-77
10	6	5	51	58	-21	1	6	58	104	-22	4	6	91	-96	-10	8	6	58	-50	-12	2	7	239	-256
12	6	5	86	-96	-19	1	6	64	-65	-20	4	6	49	-52	-8	8	6	77	76	-10	2	7	210	229
-27	7	5	40	42	-13	1	6	75	76	-16	4	6	88	98	-4	8	6	137	-126	-8	2	7	138	144
21	7	5	45	42	-11	1	6	156	-171	-16	4	6	61	-57	0	8	6	101	55	-6	2	7	135	-135
-25	7	5	62	58	-9	1	6	81	90	-14	4	6	116	-120	4	8	6	53	-51	-2	2	7	267	270
-17	7	5	58	-62	-7	1	6	131	132	-12	4	6	90	88	6	8	6	59	60	2	2	7	235	-254
-15	7	5	60	-61	-3	1	6	71	-74	-10	4	6	94	91	14	8	6	49	51	4	2	7	162	184
-13	7	5	105	100	1	1	6	79	97	-8	4	6	183	-168	-17	9	6	47	-47	6	2	7	129	133
-5	7	5	128	120	3	1	6	61	-78	-6	4	6	88	-75	-15	9	6	39	30	8	2	7	110	-119
-3	7	5	89	-82	7	1	6	118	120	-4	4	6	107	104	-7	9	6	47	51	12	2	7	170	176
-1	7	5	103	-100	15	1	6	76	75	0	4	6	184	-178	-3	9	6	73	-69	16	2	7	121	-124
1	7	5	69	73	17	1	6	62	-60	2	4	6	94	107	-1	9	6	46	47	18	2	7	39	36
9	7	5	82	85	21	1	6	49	52	4	4	6	115	122	7	9	6	44	45	20	2	7	56	49
13	7	5	80	-82	-20	2	6	73	-73	6	4	6	78	-80	-27	1	7	84	-87	-29	3	7	55	45
-13	9	5	43	-46	-6	2	6	114	-112	10	4	6	116	122	-23	1	7	100	103	-27	3	7	56	-52
-6	10	5	46	-44	C	2	6	71	67	14	4	6	76	-80	-19	1	7	57	-58	-23	3	7	70	66
-2	10	5	50	51	4	2	6	84	-78	18	4	6	57	57	-17	1	7	76	78	-21	3	7	73	-78
-28	0	6	55	46	6	2	6	64	70	-19	5	6	53	58	-15	1	7	86	93	-19	3	7	79	-78
-24	0	6	53	-84	10	2	6	48	46	-17	5	6	97	104	-13	1	7	223	-215	-17	3	7	59	56
-22	0	6	75	76	-26	3	6	57	-56	-13	5	6	68	-70	-11	1	7	88	-95	-15	3	7	76	81
-20	0	6	66	63	-25	3	6	86	95	-3	5	6	95	86	-9	1	7	208	215	-13	3	7	175	-185
-14	0	6	104	105	-21	3	6	85	-87	5	5	6	64	-64	-7	1	7	138	151	-9	3	7	173	165

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H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
-7	3	7	126	-117	-9	7	7	63	-60	-2	2	8	94	-90	-11	5	8	75	76	-11	1	9	96	-97
-5	3	7	202	-195	-7	7	7	63	54	-2	2	8	60	-57	-7	5	8	86	-91	-9	1	9	62	65
-3	3	7	64	52	-5	7	7	155	147	4	2	8	62	62	-3	5	8	110	98	-7	1	9	57	-50
-1	3	7	208	197	5	7	7	57	-63	-29	3	8	45	48	3	5	8	78	83	-5	1	9	165	-165
1	3	7	199	-207	9	7	7	95	100	-19	3	8	84	91	7	5	8	48	-49	-3	1	9	91	98
3	3	7	59	-57	12	8	7	48	-36	-15	3	8	160	-165	0	6	8	54	54	-1	1	9	152	162
5	3	7	113	124	-7	9	7	60	-55	-11	3	8	63	59	-21	7	8	42	43	1	1	9	89	-85
9	3	7	78	-76	-6	10	7	47	-46	-7	3	8	130	-122	-19	7	8	41	-41	3	1	9	98	-95
13	3	7	77	79	-32	0	8	70	-59	-5	3	8	151	146	-17	7	8	46	-52	5	1	9	60	-56
15	3	7	65	-71	-28	0	8	120	111	-1	3	8	164	-151	-11	7	8	82	-81	13	1	9	70	64
19	3	7	59	47	-26	0	8	80	-80	1	3	8	88	-88	-7	7	8	84	75	-30	2	9	56	51
-18	4	7	106	-107	-22	0	8	96	93	3	3	8	120	121	-5	7	8	50	-39	-28	2	9	46	-46
-14	4	7	94	96	-18	0	8	134	-129	7	3	8	90	-83	-3	7	8	79	-73	-26	2	9	56	-51
-12	4	7	68	-71	-14	0	8	356	338	11	3	8	44	44	3	7	8	56	-63	-20	2	9	123	-126
-4	4	7	127	-126	-10	0	8	69	-70	13	3	8	93	-94	13	7	8	38	24	-16	2	9	145	154
0	4	7	56	55	-8	0	8	66	76	15	3	8	59	-52	-22	8	8	44	49	-14	2	9	62	-61
10	4	7	63	-64	0	0	8	352	352	-28	4	8	42	-39	-18	8	8	50	-54	-12	2	9	98	-108
-27	5	7	41	36	12	0	8	55	-41	-24	4	8	51	51	-12	8	8	55	-50	-10	2	9	81	85
-19	5	7	53	53	14	0	8	113	106	-22	4	8	75	-80	-10	8	8	56	-60	-6	2	9	182	-189
-13	5	7	80	78	-33	1	8	34	-24	-18	4	8	110	116	-8	8	8	91	89	-2	2	9	204	214
-5	5	7	61	-55	-29	1	8	51	57	-16	4	8	57	-54	-4	8	8	86	-79	2	2	9	93	-97
-5	5	7	71	61	-25	1	8	64	-59	-14	4	8	109	-113	0	8	8	53	56	6	2	9	74	69
-3	5	7	93	-91	-19	1	8	76	-77	-12	4	8	55	59	4	8	8	57	-59	8	2	9	91	-87
-1	5	7	51	52	-15	1	8	146	147	-10	4	8	126	124	6	8	8	61	59	12	2	9	114	111
9	5	7	55	57	-11	1	8	129	-133	-8	4	8	132	-129	8	8	8	37	35	16	2	9	51	-55
-11	5	7	54	-54	-9	1	8	93	94	-4	4	8	140	131	10	8	8	47	-50	-27	3	9	40	-43
-24	6	7	46	-45	-5	1	8	110	-115	-2	4	8	63	-56	-7	9	8	61	56	-23	3	9	95	91
-20	6	7	85	93	-3	1	8	85	-79	0	4	8	129	-125	-3	9	8	42	-40	-19	3	9	98	-100
-16	6	7	104	-108	-1	1	8	171	174	4	4	8	77	62	3	9	8	34	-33	-15	3	9	65	57
-12	6	7	71	67	3	1	8	183	-187	6	4	8	66	-68	-31	1	9	54	51	-13	3	9	69	-72
-6	6	7	129	121	7	1	8	59	64	10	4	8	98	106	-27	1	9	69	-68	-9	3	9	96	104
-2	6	7	104	-99	17	1	8	49	-51	18	4	8	41	44	-23	1	9	56	55	-7	3	9	52	-47
2	6	7	60	61	-24	2	8	68	66	-25	5	8	59	60	-19	1	9	104	-108	-5	3	9	122	-115
8	6	7	54	53	-20	2	8	50	-48	-21	5	8	78	-82	-17	1	9	103	103	-1	3	9	68	69
-25	7	7	40	-33	-12	2	8	55	-96	-19	5	8	50	49	-15	1	9	63	64	1	3	9	92	-96
-19	7	7	63	67	-10	2	8	78	77	-17	5	8	100	107	-13	1	9	140	-140	5	3	9	71	78

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H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
5	3	9	73	-81	-5	7	9	100	-105	-20	2	10	53	52	-1	5	10	49	-62	5	3	11	53	48
13	3	9	42	46	5	7	9	73	-82	2	2	10	71	70	3	5	10	96	95	9	3	11	44	-42
15	3	9	53	-52	-9	9	9	35	36	2	2	10	89	-86	5	5	10	55	56	-16	4	11	67	64
19	3	9	34	27	1	9	9	40	35	-23	3	10	48	-46	-11	7	10	52	-53	-12	4	11	53	-55
-22	4	9	68	70	-32	0	10	95	-81	-19	3	10	59	57	3	7	10	56	-60	-8	4	11	94	95
-18	4	9	76	-79	-30	0	10	64	46	-17	3	10	60	60	0	8	10	44	46	-4	4	11	57	-50
-8	4	9	102	101	-26	0	10	74	74	-9	3	10	85	-87	4	8	10	44	-42	-23	5	11	50	-55
-4	4	9	96	-95	-26	0	10	93	-89	-5	3	10	69	75	-31	1	11	42	-44	-21	5	11	55	56
6	4	9	71	76	-22	0	10	137	128	-1	3	10	50	-47	-27	1	11	48	-46	-17	5	11	81	-83
-10	4	9	77	-83	-18	0	10	239	-227	3	3	10	50	49	-23	1	11	61	56	-15	5	11	53	-55
-27	5	9	43	37	-14	0	10	203	192	5	3	10	76	-78	-21	1	11	66	-70	-13	5	11	63	64
-25	5	9	41	-39	-12	0	10	119	-122	7	3	10	44	-47	-19	1	11	82	-79	-9	5	11	83	-83
-21	5	9	48	48	-8	0	10	202	197	9	3	10	61	63	-17	1	11	97	99	-7	5	11	69	75
-17	5	9	76	-79	-6	0	10	116	115	11	3	10	45	42	-13	1	11	71	-81	-5	5	11	58	59
-13	5	9	67	78	-4	0	10	262	-261	-32	4	10	43	47	-9	1	11	87	95	-1	5	11	45	-51
-9	5	9	58	-61	0	0	10	157	154	-28	4	10	46	42	-7	1	11	78	-89	1	5	11	51	46
-7	5	9	101	102	6	0	10	136	136	-26	4	10	44	42	-5	1	11	141	-158	-24	6	11	62	-67
-3	5	9	75	-96	8	0	10	123	123	-24	4	10	45	41	-1	1	11	64	66	-20	6	11	60	62
1	5	9	49	49	10	0	10	107	-103	-22	4	10	58	-62	1	1	11	60	-59	-16	6	11	78	-79
5	5	9	58	-59	14	0	10	66	59	-18	4	10	104	99	5	1	11	60	64	-14	6	11	59	57
-26	6	9	39	42	-33	1	10	38	-35	-14	4	10	91	-98	9	1	11	107	-98	-12	6	11	78	85
-24	6	9	59	-68	-29	1	10	56	51	-12	4	10	77	73	-34	2	11	44	-49	-10	6	11	90	-85
-22	6	9	45	-44	-21	1	10	51	54	-10	4	10	76	80	-30	2	11	51	54	-8	6	11	46	47
-20	6	9	81	85	-19	1	10	93	-93	-8	4	10	88	-89	-24	2	11	46	46	-2	6	11	85	-81
-16	6	9	66	-72	-17	1	10	71	-63	-4	4	10	146	146	-20	2	11	107	-114	2	6	11	74	75
-12	6	9	66	69	-15	1	10	128	132	0	4	10	74	-69	-18	2	11	42	-39	4	6	11	59	-56
-10	6	9	124	-122	-11	1	10	67	-71	4	4	10	80	75	-16	2	11	55	65	6	6	11	39	-35
-8	6	9	73	-77	-7	1	10	88	97	6	4	10	96	-102	-6	2	11	147	-156	8	6	11	37	31
-6	6	9	104	104	-5	1	10	89	-99	10	4	10	46	51	-2	2	11	69	77	-3	7	11	52	-53
-2	6	9	81	-77	-3	1	10	72	-80	14	4	10	42	-39	0	2	11	41	-42	1	7	11	46	50
2	6	9	57	64	-1	1	10	117	127	-29	5	10	42	-44	6	2	11	50	48	5	7	11	36	-30
4	6	9	58	-66	3	1	10	74	-76	-25	5	10	56	60	8	2	11	77	-74	-4	8	11	29	37
6	6	9	50	-58	7	1	10	54	49	-21	5	10	52	-62	-17	3	11	62	66	-32	0	12	55	-53
8	6	9	69	69	9	1	10	77	-77	-15	5	10	120	-123	-3	3	11	74	72	-26	0	12	81	-73
-23	7	9	64	-65	11	1	10	47	-49	-11	5	10	142	155	1	3	11	44	-44	-22	0	12	146	126
-15	7	9	39	35	12	1	10	55	55	-7	5	10	109	-112	3	3	11	42	-41	-18	0	12	150	-142

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 2KNS L.S. REFINEMENT PAGE 7

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
-14	0	12	61	59	6	4	12	64	-55	-27	3	13	42	-40	-7	1	14	58	68	-24	2	15	56	58
-12	0	12	161	-156	-29	5	12	49	-51	-23	3	13	41	34	1	1	14	44	43	-16	2	15	69	76
-10	0	12	121	-109	-25	5	12	52	51	-13	3	13	66	-65	3	1	14	66	-65	-14	2	15	46	-44
-8	0	12	210	198	-21	5	12	58	-54	-9	3	13	73	72	7	1	14	55	55	-12	2	15	60	-61
-4	0	12	197	-180	-15	5	12	85	-81	-5	3	13	39	-39	-16	2	14	46	-40	-10	2	15	67	72
0	0	12	61	54	-13	5	12	58	-59	-1	3	13	41	37	-14	2	14	49	-47	-2	2	15	72	76
2	0	12	122	-123	-11	5	12	49	54	7	3	13	36	-19	-25	3	14	54	53	2	2	15	45	-50
4	0	12	110	-105	-9	5	12	46	-45	-17	5	13	51	-44	-21	3	14	49	-44	-27	3	15	47	-41
6	0	12	116	112	-5	5	12	44	44	-9	5	13	60	-62	-15	3	14	53	-51	-25	3	15	36	19
8	0	12	72	74	-1	5	12	90	-92	-5	5	13	56	50	-11	3	14	61	55	-21	3	15	42	-43
10	0	12	75	-64	1	5	12	30	-47	-3	5	13	33	-47	-1	3	14	49	-51	-19	3	15	56	-53
-25	1	12	51	-54	3	5	12	55	51	1	5	13	61	58	-26	4	14	48	46	-13	3	15	52	-56
-21	1	12	85	96	7	5	12	41	-41	5	5	13	40	-43	-22	4	14	64	-64	-9	3	15	41	40
-19	1	12	70	-79	-10	6	12	51	35	-16	6	13	63	-58	-18	4	14	68	72	-5	3	15	45	-38
-11	1	12	68	-78	-1	7	12	60	58	-14	6	13	71	67	-16	4	14	42	-40	1	3	15	45	-38
-7	1	12	108	112	-14	8	12	45	45	-12	6	13	47	51	-14	4	14	60	-58	-13	5	15	41	43
-5	1	12	72	-72	0	8	12	38	36	-10	6	13	43	-49	-12	4	14	55	50	1	5	15	39	30
-3	1	12	54	-51	-23	1	13	47	47	-6	6	13	67	65	-8	4	14	67	-72	-20	6	15	45	-43
7	1	12	58	61	-21	1	13	56	-59	-2	6	13	71	-79	-4	4	14	52	49	-16	6	15	48	-41
9	1	12	53	-55	-13	1	13	60	-67	0	6	13	33	31	0	4	14	56	-59	-6	6	15	55	55
-31	3	12	37	24	-11	1	13	65	74	2	6	13	47	51	2	4	14	50	46	-2	6	15	36	-33
-25	3	12	40	32	-9	1	13	92	99	-1	7	13	38	-44	4	4	14	40	35	0	0	16	46	45
-11	3	12	110	108	-3	1	13	50	54	-26	0	14	69	-61	-19	5	14	45	42	-25	1	16	41	-35
-7	3	12	51	-46	1	1	13	85	-88	-22	0	14	79	69	-17	5	14	40	35	-15	1	16	72	-66
-3	3	12	55	58	5	1	13	85	92	-16	0	14	66	51	-7	5	14	57	-43	-11	1	16	44	-53
-28	4	12	43	-39	9	1	13	42	-37	-12	0	14	118	-103	-1	5	14	34	-37	-7	1	16	48	-44
-26	4	12	51	57	-28	2	13	33	-32	-10	0	14	95	-96	-14	6	14	37	-34	3	1	16	42	-34
-24	4	12	27	28	-24	2	13	91	96	-8	0	14	54	93	-15	7	14	35	31	-16	2	16	38	-29
-22	4	12	76	-79	-22	2	13	61	58	-4	0	14	77	-66	-9	7	14	31	24	-25	3	16	38	42
-18	4	12	79	84	-20	2	13	63	-64	0	0	14	102	92	-27	1	15	42	-37	-19	3	16	48	-46
-14	4	12	62	-64	-12	2	13	79	-83	2	0	14	80	-66	-13	1	15	53	-63	-15	3	16	65	-67
-12	4	12	71	-76	-10	2	13	57	61	4	0	14	111	-101	-3	1	15	49	-42	-7	3	16	42	-41
-8	4	12	87	-100	-8	2	13	60	66	-25	1	14	57	-62	1	1	15	41	-37	-5	3	16	47	44
-4	4	12	59	58	0	2	13	34	-31	-21	1	14	57	62	-30	2	15	37	-32	-1	3	16	34	-26
0	4	12	52	-59	2	2	13	53	-50	-13	1	14	44	36	-28	2	15	52	-51	-26	4	16	36	28
2	4	12	49	49	4	2	13	60	56	-11	1	14	77	-81	-26	2	15	39	-35	-22	4	16	50	-45

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 2KNS L.S. REFINEMENT PAGE 8

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
-18	4	16	43	44	0	4	16	36	-39	-20	2	17	57	-63	-2	2	17	48	56	-17	5	17	36	-29
-16	4	16	40	-35	-21	5	16	36	-27	-16	2	17	74	-76	-13	3	17	44	-48	-22	0	18	51	34
-14	4	16	37	-41	-17	1	17	43	40	-6	2	17	39	-51	-3	3	17	36	31	-14	0	18	52	45
-8	4	16	40	-43	-13	1	17	38	-38															

Appendix IV

Final Thermal Parameters ($\times 10^4$) with esds in parentheses.

$Pd(pmzH)Cl_3$

(i) Anisotropic thermal parameters ($\times 10^4$) of the form:-

$$\exp\{-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)\}$$

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pd	357(3)	358(3)	356(3)	-46(3)	106(2)	-28(3)
Cl(1)	590(13)	631(20)	557(13)	-245(13)	94(11)	110(12)
Cl(2)	811(17)	431(18)	729(16)	-92(14)	48(13)	111(13)
Cl(3)	568(12)	856(22)	431(11)	-339(13)	32(10)	-46(12)
S(5)	308(9)	461(14)	427(11)	18(9)	97(8)	-45(10)
C(1)	491(50)	589(70)	360(42)	44(48)	40(38)	-33(45)
C(2)	748(73)	658(92)	518(57)	126(67)	-98(53)	172(58)
C(3)	661(65)	580(87)	631(65)	220(60)	-102(51)	24(61)
C(4)	438(51)	717(94)	682(65)	240(55)	-16(47)	-20(63)
C(6)	517(52)	589(80)	445(48)	-172(50)	157(40)	-58(47)
C(7)	663(57)	450(107)	693(60)	-155(56)	68(49)	68(54)
C(8)	734(60)	310(86)	737(62)	98(57)	135(50)	-27(56)
C(9)	511(53)	420(70)	550(53)	151(47)	-16(43)	-55(49)
C(11)	360(32)	428(57)	335(33)	-4(55)	-29(26)	-10(52)
C(12)	433(38)	447(84)	366(37)	27(45)	14(30)	-7(43)
C(13)	318(38)	518(68)	429(43)	-16(40)	70(33)	27(42)
C(14)	327(37)	322(54)	398(41)	34(35)	73(32)	42(35)
N(10)	290(32)	377(49)	446(37)	52(50)	135(28)	40(32)

Pd(pmzH)Cl_3 cont.

C(15)	359(42)	549(72)	621(55)	-17(43)	200(40)	66(48)
N(17)	326(33)	478(67)	804(54)	35(32)	-25(34)	11(41)
C(20)	464(58)	2367(262)	984(94)	-309(96)	426(65)	-440(123)

(ii) Isotropic temperature factors (x 10^3, $Å^2$) of the form:- $\exp(-U \sin\theta^2/\lambda^2)$

	U		U		U
C(16A)	45(4)	C(18A)	61(6)	C(19A)	72(7)
C(16B)	40(3)	C(18B)	93(9)	C(19B)	112(11)

Pd(cpzH)Cl_3

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pd	499(6)	540(7)	538(6)	000(7)	225(4)	125(7)
Cl(1)	771(28)	520(29)	982(29)	982(34)	27(22)	268(26)
Cl(2)	772(29)	1061(45)	617(26)	79(26)	306(23)	97(23)
Cl(3)	688(26)	682(42)	677(26)	85(26)	143(22)	252(26)
Cl(4)	977(41)	718(43)	1196(48)	266(33)	330(36)	10(35)
S(5)	458(20)	559(28)	581(24)	-40(18)	199(18)	-47(18)
C(1)	487(76)	576(123)	361(68)	-172(83)	54(58)	-14(72)
C(2)	578(90)	585(131)	521(85)	-7(96)	9(72)	-198(93)
C(3)	453(85)	725(148)	416(78)	107(84)	41(68)	52(76)
C(4)	509(79)	704(127)	460(74)	76(101)	179(62)	-44(93)

$Pd(cpzH)Cl_3$ cont.

C(6)	662(108)	641(160)	688(116)	99(87)	211(92)	-19(91)
C(7)	528(104)	1147(259)	760(131)	138(121)	96(97)	-299(131)
C(8)	577(111)	1249(220)	441(96)	147(122)	224(85)	-37(109)
C(9)	429(86)	899(163)	541(98)	216(88)	149(75)	201(90)
N(10)	432(65)	577(97)	606(76)	38(61)	222(59)	102(67)
C(11)	549(91)	358(103)	403(73)	6(70)	16(68)	98(63)
C(12)	664(88)	332(100)	264(58)	-20(69)	125(58)	-45(58)
C(13)	451(82)	604(125)	517(90)	138(82)	188(72)	23(81)
C(14)	391(77)	523(108)	530(93)	19(74)	66(71)	-71(74)
C(15)	325(72)	684(132)	847(116)	-139(75)	74(76)	152(93)
C(16)	473(85)	582(142)	1047(145)	-103(77)	12(89)	-73(98)
C(17)	624(95)	571(125)	741(103)	162(83)	217(83)	251(91)
N(18)	1257(160)	899(167)	874(127)	267(126)	-323(119)	-438(115)
C(19)	1026(133)	754(153)	650(100)	77(125)	316(97)	338(109)
C(20)	1924(248)	1099(215)	758(128)	268(209)	769(155)	-243(150)

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Details of postgraduate study

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b) attended a course of lectures on Computer Programming at Sheffield City Polytechnic,

c) participated in departmental research colloquia, and presented a colloquium of his own work,

d) attended the 1981 meeting of the Dalton division on Platinum Group Metals at Bristol University,

Co-ordination of Promethazine {10-[2-(Dimethyl(amino)propyl]phenothiazine} Hydrochloride with Palladium(II): *X*-Ray Crystal Structure of a Trichloro-palladium(II) product

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Co-ordination of Promethazine {10-[2-(Dimethyl(amino)propyl]phenothiazine} Hydrochloride with Palladium(II): *X*-Ray Crystal Structure of a Trichloro-palladium(II) product

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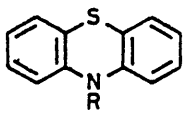
ummary Potassium tetrachloropalladate reacts with promethazine hydrochloride to give a unique complex in which the protonated promethazine is sulphur-bonded to palladium and takes up a 'scorpion' conformation, thereby facilitating electrostatic interaction between the quaternary nitrogen on the side chain and the $PdCl_3$ unit.

DRUGS based on the phenothiazine heterocycle (**1**) are well established as anti-histamines and anti-psychotics. Their interactions with metal systems both *in vivo* and *in vitro* have been extensively studied.[1] While far-i.r. spectral evidence confirms that phenothiazine (**1**) co-ordinates *via* the



(**1**) R = H
(**2**) R = $CH_2CH(Me)N^+HMe_2\ Cl^-$
(**3**) R = $CH_2[CH_2]_2N^+HMe_2\ Cl^-$

ring sulphur[2] to divalent platinum and palladium, crystallographic studies to date are limited to structures in which phenothiazine and related drugs are unco-ordinated.[3] We now report the structure of a unique palladium complex: the first crystallographic evidence for a co-ordinated phenothiazine drug.

Potassium tetrachloropalladate and promethazine {10-[2-(dimethylamino)propyl]phenothiazine} hydrochloride (**2**) (1:1 molar ratio in aqueous solution) form a palladium

$$K_2PdCl_4 + PMZ.HCl \rightarrow Pd(PMZ\ H)Cl_3 + 2\ KCl \qquad (1)$$

complex [equation (1)] which has a low conductivity in nitromethane ($2{\cdot}12 \times 10^{-3}$ S m^{-2} mol^{-1}) and the band attributed to N^+–H s,[4] at 2550 cm^{-1} in the i.r. spectrum of PMZ.HCl, is shifted to a higher frequency upon complexation.

Crystal data: The complex $C_{17}H_{21}Cl_3N_2PdS$ crystallises from dimethylformamide as dark red crystals which are monoclinic with $a = 11{\cdot}381(5)$, $b = 9{\cdot}791(4)$, $c = 9{\cdot}098(4)$ Å, $\beta = 100{\cdot}84(5)°$, space group $P2_1$, $Z = 2$, $R = 0{\cdot}036$ for 1524 independent reflections having $I/\sigma(I) > 3{\cdot}0$.†

The complex is best considered as a zwitterion with the nitrogen in the side chain being protonated and the ring sulphur co-ordinated to $PdCl_3^-$. The $PdCl_3S$ unit is almost planar and the promethazine ring-system is orientated such that the outer C_6 rings are at dihedral angles of 78 and 94° to the $PdCl_3S$ mean-plane. In contrast to the uncomplexed ligand,[3b] the side chain in the present complex is bent back over the heterocycle in a unique 'scorpion' conformation,

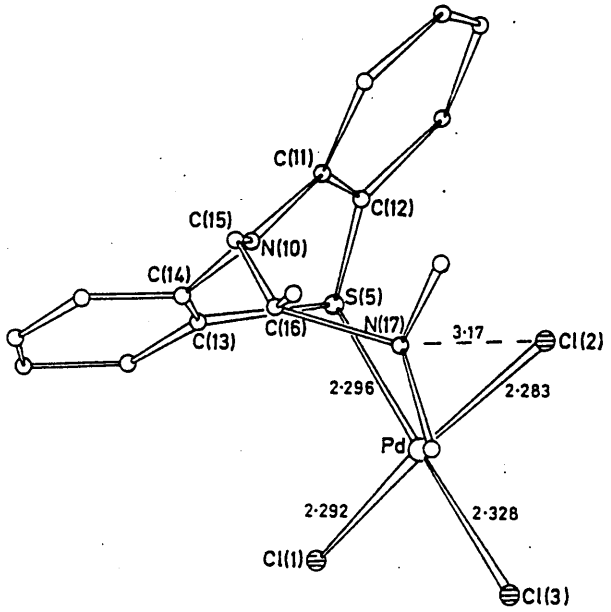


FIGURE. Molecular structure of $Pd(PMZ\ H)Cl_3$. Angles around the palladium range from 86·4 to 92·2°. The three carbon atoms attached to the quaternary nitrogen are disordered and, for clarity, only one set is shown. Bond lengths are in Å.

thereby facilitating electrostatic interaction between the quaternary nitrogen and one of the chlorine atoms. While the resulting N–Cl bond distance of 3·17 Å is very long and can only represent a weak interaction, the arrangement of carbon atoms about the nitrogen indicates that the N–H proton is directed toward Cl(2), hence facilitating hydrogen bonding.

Preliminary studies indicate that the analogous platinum complex has a similar structure and that other phenothiazine drugs, *e.g.* promazine (**3**), adopt the same 'scorpion' conformation with divalent palladium and platinum.

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† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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Interactions between Phenothiazine Drugs and Metal Ions. Part 1. Palladium(II) and Platinum(II) Complexes. Crystal and Molecular Structure of Protonated Trichloro[10-(2'-dimethylaminopropyl)phenothiazine-*S*]palladium(II)

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Phenothiazine drugs form complexes with Pd^{II} and Pt^{II} of unusual stoicheiometry, *i.e.* $[MLX_3]$ (L = protonated drug; X = Cl or Br; M = Pd or Pt). The structure of the promethazine complex with Pd^{II} has been elucidated by single-crystal *X*-ray crystallography. Crystals are monoclinic, space group $P2_1$, $Z = 2$, in a unit cell with lattice parameters $a = 11.381(5)$, $b = 9.791(4)$, $c = 9.098(4)$ Å, $\beta = 100.85(5)°$. The structure has been solved using heavy-atom methods and refined by least squares to R 0.036 (R' 0.039) for 1 524 independent reflections collected by counter methods. The drug is sulphur-bonded to a $PdCl_3^-$ unit, the counter ion being a protonated nitrogen on the drug substituent. The side chain adopts an unusual conformation bending back over the heterocycle in order to facilitate intramolecular hydrogen bonding between the protonated nitrogen and one of the chlorine atoms on the palladium. Proton n.m.r. and solution i.r. data support the existence of this hydrogen bonding in solution. Electronic spectral data both from this work and the literature show that the interaction observed for the above complex is seen for all phenothiazine drugs so far examined. Far-i.r. data confirm the similarity of the equivalent platinum(II) compounds.

PHENOTHIAZINE drugs are versatile anticholinergic [1] and antihistamine compounds. Metal-ion interactions with the drugs and with the parent heterocycle have been extensively studied both *in vivo* [2] and *in vitro*.[3] However, few genuine co-ordination complexes have been isolated. Those reported have been poorly characterised [4] or assigned erroneous structures.[5]

The interactions usually observed between metal ions and drugs of this type involve oxidation of the drug molecule *via* a free-radical mechanism,[6] or salt formation involving protonation of the phenothiazine drug.[7]

As part [8] of a study of phenothiazine–metal ion interactions we present here the results of an investigation with bivalent palladium and platinum and a variety of typical phenothiazine drugs. The structures of these complexes are useful in rationalizing the solution chemistry and spectra of these interactions, both those reported here and in the literature.

RESULTS AND DISCUSSION

On the basis of the data presented here the complexes fall into two categories, the parent heterocycle and related ligands leading to complexes $[ML_2X_2]$ whereas those ligands showing drug activity [and having a quaternary nitrogen on the N(10) side chain] lead to complexes $[MLX_3]$. The latter complexes have a novel structure in which the side chain plays an important part. Details of the complexes are given in Table 1.

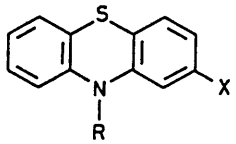
Complexes of 2 : 1 Stoicheiometry.—The reaction scheme for these complexes is as in equation (1) where

$$K_2[MX_4] + 2L \longrightarrow [ML_2X_2] + 2KX \qquad (1)$$

M = Pd, L = ptz, eptz, or dptz, X = Cl; M = Pt, L = ptz, X = Cl or Br.

From previous work [9] it seemed likely that the heterocyclic sulphur was solely involved in co-ordination and to maximise the overlap of metal *d* orbitals with those on the sulphur a *cis* configuration would be expected, giving rise to two M–S stretching modes and two M–X stretching modes in the far-i.r. spectra of these complexes. In the spectrum of $[Pt(ptz)_2Br_2]$ there are two strong bands (Pt–Br str.) at 220 and 250 cm^{-1}, and two slightly weaker bands (Pt–S str.) at 305 and 315 cm^{-1}, thus confirming the complex is of *cis* configuration with the heterocycle *S*-bonded to the platinum. The far-i.r. spectra of $[Pt(ptz)_2Cl_2]$ and $[Pd(ptz)_2Cl_2]$ are complicated by the overlap of the metal–halogen and metal–sulphur bands, showing bands at 303 and 327 cm^{-1} in the case of the platinum complex and at 288 and 322 cm^{-1} in the case of the palladium complex.

The proton n.m.r. spectrum of phenothiazine shows only two bands, a multiplet around δ 7—8 attributed to



Ligand and abbreviation		R	X
Phenothiazine	ptz	H	H
N-Ethylphenothiazine	eptz	CH_2CH_3	H
N-Dimethylcarbamoylphenothiazine	dptz	$CONMe_2$	H
Promethazine hydrochloride	pmzH·Cl	$CH_2CH(Me)NHMe_2^+ Cl^-$	H
Chlorpromazine hydrochloride	cpzH·Cl	$CH_2CH_2CH_2NHMe_2^+ Cl^-$	Cl
Thioridazine hydrochloride	tdzH·Cl	$CH_2CH_2CH(CH_2)_4NHMe^+ Cl^-$	SCH_3

TABLE 1

Physical data for the complexes

Complex	M.p. (θ_c/°C) [a]	$\lambda_{max.}$/nm	Formula	Elemental analysis (%) [b] C	H	N
$[Pd(ptz)_2Cl_2]$	280—290	515	$C_{24}H_{18}Cl_2N_2PdS_2$	49.8 (50.05)	3.25 (3.15)	4.90 (4.85)
$[Pd(eptz)_2Cl_2]$	260—270	500	$C_{28}H_{26}Cl_2N_2PdS_2$	52.6 (53.2)	4.05 (4.15)	4.30 (4.45)
$[Pd(dptz)_2Cl_2]$	265—270	510	$C_{30}H_{28}Cl_2N_4O_2PdS_2$	50.2 (50.2)	4.05 (3.95)	7.75 (7.80)
$[Pd(cpzH)Cl_3]$	250—260	432	$C_{17}H_{20}Cl_4N_2PdS$	38.25 (38.35)	3.75 (3.80)	5.20 (5.25)
$[Pd(pmzH)Cl_3]$	260—270	434	$C_{17}H_{21}Cl_3N_2PdS$	40.7 (41.0)	4.10 (4.25)	5.55 (5.60)
$[Pd(tdzH)Cl_3]$	250—260	435	$C_{21}H_{27}Cl_3N_2PdS_2$	43.2 (43.15)	4.80 (4.65)	4.70 (4.80)
$[Pt(ptz)_2Cl_2]$	280—290	430	$C_{24}H_{18}Cl_2N_2PtS_2$	42.45 (43.4)	2.80 (2.75)	3.80 (4.20)
$[Pt(cpzH)Cl_3]$	300—310	*c*	$C_{17}H_{20}Cl_4N_2PtS$	32.8 (32.85)	3.45 (3.25)	4.40 (4.50)
$[Pt(pmzH)Cl_3]$	290—300	*c*	$C_{17}H_{21}Cl_3N_2PtS$	34.75 (34.8)	3.80 (3.60)	4.55 (4.75)
$[Pt(tdzH)Cl_3]$	300—310	*c*	$C_{21}H_{27}Cl_3N_2PtS_2$	37.25 (37.5)	3.75 (4.05)	4.15 (4.15)

[a] All compounds decomposed before melting. [b] Calculated values are given in parentheses. [c] It was not possible to measure the visible spectra accurately due to overlap of the u.v. band for the heterocycle.

the aromatic protons and a singlet at δ 8.5 attributed to the secondary amine proton. The chemical shift of these signals in $[^2H_6]$dmso (dmso = dimethyl sulphoxide) is not significantly altered upon co-ordination: this aspect is receiving more detailed study but preliminary evidence suggests decomposition of the complexes in $[^2H_6]$dmso. The N–H stretching band in the i.r. is shifted from 3 350 to 3 310 cm^{-1} upon complexation. This small shift is presumably due to the change in available intermolecular N–H · · · S hydrogen bonding upon complex formation. The other ligands (dptz and eptz) form complexes of the same colour and stoicheiometry as those found for phenothiazine itself and from the similarity of the visible spectra it seems reasonable to assign a *cis* square-planar structure to these also.

Complexes of 1 : 1 *Stoicheiometry*.—The reaction scheme for these complexes is as in equation (2) where M = Pd,

$$K_2[MX_4] + LH{\cdot}Cl \longrightarrow [M(LH)X_3] + KCl + KX \quad (2)$$

L = pmz, cpz, or tdz, X = Cl or Br; M = Pt, L = pmz, cpz, or tdz, X = Cl.

The drugs were used as their hydrochloride salts, the site of protonation being the exocyclic nitrogen. Upon complexation the drug remains protonated, the counter ion being the MX_3^- system. The far-i.r. spectra of the complexes are summarised in Table 2. The system

TABLE 2

Infrared absorption bands * (250—400 cm^{-1}) of solid dispersions in polyethylene

MX_3 M	MX_3 X	Metal–ligand stretch	MX_2 asym. str. B_1	MX_2 sym. str. A_1	MX (*trans* to L) str. *A*
Pd	Cl	324(3)	348(10)	297 (sh)	308(9)
Pd	Br	324(4)	263 (sh)	253(8)	230(10)
Pt	Cl		327(10)	258 (sh)	317(10)
Pt	Br		263 (sh)	256(7)	230(10)

* Relative intensities are given in parentheses.

MX_3^- has been investigated before [10] and the assignments used in Table 2 are based on this previous work. In the case of the MCl_3^- systems (M = Pd or Pt) it was not possible to assign the metal–ligand stretch because of the overlap of the M–Cl and M–S bands. The spectra are not significantly affected by the different N(10) and 2-position substituents.

The complexes were found to be soluble in dimethyl formamide (dmf) and dmso. The ^1H n.m.r. spectra of the complexes (recorded in $[^2H_6]$dmso at 220 MHz) were identical to those of the parent drug except that the methyl groups of the quaternary nitrogen were shifted downfield by *ca.* 0.1 p.p.m. The magnitude of this shift can be attributed to decomposition of the complex in dmso, and indeed preliminary studies in $[^2H_7]$dmf indicate significant shifts upon complexation of the type expected if the quaternary nitrogen was interacting with the MX_3^- system.

The interaction most likely to take place between the quaternary nitrogen and the metal halide anion is one of hydrogen bonding. This can be observed in the i.r. spectra of both the complexes and the drugs. In the drugs the $\overset{+}{N}$–H · · · Cl interaction is observed as a broad strong band at 2 500—2 800 cm^{-1} [11] when measured both as a solid dispersion in KBr discs and as a solution in dmf or dmso. Upon complexation the intensity of this band diminishes and moves to 2 800—3 200 cm^{-1} indicating a slight weakening in the hydrogen bonding. No other changes of significance in the i.r. region are seen upon complexation.

The visible spectra of the complexes consist of a single strong band ($\varepsilon < 3\,000$ dm^3 mol^{-1} cm^{-1}) the positions of

TABLE 3

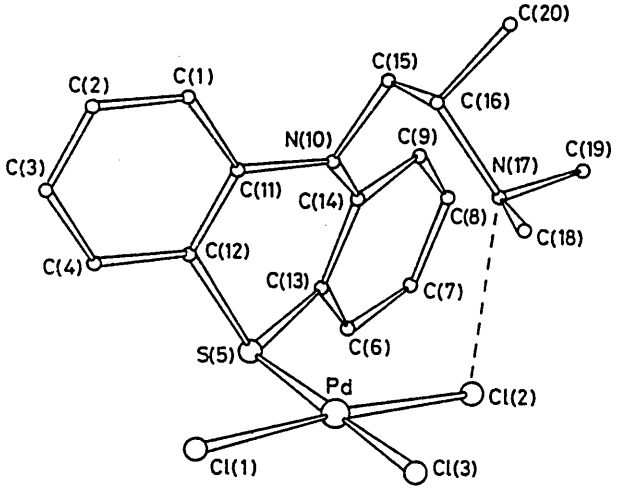
Visible spectral data for phenothiazine derivatives with M = Pd^{II} in aqueous solution from the literature

Ligand	L : M ratio	$\lambda_{max.}$/nm	Ref.
ptz	2 : 1	600	*a*
ptz	2 : 1	550	*b*
pmzH·Cl	1 : 1	495	9, *c*, *d*
cpzH·Cl	1 : 1	495	*c*, *e*
tdzH·Cl	1 : 1	490	*f*

[a] H. S. Gowda and B. Keshavan, *Mikrochim. Acta*, 1975, 437. [b] L. G. Overholser and J. H. Yoe, *Ind. Eng. Chem. Anal. Ed.*, 1942, **14**, 647. [c] L. Cavatorta, *J. Pharmacol.*, 1959, **11**, 49. [d] H. S. Gowda and B. Keshavan, *Indian J. Chem., Sect. A*, 1976, **14**, 293. [e] A. Farago, *Arch. Kriminol.*, 1967, **139**, 161; H. S. Gowda and B. Keshavan, *Fresenius' Z. Anal. Chem.*, 1975, **273**, 31; Kum-Tatt Lee and Ai-Mee Seet, *Mikrochim. Acta*, 1974, 955; J. A. Munoz Leyva and D. P. Bendito, *Quim. Anal.*, 1976, **30**, 76; M. Tarasiewicz, *Zesz. Nauk. Politech. Bialostockiej. (Ser) Nat. Fiz. Chem.*, 1976, **2**, 111. [f] H. S. Gowda, P. G. Ramappa, and B. N. Achar, *Fresenius' Z. Anal. Chem.*, 1975, **275**, 127.

which are listed in Table 1. These spectra fall into two distinct classes, the 2 : 1 non-drug complexes absorbing at 550 nm and the 1 : 1 drug complexes absorbing at 480 nm. This distinction is also noted in Table 3 which lists the relevant data from the literature. The values given in Table 3 differ from the values in Table 1, presumably because the latter were obtained as dmf solutions whilst the former were obtained in aqueous or aqueous ethanolic solutions. However, the distinction between the two classes is observed in both Tables. Thus the drugs, including types not investigated in this work,[5] all absorb, upon complexation, at the same wavelength and are all complexed with Pd^{II} in the same way.

Crystal Structure of [Pd(pmzH)Cl_3].—The protonated promethazine ligand is found to be sulphur-co-ordinated to $PdCl_3$ (Figure), such that the resulting $PdCl_3S$ unit is



Molecular structure of [Pd(pmzH)Cl_3]. For clarity all hydrogen atoms have been omitted and only one set of the disordered carbon atoms attached to N(17) is included

effectively planar and angles around Pd range from 86.4 to 92.2°. The promethazine ring system is both ' tilted ' and ' twisted ' with respect to the $PdCl_3S$ plane, with the Pd–S(5)–N(10) bond angle and the N(10)–S(5)–Pd–Cl(2) torsion angle being 90.1 and 68.5° respectively. The geometry within the fused ring system is similar to that in promethazine itself,[12] with the C_6 rings being planar and inclined at an angle of 41.3° to each other. However, 'n contrast to the uncomplexed ligand, the side chain in he present complex is bent back over the heterocycle an unusual '*scorpion*' conformation. Such an rangement appears to facilitate intramolecular hydro- en bonding and the Cl(2) · · · N(17) distance of 3.17 Å dicates the interaction to be strong. Although not cluded in the least-squares refinement, a peak was ocated near N(17) consistent with a proton attached to quaternary nitrogen and directed towards the $PdCl_3$ nit [Cl(2) · · · H 2.34 Å]. Although the scorpion con- guration does facilitate this strong intramolecular ydrogen bonding, the latter interaction does not appear o be the driving force for the orientation adopted by the romethazine ring system. Certainly the tilt of the latter with respect to the $PdCl_3S$ plane can be better attributed to the apparent use of the sp^3 orbitals by the sulphur in its σ interaction with the palladium. The deviation of the Cl(2)–Pd–S(5)–N(10) torsion angle from the expected value of 90° is more difficult to rationalise but may reflect an attempt to maximise overlap between *d* orbitals on the sulphur and palladium. In addition, in the related [Pd(cpzH)Cl_3] complex, we find the ring system adopts a similar orientation, yet the hydrogen bonding involves both intra- and inter-molecular N^+–H · · · Cl interactions.[13]

Conclusion.—The *X*-ray crystal structure confirms conclusively the different structural characteristics of the complexes of phenothiazine-based drugs compared to those of the parent heterocycle, and in particular shows the importance and novel influence of the side chain.

Whereas the parent heterocycle and related ligands lead to complexes with a 1 : 2 : 2 metal–ligand–halogen ratio, the ligand being bonded only through the heterocyclic sulphur, the drugs yield complexes with a 1 : 1 : 3 metal–ligand–halogen ratio. In addition to metal–sulphur bonding, the structure involves a type of zwitterion with the negative charge located on the MCl_3 unit and the positive charge on the quaternary nitrogen of the N(10) side chain, the two centres interacting by intramolecular hydrogen bonding.

These structural data lend strong support to the distinctions drawn earlier between the solution properties of the two sets of complexes, and in particular the difference in the visible spectra.

We also note that although in thioridazine the substituent at the 2-position is a sulphur atom, we find no evidence that this is implicated in any way in co-ordination.

This work has been limited to three types of phenothiazine drugs; evidence from the literature [5] indicates that those with a piperazine N(10) side chain (*e.g.* fluphenazine) also react in the same way, indeed all palladium(II) phenothiazine drug interactions published (>20) show the same reactions as those seen here. The far-i.r. evidence confirms the structural similarity of the platinum complexes to the palladium complex.

EXPERIMENTAL

Ligands.—The drugs were supplied by May and Baker Ltd. and by Sandoz Ltd. as the hydrochloride salts. Two of the ligands were synthesised as follows, the remainder being commercially available.

N-Ethylphenothiazine (*eptz*).—Potassium hydroxide (0.4 mol, 22.4 g) was added to dimethyl sulphoxide (200 cm^3) with stirring (5 min). Phenothiazine (Aldrich) (0.1 mol, 20 g) was then added to the mixture with stirring (45 min) followed by the addition of iodoethane (0.2 mol, 31.18 g) over 45 min with cooling and stirring. Water (200 cm^3) was added and the mixture extracted with diethyl ether (3 × 100 cm^3). Each extract was washed with water (3 × 50 cm^3). The ether solution was dried over solid $CaCl_2$ and the solvent removed under reduced pressure. Yield 13.5 g (58.9%). M.p. 101—103 °C (lit.,[14] 103—104 °C) (Found: C, 73.8; H, 5.65; N, 6.25. Calc. for $C_{14}H_{13}NS$: C, 73.95; H, 5.75; N, 6.15%).

N-Dimethylcarbamoylphenothiazine (*dptz*). *N*-Chloroformylphenothiazine (Aldrich) (0.1 mol, 26 g) was weighed into a 250-cm³ round-bottom flask. A liquid-nitrogen condenser was fitted to the top of the flask and dimethylamine (0.4 mol, 18 g) added. The mixture was allowed to reflux at room temperature for 4 h and the unreacted dimethylamine was then boiled off. The product was recrystallised from ethyl acetate–hexane (50 : 50 v/v). Yield 17.6 g (65%). M.p. 95—96 °C (Found: C, 66.5; H, 5.30; N, 10.3. Calc. for $C_{15}H_{15}N_2OS$: C, 66.4; H, 5.55; N, 10.35%).

Complexes with a 2 : 1 *Stoicheiometry*.—All complexes of 2 : 1 stoicheiometry involve ligands insoluble in water. They were prepared by mixing aqueous solutions of $K_2[MCl_4]$ with ethanolic solutions of the ligand (L) in a 1 : 2 mol ratio. This gave a green (L = ptz) or pink (L = dptz or eptz) precipitate which turned blue (M = Pd) or red (M = Pt) over a period of 5 min, the original precipitate being the water-insoluble ligand which subsequently reacts forming the complex. The precipitate was filtered off, washed with acetone, and dried *in vacuo* at 100 °C.

Complexes with a 1 : 1 *Stoicheiometry*.—These all involved ligands that are drug hydrochlorides and soluble in water. The reaction was carried out by mixing aqueous solutions of ligand (0.1 mol dm^{-3}) and $K_2[MCl_4]$. This gave a yellow (M = Pt) or a purple precipitate (M = Pd) which was filtered off, washed with water, and dried *in vacuo* at 100 °C. The complexes $[Pd(LH)Cl_3]$ (L = pmz or cpz) were recrystallised from dmf.

Instrumental Techniques.—Infrared spectra were obtained from KBr discs at 2% concentration using a Pye Unicam SP 1200 spectrophotometer calibrated with polystyrene at 1 600 cm^{-1}. Proton magnetic resonance spectra were obtained from solutions in [$^2H_7$]dmf or [$^2H_6$]dmso using a Hitachi–Perkin-Elmer FT 30 instrument. Visible spectra were obtained from dmf solutions using a Pye Unicam SP 800 spectrophotometer, far-i.r. spectra from pressed Polythene discs at 30% concentration using a Beckman FS 720 instrument.

Crystal Data.—$C_{17}H_{21}Cl_3N_2PdS$, $M = 498.21$, Monoclinic, space group $P2_1$, $a = 11.381(5)$, $b = 9.791(4)$, $c = 9.098(4)$ Å, $\beta = 100.85(5)°$, $U = 995.76$ Å³, $\lambda = 0.710\ 69$ Å, $D_m = 1.67$, $Z = 2$, $D_c = 1.69$ Mg m^{-3}, μ(Mo-K_α) = 1.32 mm^{-1}, $F(000) = 500$.

X-Ray Intensity Measurements.—A crystal of approximate dimensions 0.47 × 0.32 × 0.08 mm was mounted with the *b* axis coincident with the ω axis of a Stöe Stadi 2 two-circle diffractometer. Data were collected using monochromated Mo-K_α radiation and the background–ω scan–background technique. Corrections for Lorentz and polarisation effects were applied but not for absorption. Of the 1 790 unique reflections collected, 1 524 had $I > 3.0\sigma(I)$ and were used in the subsequent structure analysis.

Structure Determination and Refinement.—While systematic absences do not distinguish between space groups $P2_1$ and $P2_1/m$, in the centrosymmetric space group $Z = 2$ requires the molecules to possess mirror symmetry. Subsequent analysis confirmed $P2_1$ to be the correct space group,

TABLE 4

Final atomic parameters (×10⁵ for Pd; ×10⁴ for other atoms) with estimated standard deviations in parentheses for non-hydrogen atoms

Atom	*x*	*y*	*z*
Pd	24 447(5)	25 000	42 418(6)
Cl(1)	2 890(2)	4 338(3)	2 885(3)
Cl(2)	2 175(3)	555(3)	5 522(3)
Cl(3)	821(2)	1 940(4)	2 374(2)
S(5)	4 001(2)	3 200(3)	6 072(2)
C(1)	3 126(9)	1 795(13)	9 863(10)
H(1)	2 502	2 026	10 588
C(2)	3 911(11)	711(15)	10 221(13)
H(2)	3 864	79	11 181
C(3)	4 762(11)	439(15)	9 330(13)
H(3)	5 380	−401	9 603
C(4)	4 806(9)	1 247(15)	8 117(13)
H(4)	5 471	1 050	7 439
C(6)	4 095(9)	5 989(13)	6 221(11)
H(6)	4 753	5 911	5 512
C(7)	3 764(10)	7 244(14)	6 663(13)
H(7)	4 145	8 163	6 292
C(8)	2 929(10)	7 316(15)	7 589(13)
H(8)	2 680	8 305	7 960
C(9)	2 411(9)	6 167(12)	8 048(11)
H(9)	1 735	6 263	8 732
C(11)	3 117(6)	2 594(16)	8 602(8)
C(12)	4 008(7)	2 302(14)	7 747(9)
C(13)	3 579(7)	4 810(12)	6 689(10)
C(14)	2 751(7)	4 879(10)	7 643(9)
N(10)	2 306(6)	3 653(9)	8 164(8)
C(15)	1 182(8)	3 736(12)	8 821(11)
C(16A)	121(16)	3 480(24)	7 829(21)
C(16B)	329(12)	2 487(32)	8 394(15)
N(17)	181(6)	2 086(10)	6 909(11)
C(18A)	−735(20)	2 081(27)	5 654(25)
C(18B)	−323(30)	3 287(44)	5 686(36)
C(19A)	131(23)	872(34)	8 038(29)
C(19B)	−488(36)	858(52)	6 264(44)
C(20)	−948(11)	3 251(26)	8 674(17)

TABLE 5

Bond distances (Å) and angles (°) with estimated standard deviations in parentheses

(*a*) Bond distances

Pd–Cl(1)	2.292(3)	C(7)–C(8)	1.386(18)
Pd–Cl(2)	2.283(3)	C(8)–C(9)	1.372(25)
Pd–Cl(3)	2.328(2)	C(9)–C(14)	1.389(15)
Pd–S(5)	2.296(2)	C(13)–C(14)	1.397(13)
C(12)–S(5)	1.758(10)	C(6)–C(13)	1.397(16)
C(13)–S(5)	1.771(11)	C(11)–N(10)	1.396(15)
C(1)–C(11)	1.387(15)	C(14)–N(10)	1.418(13)
C(1)–C(2)	1.386(18)	N(10)–C(15)	1.515(12)
C(2)–C(3)	1.400(19)	C(15)–C(16)	1.35 *
C(3)–C(4)	1.367(18)	C(16)–C(20)	1.63 *
C(4)–C(12)	1.375(17)	C(16)–N(17)	1.50 *
C(11)–C(12)	1.418(12)	N(17)–C(18)	1.52 *
C(6)–C(7)	1.367(18)	N(17)–C(19)	1.53 *

(*b*) Bond angles

Cl(1)–Pd–Cl(2)	173.8(1)	C(11)–N(10)–C(14)	117.7(7)
Cl(1)–Pd–Cl(3)	91.0(1)	C(11)–N(10)–C(15)	119.3(8)
Cl(1)–Pd–S(5)	86.4(1)	C(14)–N(10)–C(15)	117.9(8)
Cl(2)–Pd–Cl(3)	90.6(1)	N(10)–C(14)–C(9)	123.0(8)
Cl(2)–Pd–S(5)	92.2(1)	N(10)–C(14)–C(13)	119.5(9)
Cl(3)–Pd–S(5)	176.2(1)	C(9)–C(14)–C(13)	117.6(9)
Pd–S(5)–C(12)	110.9(3)	C(8)–C(9)–C(14)	120.4(10)
Pd–S(5)–C(13)	106.1(3)	C(7)–C(8)–C(9)	121.8(13)
C(12)–S(5)–C(13)	97.3(5)	C(6)–C(7)–C(8)	118.8(12)
S(5)–C(12)–C(4)	118.9(8)	C(7)–C(6)–C(13)	119.9(10)
S(5)–C(12)–C(11)	119.8(8)	C(6)–C(13)–S(5)	119.0(8)
C(4)–C(12)–C(11)	121.6(10)	C(6)–C(13)–C(14)	121.4(10)
C(3)–C(4)–C(12)	120.7(11)	S(5)–C(13)–C(14)	119.6(8)
C(2)–C(3)–C(4)	119.5(12)	N(10)–C(15)–C(16)	114.3 *
C(1)–C(2)–C(3)	119.7(11)	C(15)–C(16)–N(17)	113.4 *
C(2)–C(1)–C(11)	120.0(10)	C(15)–C(16)–C(20)	104.4 *
C(1)–C(11)–N(10)	123.8(9)	N(17)–C(16)–C(20)	106.5 *
C(1)–C(11)–C(12)	116.4(11)	C(16)–N(17)–C(18)	112.1 *
N(10)–C(11)–C(12)	119.7(9)	C(16)–N(17)–C(19)	116.0 *
		C(18)–N(17)–C(19)	108.9 *

* C(16), C(18), and C(19) are disordered and average values are given for the bond distances and angles associated with these atoms.

'th the two molecules occupying general positions. Interretation of a three-dimensional Patterson map readily orded the x and z co-ordinates of the palladium atom. uccessive difference electron-density maps revealed the maining atoms and showed the N(10) side chain to be artially disordered. Alternative positions were found for ch of the carbon atoms C(16), C(18), C(19) and satisfactory finement was achieved by the inclusion of carbon atoms ving an occupancy factor of 0.50 at each position. Only e hydrogen atoms of the C_6 rings could be satisfactorily cated and were included in positions calculated from the metry of the molecule (C–H 1.08 Å). A common isoopic thermal parameter was applied to the located hydron atoms and refined to a final value of $U = 0.085(85)$ Å^2. ttering factors were calculated [15] using an analytical proximation and the weighting scheme adopted was $= 0.2622/[\sigma^2(F_o) + 0.0044(F_o)^2]$. Full-matrix refinent with isotropic thermal parameters for the disered carbon atoms and with anisotropic thermal paraters for all other non-hydrogen atoms gave the final $= 0.036$ and $R' = 0.039$. Final atomic parameters are en in Table 4, bond distances and angles in Table 5. ts of structure factors and thermal parameters are given upplementary Publication No. SUP 23253 (11 pp.).*

For details see Notices to Authors No. 7, *J. Chem. Soc., ton Trans.*, 1981, Index issue.

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