A STUDY OF THE INTERACTION OF COPPER WITH SELECTED PSYCHOTROPIC COMPOUNDS

BY

JUDITH CLAIRE BRYAN

A THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
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To my Father and Mother,

Mark, Stephen, Charles

and Auntie Marie

"In all thy ways acknowledge Him, and He shall direct thy paths." Proverbs 3:6.

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SUMMARY

The investigation of the interaction of copper (II) with two classes of compounds which are active in the central nervous system, the "sympathomimetic amines" (central nervous stimulants) and the phenothiazines (neuroleptics and major tranquillizers) began after noting several tenuously joined observations. The former class of compounds when administered in excess can produce varying symptoms from acute anxiety, (ephedrine) to a toxic psychosis, (amphetamine) so resembling schizophrenia that it could be used as a "model schizophrenia". The latter class could be used as a therapeutic control of the symptoms of schizophrenia, chlorpromazine being the best known member.

Both classes of compounds act via dopamine systems in the brain and one of the active enzymes in the brain bringing about the removal of dopamine, dopamine β-hydroxylase, contains copper.

Both classes have the ability to form complexes with copper. The "sympathomimetic amines" contain the aliphatic amino nitrogen atom whilst the phenothiazines also have the sulphur atom.

The literature survey introduces the importance of trace metals and their complexes in health and disease and the consequence of their excess or deficiency is discussed.

Previous work carried out in the preparation and characterization of complexes with the two classes of compounds is reported.

The preparation of new complexes of copper (II) with selected "sympathomimetic amines" and selected phenothiazines is reported and their characterization, using various analytical techniques including thermogravimetric analysis, spectroscopic techniques: infrared, electronic and electronic spin resonance spectroscopy, magnetic and conductance measurements and x-ray analysis in certain cases.

Measurements of ΔH_{vap} for methylamphetamine and amphetamine have been made and ΔH_{dissoc} for the dissociation of complexes of these bases have been determined. Several new complexes of each amine were isolated.

Key words: Sympathomimetic amines, Phenothiazines. Copper-complexes, Schizophrenia.

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CONTENTS

LIST OF FIGURES PAGE

LIST OF PLATES

LIST OF TABLES

LIST OF APPENDICES

CHAPTER ONE

INTRODUCTION

CHAPTER ONE

INTRODUCTION

1.1 Background

Until recent years, Life Scientists with few exceptions held the point of view that inorganic elements except sodium, potassium, calcium and magnesium among the non-transition metals, and iron and copper among the transition metals, were irrelevant in mammals, and that other metals were there merely by accident. The importance of the involvement of Na^+, K^+, Ca^{2+}, and Mg^{2+} in essential roles in muscle and nerve action and the fact that iron was somehow responsible for the properties of haemoglobin has been known since the turn of the century.

Although the importance of metal complexes in animals has been recognised for some time, the chemistry of living systems has tended to be considered as being organic to the exclusion of inorganic chemistry.

During the past decade advances in the study not only of metal complexes but also metal ions in solution together with modern techniques of separation eg. variations on chromatography aiding enzyme isolation have facilitated the qualitative and quantitative analysis of metals in tissues and added substantially to the understanding of the biological functions of metals in cellular and subcellular systems in animals and man. These techniques have shown that a number of metals are crucial to enzyme function. Even if it is only one atom in many thousands, without the presence of a trace metal it could not function. Quite often a tight coordination complex

is formed with the protein and isolated as a single unit i.e. metalloenzyme.

More than sixty elements have been found in micro-organisms, higher plants and animals including man. These are ordinarily present in tissues only in minute quantity, picograms-micrograms per gram of wet organ and are arbitrarily designated trace elements. About 12 are considered essential for animal life:

Cr	Cu	Ni	Mn	Si	Zn
Co	F	I	Se	Sn	Mo

1.2 Copper deficiency and excess

The absence or deficiency of these essential elements is usually characterized by impaired growth, reproductive failure, defective elastic tissues and shortened life span. On the other hand excessive accumulation, either through failure in internal mechanisms or external reasons results in toxicity. The delicate balance of metal concentration in human tissues, serum and urine often undergoes dramatic changes in response to transient infections, stress, during the administration of drugs and during the course of many diseases. After major surgery zinc is rapidly mobilized from the skin and bones and unless supplementary zinc is supplied, hypozincuria may result.

The total body content of copper in human adults is about 100-150 mg which is almost entirely protein bound. A very small amount is present as free copper (11) ions in equilibrium with the copper loosely bound to albumin and is free to diffuse across the semi-permeable membranes such as the blood brain barrier. The total content of copper, 100-150mg

is kept constant by a daily intake of 2-5 mg of the element, which in fact exceeds the normal requirement.

In normal adults a protective mechanism serves to restrict the absorption of copper and other trace metals. A classic example of the breakdown of this mechanism is Wilson's disease in which copper is absorbed in excess and diffuses into the tissues where it may accumulate, owing to an inability to excrete surplus copper at the required rate, to a high level particularly in the liver and brain where it can produce severe mental illness, liver damage and ultimately death. These patients lack ceruloplasmin and the ability to excrete excess, unwanted copper. In 1956, Walshe [1] used D-penicillamine to increase the urinary excretion of copper in patients with Wilson's disease and found that they improved, indicating that in part at least, that excess copper was responsible for the disease. It must also be mentioned that alongside of copper excess, zinc deficiency has also been reported. Copper is a component of numerous metalloenzymes and a deficiency of copper can lead to abnormalities in hair and skin pigmentation, defective elastic tissue in great vessels resulting in arterial rupture, ineffective blood formation and faulty development of bone and nervous tissue. Copper deficiency in man is quite unusual but genetic and acquired forms are recognized.

The essential role of copper in the normal development of the central nervous system was recognized in sheep 40 years ago [2] when lambs born of ewes grazing in pastures particularly low in copper exhibited incoordination in gait known as enzootic ataxia (swayback) resulting from degeneration of the central nervous system. Supplementation of the diet with copper salts prevented this.

Menke's syndrome [3] (kinky hair or steely hair disease) appears to be a partial human counterpart of the deficiency syndrome in animals. It results from defective copper transport in the intestine and is manifested by rapid central nervous system degeneration in male infants.

The work undertaken here investigates the interaction of copper with two groups of compounds that are active in the central nervous system. This came about because of several tenuously joined observations as will be explained later.

1.3 Historical

It had been known for many years that one of the most effective treatments for asthma is epinephrine (adrenaline). Epinephrine cannot be taken orally because of its instability.

The desert plant Ma-Huang has been known to the Chinese since 2800 BC. The active principle was isolated in 1885. The pure alkaloid was obtained and named ephedrine by Nagai [4] in 1887.

In 1920 it was first synthesized by Späth and Göhring [5]. Chen systematically investigated the Chinese drug codex and noticed that the desert plant Ma-Huang had been used to treat asthma. With Schmidt, after extracting the chemical ephedrine from the plant he investigated its pharmacology, administering it to asthmatic patients [6]. Ephedrine turned out to be very successful in the treatment of asthma.

In 1887 the German pharmacologist Edeleano [7] first synthesized phenylisopropylamine (benzedrine), but it was not until 1910 that the

pharmacological properties were investigated. Barger and Dale [8] investigated the effect of this and a series of closely related compounds which they called the "sympathomimetic amines". However, in England and America it was not until 17 years later that the full implications of the findings concerning these compounds was realised.

After the realisation that eventually supplies of Ma-Huang would be exhausted, Piness who was aware of Edeleano's discovery suggested to Alles the possibility of preparing a synthetic substitute for ephedrine. In 1927 Alles [9] found that amphetamine was the most effective substitute for ephedrine in the treatment of asthma, thus confirming Piness's hunch about the original amphetamine synthesized by Edeleano.

Administering the two isomers of amphetamine to himself he found that the d- isomer was at least 4-5 times as potent a central nervous stimulant as the laevo form. He noted that the drug made him feel euphoric, enhanced his abilities to focus on intellectual work and prevented fatigue. Later he found that it was an appetite suppressant and that amphetamine was active whether inhaled or taken orally.

The compound was introduced into clinical medicine in the 1930's, its first use being incorporated into a benzedrine (racemic form) inhaler marketed for nasal congestion in 1932.

Amphetamine tablets promoted for the treatment of narcolepsy and postencephalitic parkinsonism were approved by the American Medical Association (AMA) in 1937. [10]

The first addicts to the drug were reported in the late 1930's. [11] These

individuals ingested the entire contents of a benzedrine inhaler in a single dose.

In 1938 several cases were reported of individuals who developed a paranoid psychosis from the chronic use of massive doses of amphetamine ingested by the removal of the inhaler contents. Amphetamine psychosis became the commonly observed sequal to addiction.

In 1938 Young and Scoville [12] published the first medical report calling attention to the possibility of amphetamine psychosis. Similar reports followed in the early 1940's from Switzerland and Germany.

Ellinwood,[13] a psychiatrist, catalogued the histories of 13 homicides committed under the influence of amphetamine. In 1958 Connell [14] compiled the detailed histories of 42 amphetamine psychotics that had been admitted to five London hospitals. He investigated these cases over a period of three years. Very few evaluations of amphetamine psychosis had been published previously.

Psychiatrists had sought for years an experimental, drug-induced, "model schizophrenia". Amphetamine psychosis was initially suggested as a model for paranoid schizophrenia [14,15] because many patients with amphetamine psychosis had been misdiagnosed for a long time as paranoid schizophrenics. [16]

Amphetamine psychosis developed in patients on administration of gradually increasing dosage of amphetamine over a period of several days.

After research to find a "model schizophrenia" it was found that:

1. Amphetamine psychosis is the only drug psychosis known (beside cocaine psychosis) which so closely resembles schizophrenia of the acute paranoid type, that patients were regularly misdiagnosed as schizophrenics. This cannot be said for any other drug induced psychosis. [16]

2. The schizophrenia-like symptoms of amphetamine psychosis are true drug effects and not a result of sleep loss or activation of latent schizophrenia. [17,18]

3. Since the discovery of chlorpromazine in 1950, phenothiazine tranqillizers have been found to be uniquely effective in treating both amphetamine psychosis and schizophrenia. [19,20,21]

4. Amphetamines in small doses activate the symptoms of incipient or mildly symptomatic schizophrenics but fail to have this effect on schizophrenics in remission or in manic depressed patients or normal individuals. [19]

Thus a link had been established between amphetamine psychosis and schizophrenia. Many studies have been carried out in the study of schizophrenia and many hypotheses have been proposed concerning the possible biochemical abnormality which may exist in the brains of patients with schizophrenia and related psychoses.

In relating these facts it is necessary to look at certain biochemical features of brain function, especially the critical process called neurotransmission.

1.4 Neurotransmission

Information is processed by cells in the brain. These are of two types i) glial and ii) neurone. We are interested in the latter. (see appendix). Neurones are able to receive information and likewise pass on information. The space between the cells is the synapse and some nerve impulses are able to jump across the synaptic cleft whilst in others, when nerve impulses reach the nerve endings they trigger the release of a specialized chemical called a neurotransmitter, which then diffuses across the synaptic cleft and transmits information to the succeeding neurone. It is also important to realise that information processing at synapses must take place rapidly, in order to maintain functioning in the average human brain. Therefore after crossing the synaptic cleft and exciting or inhibiting the succeeding neurone, the neurotransmitter must be removed so that the neurone can be prepared for succeeding nerve impulses.

Two mechanisms are known for freeing the synaptic cleft:

1. Destruction of the neurotransmitter by an enzyme.
2. Termination of synaptic action by pumping back the neurotransmitter into the nerve ending which released it. This process is known as reuptake inactivation.

This latter mechanism is thought to operate in the removal of norepinephrine and dopamine from the synaptic cleft. A variety of drugs may exerttheir therapeutic actions via effects produced upon these reuptake processes.

Thus researchers began to look for the mode of action of amphetamines and

and phenothiazines in the brain.

1.5 Mode of action of amphetamines

In order to explain the significant interaction of drugs, neurotransmitters and schizophrenia, the neurotransmitters dopamine and norepinephrine (see appendix) are important. These compounds which are catecholamines are chemically related. In seeking a biochemical mechanism of amphetamine action, pharmacologists have a headstart in that amphetamine bears a close chemical resemblance to norepinephrine and dopamine.

For a long time they thought that in one way or another amphetamines exerted therapeutic actions via norepinephrine and or via dopamine. Direct experiments have revealed a number of ways in which amphetamines can interact with these chemicals.

Two mechanisms are currently favoured by pharmacologists. [22]

1. Direct synaptic release.
2. Inhibition of reuptake inactivation.

In either case amphetamine potentiates catecholamine effects.

Thus amphetamines do not substitute and act as surrogate neurotransmitters.

Advances in understanding brain catecholamines came with the development of a fluorescent technique whereby dopamine and norepinephrine can be detected and distinguished in specific neurons in sections of the brain that have been frozen. [23] Once brain specimens have been treated with a specially prepared formaldehyde vapour, norepinephrine and dopamine develop an intense green fluorescence, visible under the microscope. This enables the course of neurones throughout the brain to be followed. It was found that the dopamine and norepinephrine neurones cluster in well defined groups, which coursing throughout the brain together are known as "brain tracts". Knowing the detailed geography of the tracts made it possible to make reasonable inferences about their functions. Certain of these inferences have enabled certain diseases to be treated far more successfully than previously, an example being Parkinson's disease.

It had been known that dopamine was deficient in Parkinson's disease. If then the dopamine deficiency could be relieved, this should alleviate the symptoms.

Dopamine itself cannot be directly administered to patients because of its difficulty in entering the brain. In 1967 Cotzias et al [24] administered the precursor L-dopa (see appendix) (which can be converted in the brain by decarboxylation to dopamine) in very large doses to Parkinsonian patients. It proved to be very successful and was hailed as a miracle drug.

Dextroamphetamine has been employed as an effective therapeutic agent in Parkinson's disease.[25,26] It probably acts by potentiating the limited amounts of dopamine remaining in the brains of Parkinsonian patients.

Modern therapies for the disease now centre around raising the dopamine levels, or trying to make good the deficit in other ways.

It is known that if the level of dopamine is over restored in Parkinson's disease then these patients can develop psychotic symptoms. This leads to the inference that the psychoses could be caused by an excess of dopamine in a certain part or parts of the brain.

Therapeutic agents aimed at inhibiting dopamine at the receptor sites in the brain are effective in controlling some types of schizophrenia and given in excess they can produce Parkinsonian side effects.

Biochemical studies on samples of human post-mortem brain have shown that it is possible to detect abnormalities in neurotransmitters or related enzymes in other neurological diseases including Huntington's Chorea, [27] and senile dementia.[28]

On this basis Bird et al [29] decided to test the dopamine hypothesis for schizophrenia which suggests that an increased release or response to dopamine in the central nervous system might underline schizophrenic psychosis by studying samples of human post-mortem brain from more than 60 patients dying with a hospital diagnosis of schizophrenia together with 15 patients with a hospital diagnosis of schizophrenia who committed suicide and from 50 control patients.

A large number of cases is essential in brain neurotransmitter studies as individual levels vary greatly (in these subjects) and the large variations can easily mask true differences if the sample is not big enough.

As biochemical markers for the specific neurons, dopamine, norepinephrine choline acetyltransferase and glutamic acid decarboxylase were measured in 14 different regions of post mortem brain.

No statistically significant differences were found in any brain region except for dopamine in which an increase was observed in the limbic forebrain.

More recently Kokkinidis and Anisman [30] have suggested a dual model for amphetamine psychosis and schizophrenia. They said that schizophrenia should be considered in terms of an interaction between norepinephrine and dopamine systems.

1.6 Interaction of Phenothiazines with Dopamine Receptors

As the chemical similarities of amphetamine and the catecholamines norepinephrine and dopamine portended their pharmacological relation, findings of a more subtle resemblance of catecholamines to phenothiazines may explain certain therapeutic effects of phenothiazines. [31]

Phenothiazines which are selectively antischizophrenic and are unique antidotes to amphetamine psychosis alter dopamine metabolism in a way that suggests they inhibit dopamine receptors in neurones in the brain.

The antipsychotic and dopamine-blocking potencies of phenothiazines are closely correlated and it has been suggested that the anti-schizophrenic activity of these drugs is related to the blockade of dopamine receptors at one or another of the dopamine tracts. [32,33]

Carlsson [34] described some effects of chlorpromazine on the rate of destruction of dopamine and norepinephrine in the brain. Chlorpromazine was effective, haloperidol (see appendix) was almost 100 times as potent as chlorpromazine, and promethazine was devoid of any activity.

Haloperidol is a drug of the butyrophenone class, chemically different from the phenothiazines and about 100 times as potent as chlorpromzine in human subjects. Promethazine though clinically similar to chlorpromazine has virtually no antischizophrenic activity and therefore any biochemical action of phenothiazines which is related to effects in schizophrenia should be exerted by chlorpromazine and not promethazine. This indeed is the case.

Accepting the hypothesis that dopamine receptor blockade could explain the clinical action of phenothiazines was difficult because of the lack of chemical similarity between phenothiazines and catecholamines.

Snyder and Horn [31] investigated the conformations of dopamine and chlorpromazine as determined by x-ray crystallography and found that it was possible for chlorpromazine in its preferred conformation to mimic the dopamine molecule in its preferred conformation at receptor sites. If this was the case then it seems reasonable to assume that the ability of the phenothiazine drugs to assume the dopamine-like conformation should be related to their antischizophrenic activity.

A substituent at position 2 of ring 'a' (Figure 1) of phenothiazines is crucial for antischizophrenic activity.[35] Without the substituent, rings 'a' and 'c' would be almost symmetrical with the side chain fully extended, lessening the probability that the resultant compound would be able to assume the dopamine-like conformation and mimic its action. Thus if antischizophrenic activity is determined by the blockade of dopamine receptors then it would naturally follow that a phenothiazine compound lacking the 'a' ring substituent would be less effective as an antischizophrenic agent. Of the phenothiazine tranquillizers widely employed clinically only two mepazine and promazine lack a substituent on ring 'a' and are significantly less effective as antischizophrenic drugs than the other phenothiazines.

Another major requirement for activity is separation of the side chain amine from the ring system by 3 carbon atoms.[31] Molecular models indicate that shortening of the side chain to 2 carbon atoms makes it difficult for the phenothiazine compound to assume the dopamine-like conformation. Accordingly phenothiazines with a separation of 2 carbon atoms such as promethazine and diethazine appear to lack antischizophrenic activity.

Thus all this information leads us to the conclusion that amphetamines elicit psychosis via dopamine systems, and phenothiazines relieve the symptoms of schizophrenia and amphetamine psychosis by altering the same system.

1.7 Classes of chemical compounds investigated

Major Tranquillizers (Neuroleptics)

Chlorpromazine belongs to the class of major tranquillizers. These

compounds can be grouped into two classes depending on the structure of their side chains. One group have the alkylamino group in their side chain and tend to produce more sedating side effects as well as lowering blood pressure. They are also less potent on a weight basis. Chlorpromazine is a typical example of this group. The second group containing the piperazine ring in their side chain act in smaller doses, producing less sedation and lowering of blood pressure but higher incidence of Parkinson-like side effects as compared with the former class. The phenothiazines possess reactive sites which could complex with copper.

Sympathomimetic Amines

The amphetamines belong to the group of compounds of varying potency which stimulate the central nervous system. These "sympathomimetic amines" have the basic phenylethylamine skeleton containing the aliphatic amino nitrogen atom which is known to have a marked affinity for copper.

Thus we have two families of drugs at opposite ends of a scale in their action. One family the sympathomimetic amines (stimulants) favour Cu(II) in reactions, whereas the others the tranquillizers reduce Cu(II) to Cu(I).

1.8 Observations leading to basis of work

1. During the course of a study on respiration in 1918, it was reported that intravenous administration of small doses of a dilute sodium cyanide solution relieved the symptoms of schizophrenia. [36]

2. Cyanide reduces copper (II) to copper (I).

3. Phenothiazines have antioxidant properties. Their use as antioxidants interacting with metal containing intermediates has been reported. [37]

4. Solutions of copper (II) in amines are on the other hand oxidising agents.

5. The possibility of the involvement of metals in the chemistry of certain types of schizophrenia was implicated in 1929 by English who reported on the use of intravenous manganese chloride in 181 schizophrenic patients and found that half of them improved. [38]

In 1934 Hoskins [39] repeated in part some of this work using suspended manganese dioxide which was administered intramuscularly, to only a small number of schizophrenics. He reported that no improvement was observed, which is not surprising as the compound is mobilized too slowly.

6. Pfeiffer and Ilieve [40] knowing that elements may substitute for a given trace element and that the function of the enzyme could be enhanced or depressed, suggested that in the schizophrenic copper or iron could be in excess and zinc and manganese could be deficient. They concluded that a probable etiological factor in some schizophrenics is a combined deficiency of zinc and manganese with a relative increase in iron, copper or both.

One of the earliest studies of the implication of serum copper in schizophrenia was reported in 1941 by Heilmayer et al.[41] This stimulated further studies in copper research in schizophrenia.[42-45]

7. The first published results on cerebrospinal fluid copper in

schizophrenia was reported by Tyrer et al [46] who looked at the differences between copper levels in the cerebrospinal fluid of schizophrenic subjects and non-schizophrenic controls who had brain damage and normal subjects.

Although the results indicated no difference in the levels between the groups, the number of subjects, 12 was too small to make any firm conclusions. Bird et al [31] have shown that a large number of subjects must be used to make any valid conclusions.

8. Copper is the next most common transition element to iron in the brain. In 1960 [47] after partial purification of dopamine β-hydroxylase it was shown that the enzyme catalysed the conversion of dopamine to norepinephrine according to the equation:

$$\text{Dopamine} + O_2 + \text{ascorbate} \xrightarrow{\text{fumarate}} \text{L-norepinephrine} + \text{dehydroascorbate} + \text{water} \qquad (1)$$

It was also shown that the enzyme was not specific to dopamine but would also catalyse the side chain hydroxylation of many analogues of phenylethylamine.[48-51] It was suspected that a metal played a role in the reaction since the enzyme was sensitive to a wide variety of chelating agents. [52,53-55] Later the metal in the enzyme was identified as copper and it was shown that part of the copper undergoes reduction and oxidation during the enzyme catalysed hydroxylation reaction. (In general copper-protein complexes function as oxidases, using molecular oxygen as an electron acceptor. It is believed that these cuproprotein enzymes operate by means of a redox cycle - the 'valence shuttle' hypothesis which involves oxidation of the substrate

by copper (II) then subsequent regeneration of this ion from copper (I) using molecular oxygen as the electron acceptor. Copper could function by oxidation or it could be involved in a step leading to oxidation). The enzyme was freed from the metal by treatment with cyanide and ammonium sulphate.[56] 98% of the copper was removed and the enzyme was left inactive. The addition of copper (II) ions restored 40% (maximum) of the activity. Excess addition however causes inhibition. At concentrations of 5 M, Mn(II), Mo(Vl), Mn (II), Al(III), Mg(II), Co(II) and Fe(II) were unable to restore activity. Dopamine β-hydroxylase was found to be the predominant cupropoprotein enzyme present.

At least two of the enzymes involved in the regulation of dopamine are copper dependent: dopamine β-hydroxylase which converts dopamine to norepinephrine and tyrosine hydroxylase, which catalyses the hydroxylation of tyrosine to produce dihydroxyphenylalanine (dopa). From all the observations listed it was thought interesting to speculate:

1. Whether central nervous system stimulants such as the amphetamines might mediate in oxidations by copper containing species/enzymes.
2. Whether the chemistry of paranoid schizophrenia might involve copper compounds and their action with neurotransmitters.

On this basis a worthwhile preliminary step towards the understanding of a possible role of copper in schizophrenia would be to examine the simple amines and selected members of the phenothiazine group of major tranquillizers (neuroleptics). After investigating the simple system in the absence of copper containing enzymes, the next step would be to investigate the interactions of compounds from the two groups mentioned with copper containing enzymes.

All of the compounds in the text that follows will be referred to by their trivial names. Appendix 1 Tables 1,2 gives their systematic name and other names by which they are sometimes referred to.

1.9 Previous work

Very little work has been carried out up to date on the formation and full characterization of complexes with these two groups of compounds. The work carried out has been rather sporadic without any attempts of correlation between members in the same group.

1.10 The Sympathomimetic Amines

The first suggestion of complexation between Cu(II) and any of the amines was a sensitive colour test first described by Nagai [57] in 1892. Chen and Kao [55] further investigated this reaction.

L-ephedrine* (1 ml), 10% $CuSO_4\ 5H_2O$ (0.1 ml) and 20% NaOH (1 ml) were shaken together. A purple colour developed which could be extracted using ether. Other workers synthesized the complex using a 2.1 ratio of ephedrine hydrochloride to $CuSO_4\ 5H_2O$ in the presence of base usually sodium hydroxide.

Various solvent/solvent systems were used for recrystallisation:- acetone, cold benzene, hexane, mesitylene, cyclohexane, butanol.

*ɔ L-ephedrine has a very low melting point (40-41°). The presence of a small amount of impurity would prevent crystallisation.

Methods of investigation used by workers [59-61,63] ranged from just elemental analysis to X-ray crystallography of a complex that had crystallised with benzene i.e. clathrate. The complex was thought to be a trans square planar chelate, Cu(II) replacing two H+ atoms of ephedrine base.

In a very much similar way complexes of N-methylephedrine [62,63] (which could not be purified) d-pseudoephedrine, [59-61] phenylpropanolamine [62,65,66] have been isolated.

Recently, 1981 a complex of phenylephrine has been isolated. [67]

(All these complexes were violet except for the phenylpropanolamine complex which was said to be deep blue)

Rajan et al [68] have studied the thermodynamic stabilities of the coordinate binding of Cu(II) with adenosinetriphosphate and phenylephrine, amphetamine, ephedrine, phenylethylamine and phenylpropanolamine in aqueous model systems.

The technique of potentiometric equilibrium measurement of H+ ion concentration of the ligands in the presence and absence of equimolar amounts of Cu (II) ion was employed. The metal ligand reactions were carried out at 25°C and at a constant ionic strength of 1.0 (KNO_3). 0.02M solutions of the amines as their hydrochlorides were used. The ternary chelate systems consisted of Cu(II) -ATP- amine in a 1:1:1 ratio. The binding strengths were found to decrease along the series from phenylephrine to phenylpropanolamine, in the order given above.

Complexes of methylamphetamine (mamp) have been reported with copper (II) chloride by Watt and Wells[69]. The complexes reported were: dichloro-bis (dl-N, α- dimethylphenylethylamine) copper (II), Cu $(mamp)_2Cl_2$ and dichloro-bis (d-N, α -dimethylphenylethylamine) copper (II), Cu $(mamp)_2Cl_2$

The other products obtained were salts of the formulae: (mampH) CuCl Bis-dl-N,α -Dimethylphenylethylammonium tetrachlorocuprate (II) and $(mampH)^+CuCl^-$, dl-N, α-Dimethylphenylethylammonium trichlorocuprate.

1.11 The Phenothiazines

A reaction between certain trace metals and phenothiazines was first suggested by Borg and Cotzias [70] in 1962, on the observation that chlorpromazine markedly suppressed the binding of Mn(II) by tissues and soluble protein. At this time it was not clear as to whether it was a direct reaction or competition for binding sites. They suggested that the metal-phenothiazine reactions could be used as prototypes for the further study of the biochemical roles of trace metal ions 'in vivo'. Experiments did not prove that phenothiazines interacted with metals 'in vivo' but none the less demonstrated the specific reactions with biological trace metals under conditions which might prevail 'in vivo'.

Huang and Gabay [71], 1974 reported the isolation of complexes of chlorpromazine, promazine and fluphenazine with copper (II) chloride. The chlorpromazine product isolated was a microcrystalline salt of formula CPZ $CuCl_2$ 2HCl, which almost certainly contains $(CuCl_4^{2-})$ and protonated chlorpromazine (CPZ = chlorpromazine). It was the only

compound of the three investigated further by means of I.R., ESR, UV/Visible absorption, and mass spectra.

Rajan et al [72] studied the interactions of phenothiazines with the metal ions Ca^{2+}, Mg^{2+}, and Cu^{2+}, in aqueous electrolyte media by means of the potentiometric equilibrium method and absorbtion spectral technique. In 1978, Harris and Gabay [73] studied the product of the reaction between copper (11) chloride and chlorpromazine by X-ray crystallography and reported the structure of the compound isolated as $(CPZ2H^{2+})(CuCl_4^{2-})$

CHAPTER TWO

EXPERIMENTAL

PHYSICAL MEASUREMENTS

CHAPTER TWO

EXPERIMENTAL

2.1 Physical Measurements

2.1.1 Magnetic Techniques

The structure and bonding in compounds of transition metal elements is sensitively connected with the magnetic properties, and changes in bonding and structure produce, particularly in the case of copper (II) the most obvious changes in magnetic behaviour, and correlation between the electronic properties of copper (II) complexes and the local stereochemistry of the copper (II) ion present is possible.

The most important physical techniques giving information on the stereochemistry of the copper (II) ion in a complex of unknown crystal structure from measurements on a polycrystalline sample are:

(1) the room temperature magnetic moment; (2) the electron spin resonance spectrum; (3) the electronic reflectance spectrum. [74]

2.1.2 Electronic Spectra

The spectra were recorded in the region 30 000 - 11 500 on a Unicam SP 800 Spectrophotometer. The solids were examined as finely ground powders supported on filter paper on the diffuse reflectance accessory supplied with the instrument.

Solution spectra were obtained for the complexes which were soluble

in chloroform or acetonitrile using matched cells of path length 1 cm.

The assignments of stereochemistry were made by comparing the spectra obtained with examples of spectra from the literature.

2.1.3 Electron Spin Resonance Spectra

The electron spin resonance spectra were recorded on a Japan Electron Optics Limited (JEOL) JES-PE Spectrometer operating in the x-band microwave region at 100 KHz modulation. The microcrystalline powders, in sealed glass melting point tubes were placed in a cylindrical quartz sample tube which was placed in the sample cavity of the instrument. The cavity is a high (Q) cylindrical reflection cavity operating in the TE_{011} mode.

2.1.4 Measurement of g- values

The standard sample used was a manganese (II) salt, diluted with magnesium oxide sealed in a melting point tube.

Manganese with a nuclear spin of $I = 5/2$ gives rise to an esr spectrum of 6 sharp lines = $(2I + 1)$.

Knowing that the separation of the central two lines is 86.9 gauss and the g value of the fourth line is 1.981, the g value of the unknown sample was calculated using the equation:

$$g = \frac{g_1 \ H_1}{H + \Delta H}$$

Where: g is the g-value of the unknown sample

g_1 is the g-value of the standard peak

H is the value of the field at the unknown peak

H_1 is the value of the field at the standard peak

ΔH is the difference in field position between the unknown and standard peaks.

2.1.5 Magnetic Susceptibility Measurements

The magnetic susceptibilities were determined at room temperature using the Gouy Method.[75] The measurements were obtained using a semi-micro Stanton balance in conjunction with a water-cooled electromagnet, operating at a current of 10 amps. The powdered samples were packed into the double length uniform glass specimen tube, (chosen to reduce the diamagnetic correction applied, due to the diamagnetism of the tube) a little at a time by tapping on a hard surface several times between each addition, and each measurement (outlined in Table 2.1.5) repeated, in order to reduce the main error in this method due to packing. Care was also taken to make sure after each weighing, that the tube which was encased in a glass draught shield was suspended vertically, and that no static charge had developed between the specimen tube and draught shield.

The tube was calibrated using $HgCo(NCS)_4$ The susceptibility per gram, χ at 20° is χ_{20° = 16.44×10^{-6} cgs ($\pm$ 0.5 per cent).

The magnetic susceptibility of the sample was calculated using the equation:

$$10^6\chi = \frac{\alpha+\beta F'}{\omega}$$

Where α is a constant allowing for the displaced air.

β is the tube calibration constant determined using $HgCo(NCS)_4$

W is the weight of the specimen in g.

F′ is the force on the specimen i.e. (F - δ)

F being the observed force, δ being the force on the tube in mg.

An example of the calculation can be found in (75).

Once the gram susceptibility is known, the molar susceptibility can be calculated, the diamagnetic correction for the ligands obtained using estimated values [75] and the effective magnetic moment calculated using the equation:

$$\mu_{eff} = 2{\cdot}83\sqrt{\chi'_M T}$$

The variation of magnetic susceptibility with temperature was obtained for one sample displaying low magnetic moment , outside the range 1.72 - 2.0 BM.

Table 2.1.5

Magnetic Susceptibility Measurements

Weight of empty Gouy tube, magnet 'off'	=
Weight of empty Gouy tube, magnet 'on'	=
Temperature	=
Weight of Gouy tube filled with water	=
Weight of Gouy tube filled with sample magnet 'off'	=
Weight of Gouy tube filled with sample magnet 'on'	=

2.2 Infrared Spectroscopy

The infrared spectra were recorded on a Perkin Elmer 599B spectrophotometer in the region 4000 - 200cm^{-1}. The finely ground solids were examined as KBr discs and then checked as mulls in Nujol between CsI plates, in order to exclude the possibility of halide exchange between the complex and KBr disc which can occur in the pressing of the KBr disc.

In the region 400 - 200cm^{-1} the solids were examined in polyethylene media by mixing the finely gound powders with polyethylene powder and pressing into discs. Polyethylene is a useful window material since a thin film absorbs little radiation below 700cm^{-1}.

When the spectra in this far infrared region were being recorded the instrument was purged with nitrogen, because although this region contains the vibrations of bonds between transition metal-ions and their ligands, it also contains bonds of low force constant and thus carbon dioxide and water especially absorb strongly in this region. Nitrogen does not absorb strongly in the infrared region and is a suitable gas for this purpose. Expanded spectra were also recorded in this region to aid in the assignment of bands.

Complexes were prepared using ^{63}Cu and ^{65}Cu to give definitive band assignments in this low frequency region.

Isotopic shifts were measured from multiple scans over metal isotope bands using a wavenumber marker. In all cases the shift values were reproducible to ~ 0.2 cm^{-1} in the 400 - 200 cm^{-1} region.

Infrared spectra were obtained for the free ligands, the hydrochloride or sulphate where applicable and also for the complexes.

The characteristic group frequencies of the amine and hydroxyl groups, were assigned in the spectra of the ligands and salts, and by comparing these spectra with those of the respective complexes, and noting the band shifts, conclusions were made on the bonds formed between the donor atom or atoms of the ligand, and the copper atom/ion.

2.3 Conductivity Measurements

Solution conductivities were measured at room temperature using a Mullard bridge with a "magic eye" balanced detector in conjuction with a dipping cell fitted with platinum electrodes of area 1 cm^2 separated by 1 cm.

The solvent acetonitrile was dried over NaOH and distilled.

2.4 Measurement of equilibrium vapour pressures

This was carried out using the designed apparatus illustrated in Figure 2.4 in a thermostatted water bath.

The solids were placed in bulb A, the column filled with mercury and the apparatus evacuated on the vacuum line and sealed off. In the case of the liquids before sealing under vacuum, d-amphetamine and d-methylamphetamine were degassed by freezing and thawing.

The vapour pressure was determined by measuring the difference between the heights of the mercury columns once equilibrium had been reached at temperatures ranging from room temperature to 77°C. Wide columns were chosen to avoid capillary effects of the mercury meniscus which is a source of error in narrow capillary tubes.

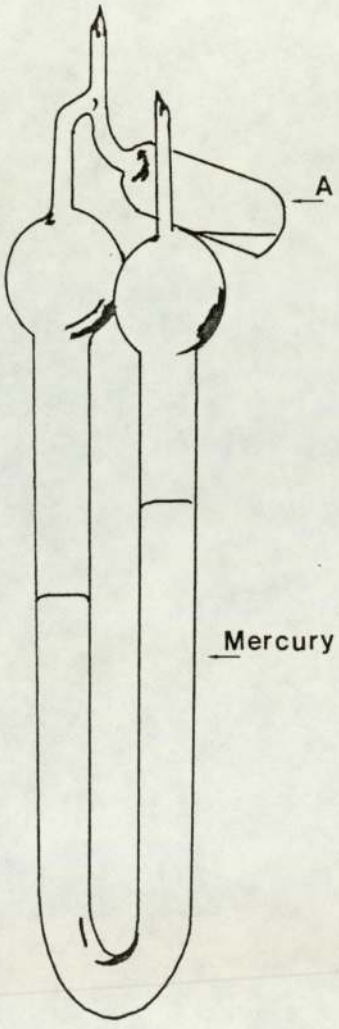


Figure 2.4

2.5 Correction for the expansion of mercury with increasing temperature

Knowing that the cubic expansivity, γ of a substance is defined by:

$$\gamma = \frac{\Delta V}{Vo\ \Delta\theta}$$

Where V is the change in volume in m^3

Vo is the initial volume in m^3

θ is the temperature in K

For the column of mercury

$$\gamma = \frac{(h_2 - h_1)}{h_1(T_2 - T_1)}$$

Where h_1 is the initial height of mercury in mm

h_2 is the final height of mercury after expansion

T_1 is the initial temperature at h_1 in K

T_2 is the final temperature at h_2

The final height, h_1 of the mercury column is given by:

$$h_1 + h_1 (T_2 - T_1)$$

Using $\gamma = 1.82 \times 10^{-4}\ K^{-1}$ and applying this equation to the results obtained, the expansion of the volume of mercury was so small that it could be taken to be neglible and this correction was ignored.

2.6 Analytical Methods

2.6.1 Elemental Analysis

The carbon, hydrogen and nitrogen content of the compounds, was determined by micro-analytical techniques carried out in the micro analytical laboratories in the Chemistry Department of Aston University using a Perkin Elmer 240B Elemental Analyser. The chlorine and sulphur content of the compounds was estimated volumetrically by the Oxygen Flask Method.

2.6.2 Copper Analysis

Copper was determined by two methods 1) Atomic Absorption spectroscopy in which the accurate working range is 2—8 $\mu g cm^{-3}$ copper. The complexes were dissolved in a solution of 20% aqueous ethanol. A standard solution of 100 $\mu g\ cm^{-3}$ coppper was prepared initially using $CuCl_2 . 2H_2O$ in 20% aqueous ethanol, from which solutions of 1-5 $\mu g cm^{-3}$ were prepared for the calibration curve. 2) Titration with the disodium salt of ethylenediaminetetra-acetic acid E.D.T.A. following the general method outlined in reference (76). A 0.025M solution of E.D.T.A. prepared by dissolving 9.3063g in water and diluting to 1 litre in a volumetric flask was employed.

Fast Sulphon Black F (the sodium salt of 1-hydroxy-8-(2-hydroxynapthylazo) -2- (sulphonaphthylazo)-3, 6- disulphonic acid) which is specific with copper (II) in ammoniacal solution was used as an indicator. Figure 2.6. At the end point the colour change is from magenta or pale blue to bright green.

0.5g was dissolved in 100 ml of water.

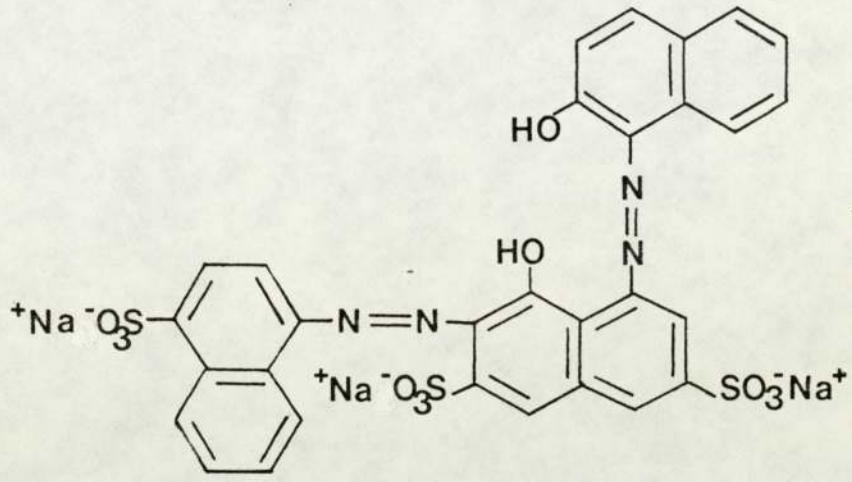


Figure 2.6

The solution was buffered using ammonia solution

1 ml of 0.025M E.D.T.A. $\equiv$ 1.5885 mg of Cu.

2.6.3 Thermogravimetric Analysis

Thermogravimetric Analysis of the compounds was carried out on the Stanton Automatic Thermo-recording Balance in the temperature range room temperature to 700° in air. Analysis was also carried out on a Stanton Redcroft T.G-750 Thermogravimetric Analyser in an atmosphere of nitrogen. The heating rate employed through pyrolysis was 30 degrees per minute and the temperature range room temperature to 1000°. The instruments were checked using the pure compound calcium oxalate and also using copper (11) sulphate pentahydrate.

2.6.4 X-ray single crystal Analysis

Data were collected on a Phillips PW 1720 x-ray diffractometer using Ni filtered CuKα radiation and also on a CAD 4 Kappa diffractometer using Zr filtered MoKα radiation, on a crystal of bis(d-pseudoephedrinato)copper(II) grown from methanol and petroleum ether.

CHAPTER THREE

(i) PREPARATION AND PURIFICATION OF MATERIALS

(ii) PREPARATION OF COMPLEXES

CHAPTER THREE

3.1 Preparation and Purification of Materials

With the following exceptions reagent grade chemicals were employed without further purification and/or analysis.

Anhydrous copper (II) chloride was prepared by heating reagent grade $CuCl_2 . 2H_2O$ at 100° to constant weight.

The copper isotopes ^{65}Cu (99.69%) and ^{63}Cu (99.83%) were obtained from the stable isotope unit, A.E.R.E. Harwell.

β - phenylethylamine was dried over NaOH pellets and distilled at normal pressure. The middle fraction was used in the synthesis of the complexes.

Unless otherwise stated the alcohol/ethanol referred to throughout the experimental work was absolute alcohol B.P. 78.5°(b.p)

The petroleum ether used was either b.p. 40-60° or 60-80°.

The free bases of the hydrochlorides of d-pseudoephedrine (dψ-ephedrine), dl-phenylpropanolamine, dl - N - methylephedrine, l - phenylephrine and chlorpromazine were obtained by the addition of the required amount of NaOH in ethanol to the hydrochloride in ethanol. The resulting precipitate of NaCl, was filtered off and the volume of ethanol reduced by rotary evaporation. On cooling to below 0°, crystals of the bases were obtained.

To prepare d-methylamphetamine a similar procedure was adopted but the liquid base was purified by distillation under reduced pressure.

d and dl-amphetamine were prepared from the sulphate by neutralisation using NaOH in aqueous media, extraction with diethyl ether, drying over Na_2SO_4 and evaporation of diethyl ether. The liquid base was then distilled under reduced pressure.

Trifluoperazine was prepared from the dihydrochloride by neutralisation using NaOH in aqueous media, extraction with chloroform, drying over Na_2SO_4 and evaporation of chloroform.

3.1.1 Preparation of Copper (I) chloride

Copper (I) chloride was prepared using $CuSO_4 . 5H_2O$ and NaCl.

30g of $CuSO_4 . 5H_2O$ was dissolved in the minimum volume of water and added to 15g of NaCl dissolved in the minimum volume of water. The resulting solution was heated and reduced by bubbling SO_2 gas through it.

The white crystals were washed after rapid filtration with sulphurous acid and glacial acetic acid and dried in an evaporating dish.

3.1.2 Preparation of Isotopic $CuCl_2$

The copper isotopes ^{65}Cu(99.69%) and ^{63}Cu(99,83%) were obtained as the free metal and converted to the chloride by the following method:

Isotopic $CuCl_2$ was prepared from ^{63}Cu and ^{65}Cu foil by oxidation using chlorine which was prepared as illustrated in Figure 3.1.2 by placing

potassium permanganate in the flask fitted with a funnel and delivery tube and slowly adding concentrated hydrochloric acid in the cold in a fume cupboard. After washing twice with water the chlorine was made to pass over the copper foil which was being heated gently in concentrated hydrochloric acid.

The equation for the preparation of chlorine is as follows

$$2KMnO_4 + 16HCl \longrightarrow 2KCl + 2MnO_2 + 8H_2O + 7Cl_2$$

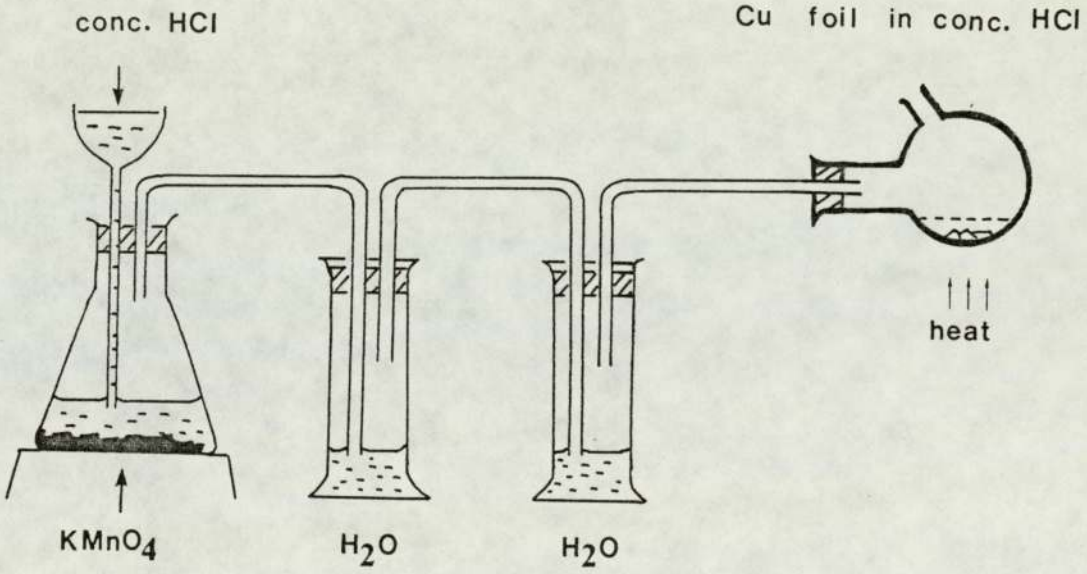


Figure 3.1.2

Evaporation of hydrochloric acid on a watch glass in an oven gave dark brown crystals of anhydrous isotopic cupric chloride which was used to prepare complexes.

3.2 Preparation of complexes

Unless otherwise stated, after preparation of the complexes in solution, the complexes were collected by suction filtration using a sintered glass funnel of appropriate size fitted to a dry filter tube or flask. They were washed two or three times with the mother liquor, then the solvent and dried in a vacuum desiccator over self-indicating silica gel until there was no colour change in the silica gel, or NaOH pellets. The basic methods used to prepare the complexes are outlined. Initially the complexes were prepared on a small scale and after establishing a successful method of preparing the complexes, whenever possible they were prepared on a scale large enough to enable characterization to be performed. All of the ratios used throughout preparation of the complexes are molar ratios.

Complexes of d-pseudoephedrine

3.2.1 Bis (d-pseudoephedrinato) copper(II), $Cu(C_{10}H_{14}NO)_2$ Method A

Hydrated copper (II) chloride (0.8524g) was dissolved in water (10 ml), and added to d-pseudoephedrine hydrochloride (2.017g), dissolved in water (10 ml). 1M NaOH (20 ml) was then added with constant stirring. A reddish-violet microcrystalline precipitate was immediately formed.

Földi et al[63] reported that by adding water (0.5 ml) to the complex (0.2g) in methanol (5 ml), warming the resulting solution and filtering and then diluting the solution with water (5 ml), they recrystallised this complex. However, by following this procedure no crystals could be obtained from the solution of the complex in methanol and water. A method of obtaining crystals of the complex which was successful on every occasion was found, where the complex (1.56g) after drying was dissolved in methanol (1.5 ml) and petroleum ether (100 ml) was added. The solution left at room temperature overnight became colourless yielding reddish-violet needles (Plate 1, Figure 1). By using less petroleum ether in the recrystallisation process, hexagonal blocks grew out of solution leaving the petroleum ether colourless.

Analytical data for the complex are presented in Table 3.2.1.

By using a 4:1 ratio of d-pseudoephedrine hydrochloride (2.017 g) to hydrated copper (II) chloride (0.4262 g), and 1 M NaOH (20 ml) and following the procedure outlined above a pale violet precipitate was obtained from a colourless mother liquor. Using the same recrystallisation solvent system the same complex as above was obtained: $Cu(C_{10}H_{14}NO)_2$

together with needles of d-pseudoephedrine base. Separation of the base from the complex was achieved by warming the mixture of crystals in petroleum ether in which only the d-pseudoephedrine base was soluble. The complex could also be purified by washing with acetone.

Synthesizing the complex was found to be possible using hydrated copper (II) perchlorate or hydrated copper (II) sulphate.

3.2.2 Di-μ-chlorobis (d-pseudoephedrinato)copper (II) Method B

Anhydrous copper (II) chloride (0.6722 g) was dissolved in alcohol and added to d-pseudoephedrine base (1.6524 g) dissolved in alcohol with stirring. A fine turquoise precipitate was formed immediately from solution which was insoluble in all of the common organic solvents. (Plate 1 Figure 3) No solvent could be found for recrystallisation.

Analytical data for the complex are presented in Table 3.2.1.

3.2.3 $[\{Cu(C_{10}H_{15}NO)(C_{10}H_{14}NO)\}_2]Cl_2$ Method C

Anhydrous copper (II) chloride (0.3361 g) was dissolved in methanol and added to d-pseudoephedrine base (1.6524 g) dissolved in methanol. Many attempts were made to obtain a product from solution over several weeks. Crystals could be obtained by mixing the solution with petroleum ether. Two layers were formed initially as the complex was distributed between the methanol and petroleum ether. The petroleum ether was separated and more petroleum ether shaken with the methanol until all of the complex had been transferred to the petroleum ether layer, except a small liquid fraction which was turquoise blue in colour.

By allowing very slow evaporation of the petroleum ether, royal blue needles (Plate 1 Figure 2) were obtained. Slow evaporation of the petroleum ether was achieved by covering the solution in a beaker with "cling film". This technique is explained in section 3.2.4.

Analytical data for this complex are presented in Table 3.2.1.

The turquoise fraction remaining after removal of the blue complex turned out to be the complex prepared in section 3.2.2.

In several different attempts to prepare the royal blue complex the violet complex bis (d-pseudoephedrinato copper(11), that could be prepared using the hydrochloride and aqueous copper (11) chloride, aqueous copper (11) sulphate or aqueous copper (11) perchlorate in alkali media kept growing out of solution.

Table 3.2.1 Analytical Data for complexes of d-pseudoephedrine

Complex	Element	Required %	Found %	MP°C
$Cu(C_{10}H_{14}NO)_2$	C	61.3	61.6	181-182
	H	7.2	7.3	
Reddish violet	N	7.2	7.2	
	Cu	16.2	16.1	
$[Cu(C_{10}H_{14}NO)Cl]_2$	C	45.5	45.0	161-162
	H	5.3	5.5	
Turquoise blue	N	5.3	5.5	
	Cl	13.4	14.9	
	Cu	24.0	24.1	
$\left[(Cu(C_{10}H_{15}NO)(C_{10}H_{14}NO)\right]_2$	C	56.1	55.8	131-133
Cl_2	H	6.8	6.5	
	N	6.5	6.4	
Bright blue	Cl	8.3	8.5	
	Cu	14.8	14.7	

Complexes of l-ephedrine

3.2.4 Bis (l-ephedrinato) copper(II), Cu $(C_{10}H_{14}NO)_2$

The same procedure as outlined for the bis (d-pseudoephedrinato copper(II) was followed but initially only oils could be obtained, which could not be induced to crystallise. Mixing the appropriate ratio of l-ephedrine hydrochloride (2.017g) to hydrated copper (II) sulphate (1.585g) in 1M NaOH (20 ml) in an ice bath gave a violet solution. Left at room temperature for four weeks, the solution yielded small violet blocks which could then be used to induce crystallisation in similar solutions. Many solvent/solvent systems were employed in attempts to recrystallise the complex. Attempts to recrystallise this complex by previous workers gave a product in which the solvent was a part of the complex. [59,60]

After noting in a simple experiment the different evaporation rates of solvents through polyethylene cling film and after exhausting conventional methods of recrystallisation a solution of this complex in petroleum ether was left in a beaker covered with cling film at room temperature. It had been previously observed that the cling film could control the rate of evaporation and it was thought that it might be possible to recrystallise this complex using this method. This method proved to be successful and by controlling the rate of evaporation it was possible to grow crystals of various sizes. (Plate 1 Figure 6).

3.2.5 Di-μ-chlorobis(l-ephedrinato) Copper (II) $[Cu(C_{10}H_{14}NO)Cl]_2$

This complex was prepared following method B outlined in section 3.2.2 page 39 using anhydrous copper (II) chloride (0.672g) and l-ephedrine base (1.6524g) in ethanol. It was difficult to isolate the pure complex, l-ephedrine hydrochloride grew out of solution together with the complex. The complex was finally isolated in the pure state by redissolving the mixture in the mother liquor and adding methanol (2 ml). (Plate 1 Figure 7)

3.2.6 $[\{Cu(C_{10}H_{15}NO)(C_{10}H_{14}NO)\}]_2\ Cl_2 \cdot\ 2H_2O$

This complex was prepared following method C outlined in section page 3.2.3 anhydrous copper (II) chloride (0.3361g) was dissolved in methanol and added to l-ephedrine base (1.6524g) in methanol or ethanol. On leaving the solution at -15°C, bright blue octahedra grew out of solution. Once out of contact with the mother liquor, ethanol or methanol vapour the crystals became opaque. (Plate 1 Figure 5).

This complex could also be isolated using a 2:1 ratio of l-ephedrine base (1.6524g) to copper (I) chloride (0.4949g) in alcohol.

During attempts to recrystallise the violet chelate, bis-(l-ephedrine) copper (II) from toluene, the blue complex grew out of solution.

Table 3.2.4 Analytical Data for complexes of l-ephedrine

Complex		Required %	Found %	MP°C
$Cu(C_{10}H_{14}NO)_2$	C	61.3	61.8	154-156
	H	7.2	7.6	
Dark violet	N	7.2	7.4	
	Cu	16.2	16.2	
$[Cu(C_{10}H_{14}NO)Cl]_2$	C	45.5	45.6	126
	H	5.3	5.3	
Bright green	N	5.3	4.6	
	Cl	13.4	14.6	
	Cu	24.0	24.1	
$\left[\{Cu(C_{10}H_{15}NO)(C_{10}H_{14}NO)\}\right]Cl_2$ $2H_2O$	C	53.8	54.4	102-104
	H	7.0	7.0	
	N	6.3	6.1	
Bright blue	Cl	7.9	7.9	
	Cu	14.2	14.2	

Complexes of dl-phenylpropanolamine

3.2.7(i) Bis(dl-norephedrinato)copper(II)trihydrate $Cu(C_9H_{12}NO)_2.3H_2O$

3.2.7(ii) Bis(dl-norephedrinato)copper(II)methanol. $Cu(C_9H_{12}NO)_2.CH_3OH$

Hydrated copper (11) chloride (0.8524g) was dissolved in water (10 ml) and added to dl-phenylpropanolamine hydrochloride (1.877g) dissolved in water (10 ml). 1M NaOH (20 ml) was added with constant stirring. A pale lilac precipitate was immediately formed which was dried over silica gel for 3 days. It was then dissolved in hot methanol. After a few minutes violet-red needles grew out of solution. Once the needles were out of solution or out of contact with methanol or its vapour they became pale violet and opaque. (Plate 2)

If the violet-red needles were left in a small volume of mother liquor then over time they changed into blue blocks. (Plate 2 Figure 10 and Plate 4) hydrated copper (11) sulphate also gave the same products.

3.2.8 di-μ-chlorobis(dl-norephedrinato)copper(II) $Cu(C_9H_{12}NO)_2Cl_2$

Using a 2:1 ratio of dl-phenylpropanolamine base (1.5125g) to anhydrous copper (11) chloride (0.6722g) in ethanol or methanol and following method B a green microcrystalline complex was obtained, which could also be obtained using copper (1) chloride (0.4949g) and phenylpropanolamine base (1.5125g) in alcohol. Plate 1 Figure 8.

Using a 4:1 ratio of dl-phenylpropanolamine base (1.5125g) to anhydrous copper (11) chloride (0.3361g) in methanol or ethanol and following method C, blue blocks were obtained on leaving the solution at -15°C. These turned out to be the same product obtained as that produced by a change in the red-violet needles described above.

Table 3.2.7 Analytical Data for complexes of dl-phenylpropanolamine

Complex	Element	Required	Found	MP°C
$(C_9H_{12}NO)_2Cu.CH_3OH$	C	57.6	56.7	
	H	7.1	7.3	
Dark violet/red	N	7.1	6.9	
	Cu	16.0	15.9	
$(C_9H_{12}NO)_2Cu.3H_2O$	C	51.7	51.2	154-155
	H	7.2	7.3	
Bright blue	N	6.7	6.6	
	Cu	15.2	15.4	
$[(C_9H_{12}NO)CuCl]_2$	C	43.4	43.3	169-170
	H	4.9	5.1	
Olive green	N	5.6	5.6	
	Cl	14.2	15.4	
	Cu	25.5	25.2	

Complexes of dl-N-methylephedrine

3.2.9 $[(C_{11}H_{16}NO)Cu(C_{11}H_{17}NO)OH]_2\ 8H_2O$

This complex was prepared by adding hydrated copper (II) chloride (0.8524g) or hydrated copper (II) sulphate (1.2984g) dissolved in water 10 ml to dl-N-methylephedrine hydrochloride (2.157g) dissolved in water.

1M NaOH (20 ml) was added with constant stirring.

The fine violet precipitate formed was filtered, washed and dried following the standard procedure outline in section 3.2 Attempts to recrystallise this complex by previous workers gave a product which was not pure.[62,63] All of the usual solvents were employed in an attempt to recrystallise the complex and after many trials with solvent systems it was found that by dissolving the complex in a small volume of acetone and adding water, on leaving for a few days to stand in a warm place, violet needles and blocks grew out of solution leaving the mother liquor colourless. (Plate 2 Figure 11).

3.2.10 di-μ-chlorobis(dl-N-methylephedrinato)copper(II) $[Cu(C_{11}H_{16}NO)Cl]_2$

The complex was prepared using a 2:1 ratio of dl-N-methylephedrine base (1.7925g) to anhydrous copper (II) chloride (0.6722g) in ethanol. The resulting green complex was filtered, washed with alcohol and dried in a vaccum desiccator. (Plate 2 Figure 12).

Using a 4:1 ratio of the free base (1.7925g) to anhydrous copper (11) chloride (0.3361g), the same product was isolated.

Analytical data for these two complexes are presented in Table 3.2.9.

Table 3.2.9 Analytical Data for complexes of dl-N-methylephedrine

Complex	Element	Required %	Found %	MP°C
$(C_{11}H_{16}NO)Cu(C_{11}H_{17}NO)OH\ 2H_2O$	C	56.5	56.5	75
	H	7.8	7.7	
pale violet	N	6.0	5.8	
	Cu	13.6	13.3	
$[(C_{11}H_{16}NO)Cu(C_{11}H_{17}NO)OH]_2 8H_2O$	C	50.2	50.4	69-70
	H	8.0	7.7	
Dark violet	N	5.3	5.3	
	Cu	12.1	12.4	
$[(C_{11}H_{16}NO)CuCl]_2$	C	47.7	47.3	120
	H	5.8	6.2	
Bright green	N	5.0	4.6	
	Cl	12.8		
	Cu	22.9	22.4	

Complexes of l-phenylephrine

3.2.11 Bis(l-phenylephrinato)copper(II) dihydrate $Cu(C_9H_{12}NO_2).2H_2O$

Hydrated copper (II) sulphate (1.2484g) was dissolved in water (10ml) and added to l-phenylephrine hydrochloride (2.037g) dissolved in water (10 ml) 1M NaOH (30 ml) was added with constant stirring to give a violet solution. After leaving at 0° for several weeks microcrystals grew out of solution. No suitable solvent or solvent/system could be found to recrystallise the complex. (Plate 2 Figure 13).

3.2.12 di-μ- dichlorobis(l-phenylephrinato)copper (II) $(C_9H_{13}NO_2)CuCl_2$

This complex was prepared by following method (B) outlined in section 3.2.2 using anhydrous copper (II) chloride (0.6722g) and l-phenylephrine base (1.672g) in methanol (10 ml). The resulting solution yielded a green precipitate which was recrystallised by dissolving in the minimum volume of acetone and adding water (5 ml). (Plate 2 Figure 14).

By using a 4:1 ratio of l-phenylephrine base (1.672g) to anhydrous copper (II) chloride (0.3361g) in alcohol a blue solution was obtained but no product could be isolated.

Analytical data for these complexes are presented in Table 3.2.11.

Table 3.2.11. Analytical Data for complexes of l-phenylephrine

Complex	Element	Required %	Found %	MP°C
$(C_9H_{12}NO_2)_2Cu2H_2O$	C	50.0	50.0	185-186
	H	6.5	6.3	
Bright violet	N	6.5	6.3	
	Cu	14.7	14.5	
$[(C_9H_{13}NO)CuCl_2]_2$	C	35.8	36.6	168-169
	H	4.4	4.4	
Green	N	4.6	4.5	
	Cu	21.1	21.0	

Complexes of Amphetamine

3.2.14 Dichlorobis(d-amphetamine)copper(II) $(C_9H_{13}N)_2\ CuCl_2$

This complex was prepared using a 1:4 ratio of anhydrous copper (11) chloride (0.3361g) dissolved in ethanol to amphetamine (1.45 ml) in ethanol (5 ml) in an ice bath. Heat was evolved during the mixing of the solutions. The resulting solution was dark green. On leaving at -15° overnight a blue complex grew out of solution. Attempts to recrystallise this complex were unsuccessful. It was filtered and dried following the standard procedure outlined. (Plate 2 Figure 16).

3.2.15 $[Cu_2C_{10}H_{17}NO\ Cl_2]_2$

This complex was prepared in methanol using a 1:2 ratio of anhydrous copper (11) chloride (0.6722g) to amphetamine (1.45 ml). Heat was evolved during mixing and an oil was formed. After several days at -15° a bright green precipitate was formed which was filtered washed with methanol and dried following the standard procedure.

Analytical data for these complexes are presented in Table 3.2.14.

Table 3.2.14 Analytical Data for complexes of dl and d-amphetamine

Complex	Element	Required	Found	MP°C
$(C_9H_{13}N)_2CuCl_2$	C	53.4	53.7	137-140
	H	6.5	6.6	
Bright blue	N	6.9	6.6	
	Cl	17.5	16.6	
	Cu	15.7	15.5	
$(C_9H_{13}N)_2CuCl_2$	C	53.4	52.9	138
	H	6.5	6.4	
Bright blue	N	6.9	7.0	
	Cl	17.5	16.9	
	Cu	15.7	15.8	
$[Cu_2C_{10}H_{17}NO\ Cl_2]_2$	C	31.3	30.9	149-153
	H	9.2	4.6	
Green	N	3.65	3.7	
	Cu	33.1	33.6	

Complexes of Methylamphetamine

3.2.16 Dichlorobis(d-N,α-dimethylphenylethylamine)copper(II) $(C_{10}H_{15}N)_2Cu\ Cl_2$

This complex was prepared using a 1:4 ratio of anhydrous copper (11) chloride (0.6722g) to methylamphetamine (3.2 ml) in ethanol (10 ml). The dark green solution resulting from the addition of the metal solution to the methylamphetamine solution was left at -15° overnight yielded a bright purple complex, which was unstable. If filtered slowly or if left opened to the atmosphere it turned green. It was found that by rapid filtration and exclusion of air a dry complex could be isolated that was quite stable in the absence of solvent. The complex was dried over silica gel in a vacuum desiccator.(Plate 2 Figure 15).

3.2.17 Di-μ-dichlorobis(d-N,α-dimethylphenylethylamine)copper(II) $[(C_{10}H_{15}N)CuCl_2]_2$

By using a 1:2 ratio of anhydrous copper (11) chloride (0.3361g) to methylamphetamine (3.2 ml) in methanol a green complex was isolated after leaving the solution at -15° for several days. The complex was collected and dried following the standard procedure outlined.

Analytical data for these complexes are presented in Table 3.2.16.

Table 3.2.16 Analytical Data for complexes of d-methylamphetamine

Complex	Element	Required %	Found %	MP°C
$(C_{10}H_{15}N)_2CuCl_2$	C	55.5	54.9	94
	H	7.0	6.9	
Bright violet	N	6.5	6.2	
	Cl	16.3		
	Cu	14.7	14.7	
$(C_{10}H_{15}N)CuCl_2$	C	42.4	42.5	80
	H	5.3	6.1	
Green	N	4.9	4.5	
	Cl			
	Cu	22.4	22.2	

Complexes of β-phenylethylamine

The preparation of complexes and salts of β-phenylethylamine with copper (11) chloride has been described by Watt and Durney [74]. Throughout the synthesis of these complexes they used an 80:20 mixture of ethanol and triethylorthoformate as the reaction medium and nitromethane as a recrystallisation solvent.

In the preparation of the complexes described below methanol or ethanol were used as the solvents.

3.2.18 Dichlorobis(β-phenylethylamine)copper(II) $Cu(C_8H_{11}N)_2Cl_2$

Following method (C) outlined in section 3.2.3. The addition of copper (11) chloride (1.344g) dissolved in ethanol (5 ml) to β-phenylethylamine (5 ml) dissolved in ethanol (5 ml) gave a turquoise microcrystalline complex. The complex grew out of solution after a few seconds at room temperature. It was found that if the complex was washed with ethanol or methanol it decomposed to give a different complex that was green in colour. Therefore the complex was filtered immediately and dried. The filtrate was left a -15°C for three days. Royal blue needles (Plate 3 Figure 17) grew out of solution which were filtered and washed with the mother liquor only. Washing in alcohol resulted in the complex changing to a green complex. See Figure 3.2.18.

The complex was analysed as $Cu(C_8H_{11}N)_4Cl_2$. Dichlorotetrakis(β-phenylethylamine)copper(II).

If this royal blue complex was left in a sealed container under nitrogen it was stable. If however, it was sealed in the presence of air after time

it decomposed giving a complex analysing as $Cu(c_8H_{11}N)_3Cl_2$ showing that it had lost one mole of β-phenylethylamine.

Analytical data for these complexes are presented in Table 3.2.18.

3.2.19 $Cu_2C_{18}H_{26}N_2Cl_3$, $Cu_2C_{17}H_{24}Cl_3$ and $Cu_2C_{16}H_{22}N_2Cl_3$

Using a 2:1 ratio of β-phenylethylamine (2.5 mls) to anhydrous copper (11) chloride (0.6722g) in ethanol gave a mixture of two complexes. One of which was the same as the complex prepared using method (C) i.e. $Cu(C_8H_{11}N)_2Cl_2$. The other complex was green. Washing the mixture in ethanol partly dissolved in the bright turquoise complex giving a green solution. See Figure 3.2.18. Dissolving the mixture of complexes in alcohol gave a deep turquoise green solution. After a few minutes green needles grew out of solution leaving the filtrate turquoise. These needles were filtered and collected.

After leaving the filtrate for a few more seconds more green needles grew out of solution and then the turquoise complex grew out of solution. Redissolving this mixture in the mother liquor and allowing to cool gave green needles which were filtered and collected. The filtrate which was bright turquoise subsequently yielded a turquoise complex of composition $(C_8H_{11}N)_2CuCl_2$.

If however, the mixture was not dissolved in the mother liquor but in methanol by heating, then brown and green needles could be isolated (Plate 3. Figs.19 and 20).

Analytical data for these complexes are presented in Table 3.2.18.

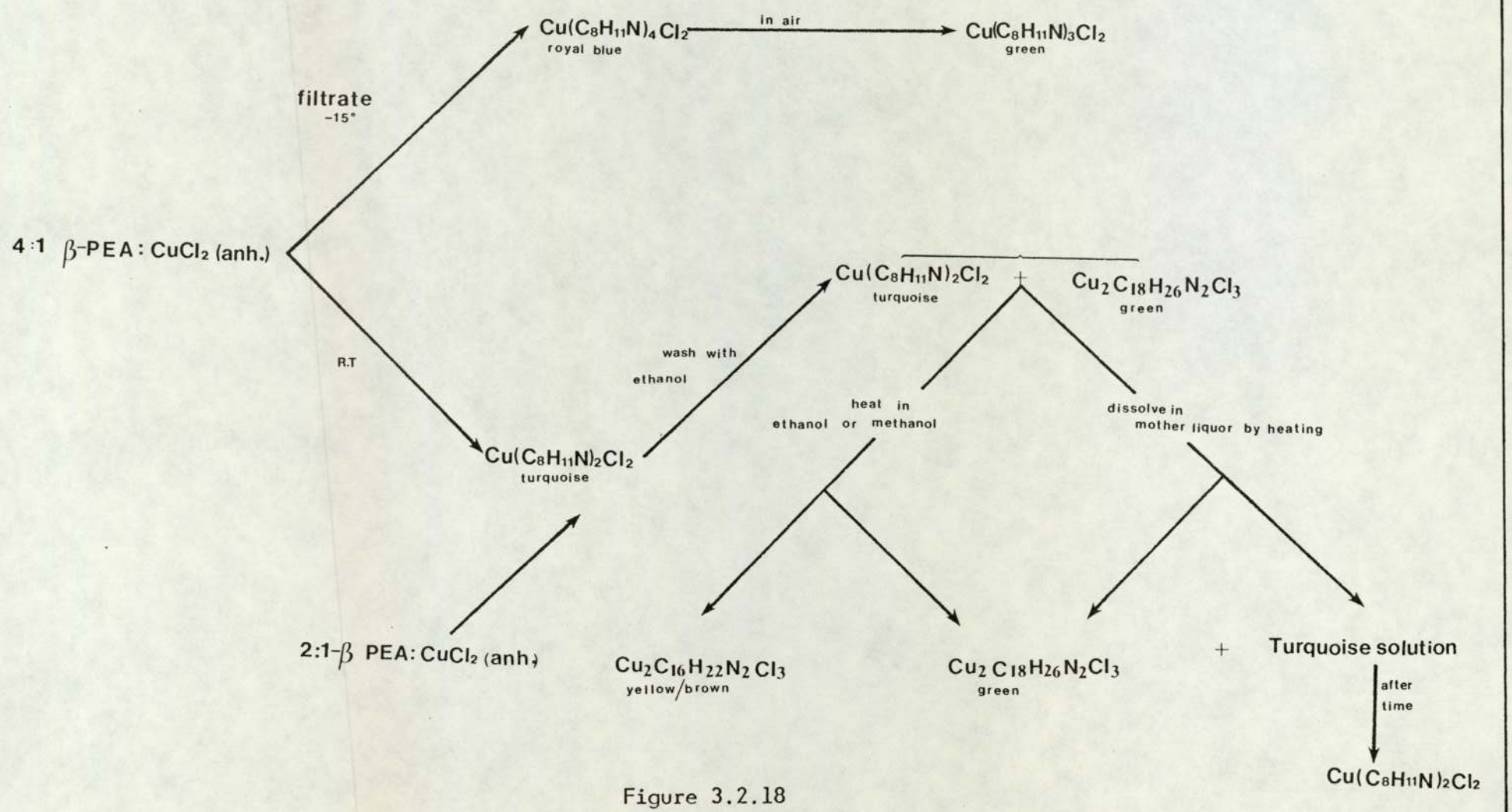

4:1 β-PEA : CuCl2 (anh.)
filtrate
-15°
Cu(C8H11N)4Cl2
royal blue
in air
Cu(C8H11N)3Cl2
green
R.T
Cu(C8H11N)2Cl2
turquoise
wash with
ethanol
Cu(C8H11N)2Cl2
turquoise
+
Cu2C18H26N2Cl3
green
heat in
ethanol or methanol
dissolve in
mother liquor by heating
2:1-β PEA: CuCl2 (anh.)
Cu2C16H22N2Cl3
yellow/brown
Cu2C18H26N2Cl3
green
+
Turquoise solution
after
time
Cu(C8H11N)2Cl2

Figure 3.2.18

Table 3.2.18 Analytical Data for complexes of β-phenylethylamine

COMPLEX		Required %	Found %	MP°C
$Cu\ (C_8H_{11}N)_4Cl_2$	C	62.1	62.3	95-96
	H	7.2	7.5	
Bright blue	N	9.0	8.8	
	Cl	11.5	11.9	
	Cu	10.3	10.3	
$Cu(C_8H_{11}N)_2Cl_2$	C	51.0	51.2	141-143
	H	5.9	6.2	
Turquoise	N	7.4	7.3	
	Cl	18.8	19.3	
	Cu	16.9	16.7	
$Cu(C_8H_{11}N)_3Cl_2$	C	57.9	57.9	
	H	6.7	6.6	
Green	N	8.4	8.0	
	Cl	14.2	12.8	
	Cu	12.8	12.8	
$Cu_2C_{18}H_{26}N_2Cl_3$	C	43.0	43.0	>250
	H	5.0	5.1	
Green	N	5.6	6.0	
	Cl	21.2	20.3	
	Cu	25.3	25.5	
$Cu_2C_{17}H_{24}N_2Cl_3$	C	41.7	41.7	>250
	H	4.9	4.8	
Green	N	5.7	6.0	
	Cl	21.7	21.5	
	Cu	25.9	25.9	
	C	40.5	40.1	
	H	4.5	4.6	179-180
$Cu_2C_{16}H_{22}N_2Cl_3$	N	5.9	5.9	
	Cl	22.4	21.5	
yellow/brown	Cu	26.8	26.3	

3 2.19(c) Dichlorobis (dl-α-phenylethylamine)copper(II) $Cu(C_8H_{11}N)Cl_2$

Following method (c) outlined in section 3.2.3, the addition of copper(II) chloride (1.344g) dissolved in ethanol (5ml) to α-phenylethylamine (5ml) dissolved in ethanol (5ml) gave a turquoise microcrystalline complex.

Plate 3 Figure 21. The complex was dried following the standard procedure.

Analytical data for this complex are present in Table 3.2.19(c).

Table 3.2.19(c) Analytical Data for complex of Dl-α-phenylethylamine

	Element	Required %	Found %	MP°C
$Cu(C_8H_{11}N)_2Cl_2$	C	51.0	51.2	
	H	5.9	5.8	
	N	7.4	7.2	
Turquoise	Cl	18.8	18.4	
	Cu	16.9	17.3	

3.2.20a Preparation of complexes from isotopic copper (II) chloride

Bis(d-pseudophedrinato)copper(II) $Cu(C_{10}H_{14}NO)_2$

Anhydrous isotopic copper (II) chloride ($^{65}CuCl$, $^{63}CuCl$) (0.04g) was dissolved in water (0.5 ml) and d-pseudoephedrine hydrochloride (0.120g) added with shaking. IM NaOH was added dropwise with a pipette until the solution turned violet in colour. Within a few minutes a fine microcrystalline precipitate was formed which was filtered. After standing for some time the mother liquor yielded violet needles which were collected and dried following the procedure outlined in section 3.2.1 page

Di-μ- chlorobis(d-pseudophedrinato)copper(II) $[Cu(C_{10}H_{14}NO)Cl]_2$

Anhydrous isotopic copper (II) chloride (0.04g) was dissolved in alcohol (1 ml) and added to d-pseudoephedrine base (0.098g) dissolved in alcohol (1 ml).

The resulting turquoise solution was left at -15° for two days and then dried following the standard procedure.

Dichlorobisamphetamine copper (II) $Cu\ (C_9H_{13}N)_2\ Cl_2$

Anhydrous isotopic copper (II) chloride (0.04g) was dissolved in alcohol (1 ml) and added to d-amphetamine (0.080g) dissolved in alcohol (1 ml).

The resulting dark solution was left at -15°C for 24 hours, and the blue compound formed, filtered, collected and dried over silica gel.

3.2.20 b Copper (II) doped complexes

In an attempt to obtain esr spectra of the complexes with fine structure attempts to prepare dilute crystals of copper (II) -doped zinc (II) complexes with selected ligands were made. At first the copper doped systems were prepared by mixing together solutions in ethanol or methanol of 20%, 25% or 33% copper (II) chloride with the appropriate base dissolved in methanol or ethanol in a 4:1 molar or 2:1 molar ratio and adding this to a solution in ethanol of 80%, 75% or 67% zinc (II) chloride respectively with the same base dissolved in ethanol or methanol.

Method i) No copper-doped complexes could be isolated with any of the ligands except l-ephedrine. This complex was prepared using a 4:1 molar ratio of l-ephedrine base (1.6524g) dissolved in ethanol to anhydrous 25% cooper (II) chloride (0.084g) and 75% zinc (II) chloride (0.2555g) dissolved in ethanol. After leaving the resultant royal blue solution at -15°C for six days clusters of royal blue needles grew out of solution.

Analytical data for this complex are presented in Table 3.2.20b

Using a copper (II) concentration of 20% and zinc (II) concentration of 80% and following the procedure outlined above, royal blue clusters of needles grew out of solution.

Analytical data for this complex are presented in Table 3.2.20

Method ii) l-ephedrine base (0.826g) was dissolved in ethanol (5 ml) and added to copper (II) chloride (0.084g) dissolved in ethanol (5 ml). This solution was then added to a solution of l-ephedrine base (0.8262g) and zinc (II) chloride (0.2555g) in ethanol (10 ml). After leaving for six days at -15° clusters of royal blue needles grew out of solution.

When difficulties were encountered in isolating the copper doped complexes cadmium (II) chloride was used instead of zinc (II) chloride. The same procedure was adhered to as outlined above. No complexes could be isolated with any of the ligands including ephedrine.

When method ii) also failed to give complexes using cadmium (ll) chloride, even with l-ephedrine then attempts to prepare complexes with zinc (II) chloride and cadmium (II) chloride in the absence of copper were made following the methods that gave successful copper complexes.

No complexes could be isolated using Cd(II) or Zn(II) with any of the ligands even l-ephedrine. Thus these ligands did not appear to have any affinity for Zn(II) or Cd(II). In fact when d-ψ-ephedrine was used as a ligand, what was initially thought to be a complex turned out to be the d-ψ-ephedrine base.

Table 3.2.20(b) Analytical Data for copper(II)-doped zinc(II) complexes

	$CuZnC_{20}H_{30}N_2O_4Cl_2$ Royal blue		
Element	Required %	Found %	MP°C
C	42.9	43.2	165-166
H	5.4	5.4	
N	4.99	4.6	

Complexes of Chlorpromazine

3.2.21 $Cu_2C_{34}H_{38}N_4Cl_5S_2$

Using a 2:1 ratio or 1:1 ratio of chlorpromazine base (6.362g) or (3.181g) to anhydrous copper (II) chloride (1.344g) dissolved in alcohol (20 ml) in an ice bath the same complex was obtained. A bright orange precipitate was formed immediately on the addition of the metal solution to the chlorpromazine solution which was filtered rapidly in the absence of air and dried. The complex was only stable if it could be isolated rapidly. No suitable solvent/solvent system could be found to recrystallise the complex.

3.2.22 $[CuC_{17}H_{19}N_2SCl_3]_2$

Using a 2:1 ratio of chlorpromazine base (3.181g) to anhydrous copper (II) chloride (0.4949g) in acetonitrile a green complex was obtained.

Trifluoperazine complex

3.2.23

A brown/orange precipitate was formed by the addition of (4.840g) of trifluoperazine dissolved in alcohol to anhydrous copper (II) chloride (1.344g) dissolved in alcohol.

The complex was prepared and dried following the same method outlined for the complex of chlorpromazine.

Table 3.2.21 Analytical data for complexes of chlorpromazine

Complex	Element	Required %	Found	MP°C
$Cu_2C_{34}H_{38}N_4S_2Cl_5$	C	46.8	46.4	91
	H	4.4	4.5	
Orange	N	6.4	6.7	
	Cl	20.3	20.8	
$Cu\ C_{17}H_{19}N_2S\ Cl_3\ 2$	C	45.0	45.0	105
	H	4.2	4.3	
Green	N	6.2	9.4	
	Cl	23.5	18.5	

KEY TO FIGURES 1-25 OF PLATES

PLATE 1

Figure 1. Bis(d-pseudoephedrinato)copper(II)

Figure 2. $\left[\{Cu(C_{10}H_{15}NO)(C_{10}H_{14}NO)\}\right]_2Cl_2$

Figure 3. Di-μ-chlorobis(d-pseudoephedrinato)copper(II)

Figure 4. CuZn $C_{20}H_{30}N_2O_4$

Figure 5. $\left[\{Cu(C_{10}H_{15}NO)(C_{10}H_{14}NO)\}\right]_2Cl_2.2H_2O$

Figure 6. Bis(l-ephedrinato)copper(II)

Figure 7. Di-μ-chlorobis(l-ephedrinato)copper(II)

Figure 8. Di-μ-chlorobis(dl-norephedrinato)copper(II)

PLATE 2

Figure 9. Bis(dl-norephedrinato)copper(II)trihydrate

Figure 10. Bis(dl-norephedrinato)copper(II)methanol

Figure 11. $[C_{11}H_{16}NO)Cu(C_{11}H_{17}NO)OH]_2.8H_2O$

Figure 12. Di-μ-chlorobis(dl-N-methylephedrinato) copper(II)

Figure 13. Bis(l-phenylephrinato)copper(II)dihydrate

Figure 14. Di-μ-dichlorobis(l-phenylephrinato)copper(II)

Figure 15. Dichlorobis(d-N, α-dimethylphenylethylamine)copper(II)

Figure 16. Dichlorobis(d-amphetamine)copper(II)

PLATE 3

Figure 17. Dichlorotetrakis(β-phenylethylamine)copper(II)

Figure 18. Dichlorobis(β-phenylethylamine)copper(II)

Figure 19. $Cu_2H_{18}H_{26}N_2Cl_3$ and $Cu_2C_{17}H_{24}Cl_3$

Figure 20. $Cu_2C_{16}H_{22}N_2Cl_3$

Figure 21. Dichlorobis(dl-α-phenylethylamine)copper(II)

Figure 22. Dichlorotris(β-phenylethylamine)copper(II)

Figure 23. $Cu_2C_{34}H_{38}N_4S_2Cl_5$

Figure 24. Complex of Trifluoperazine

PLATE 4

Figure 25. Bis(dl-norephedrinato)copper(II)methanol

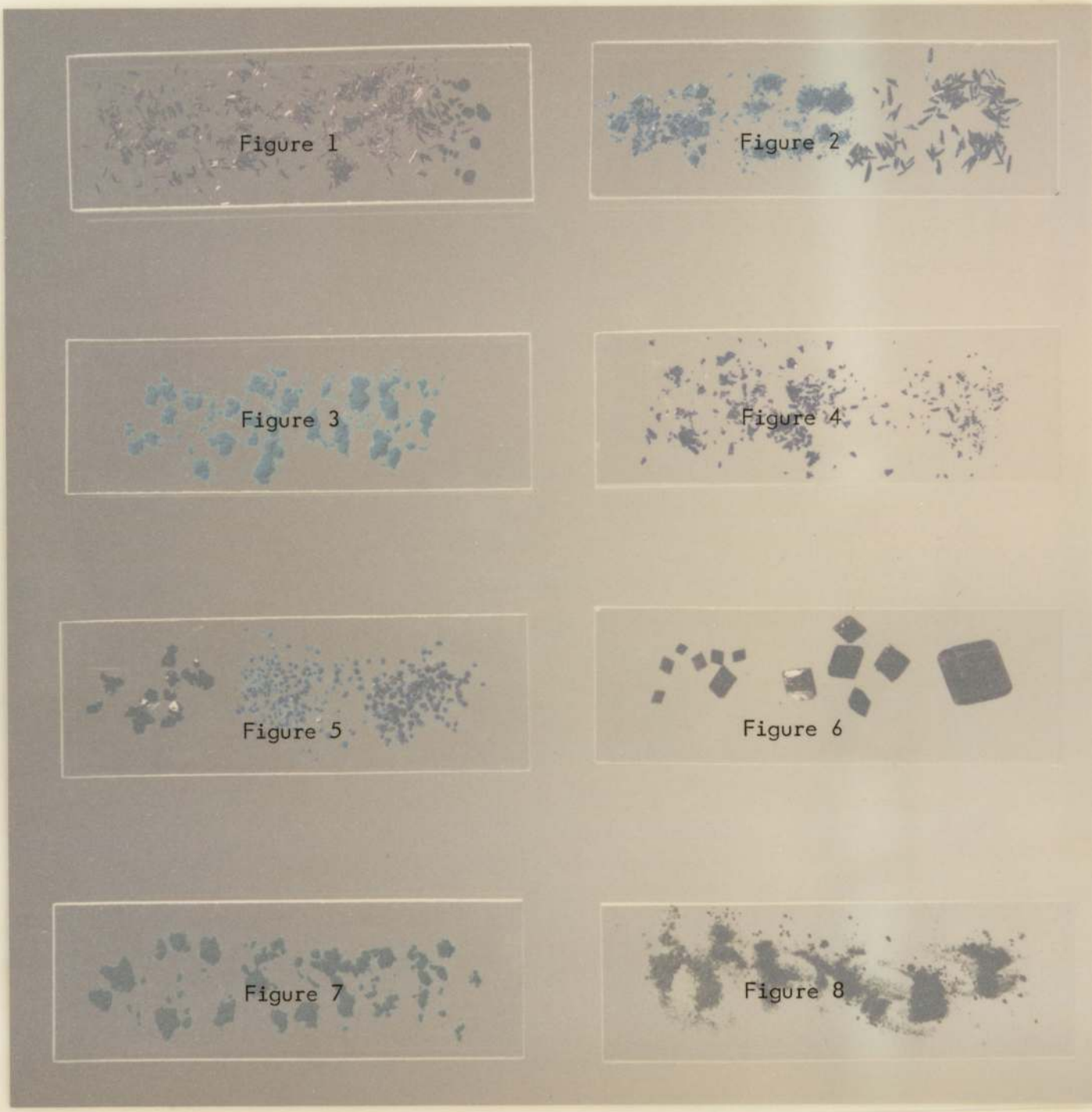


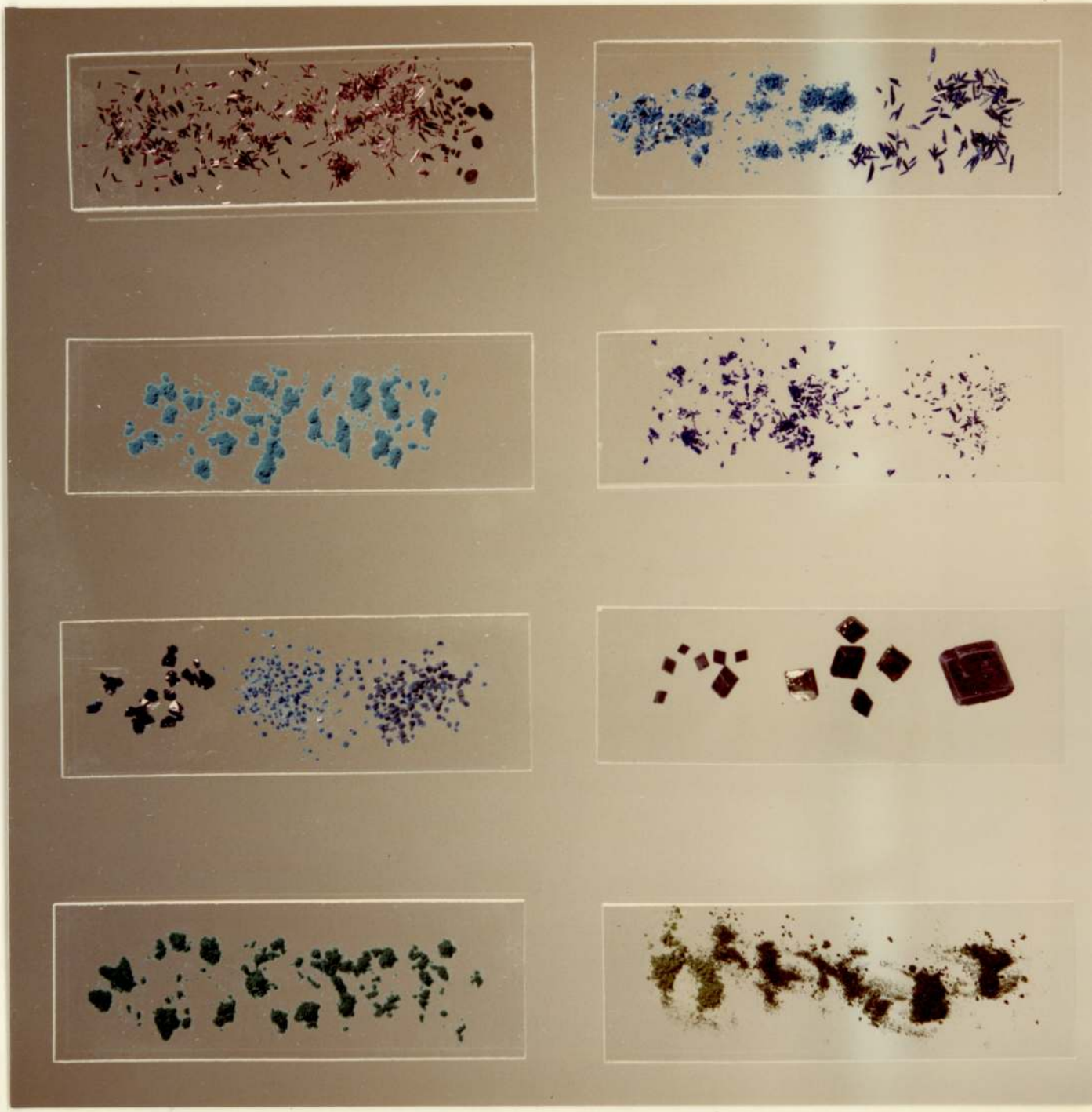
PLATE 1

Compelexes of d-pseudophedrine. Figures 1,2 and 3

Complexes of l-ephedrine. Figures 4,5,6 and 7

Complex of dl-phenylpropanolamine. Figure 8

Key to Figures page 66.



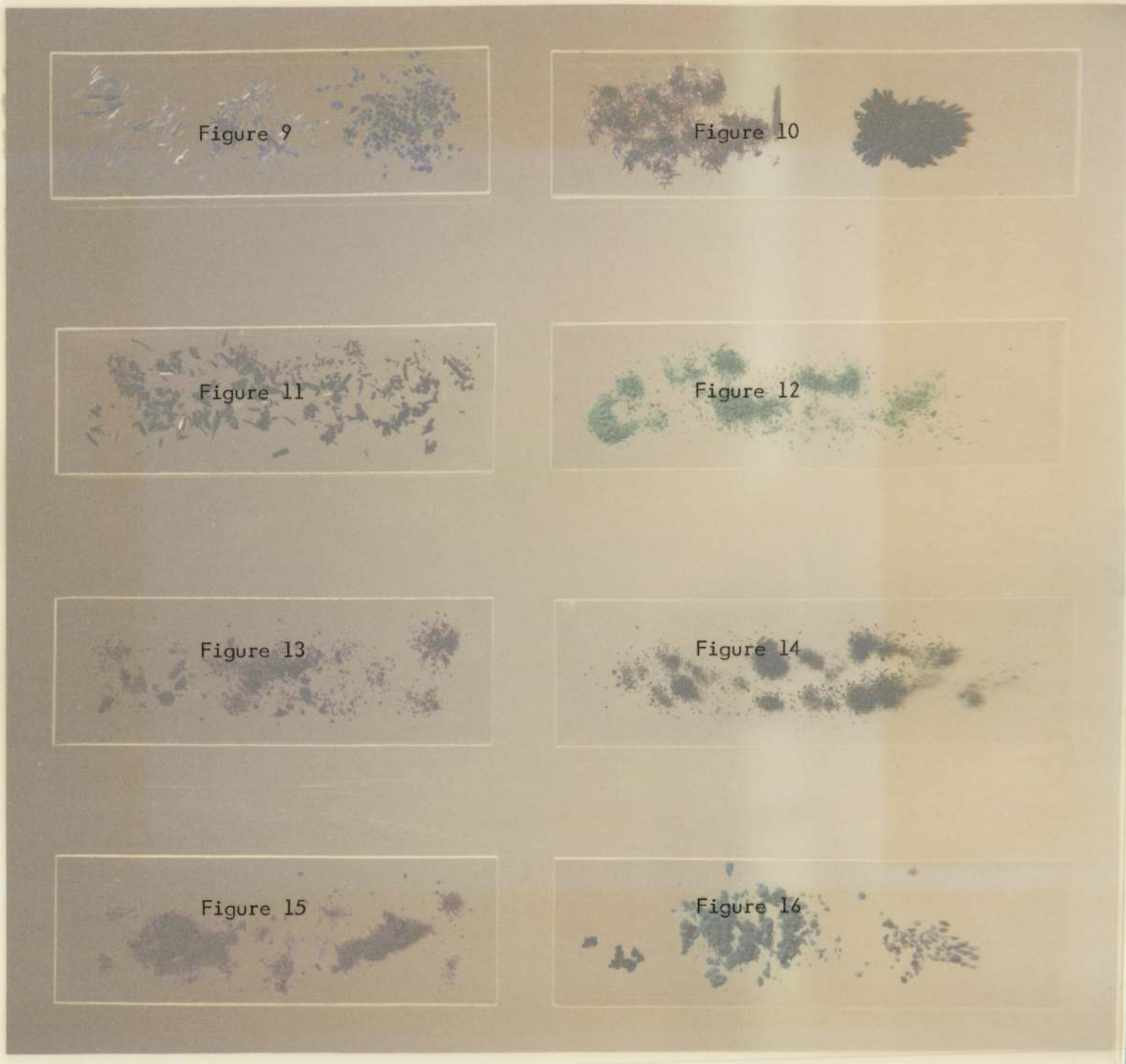
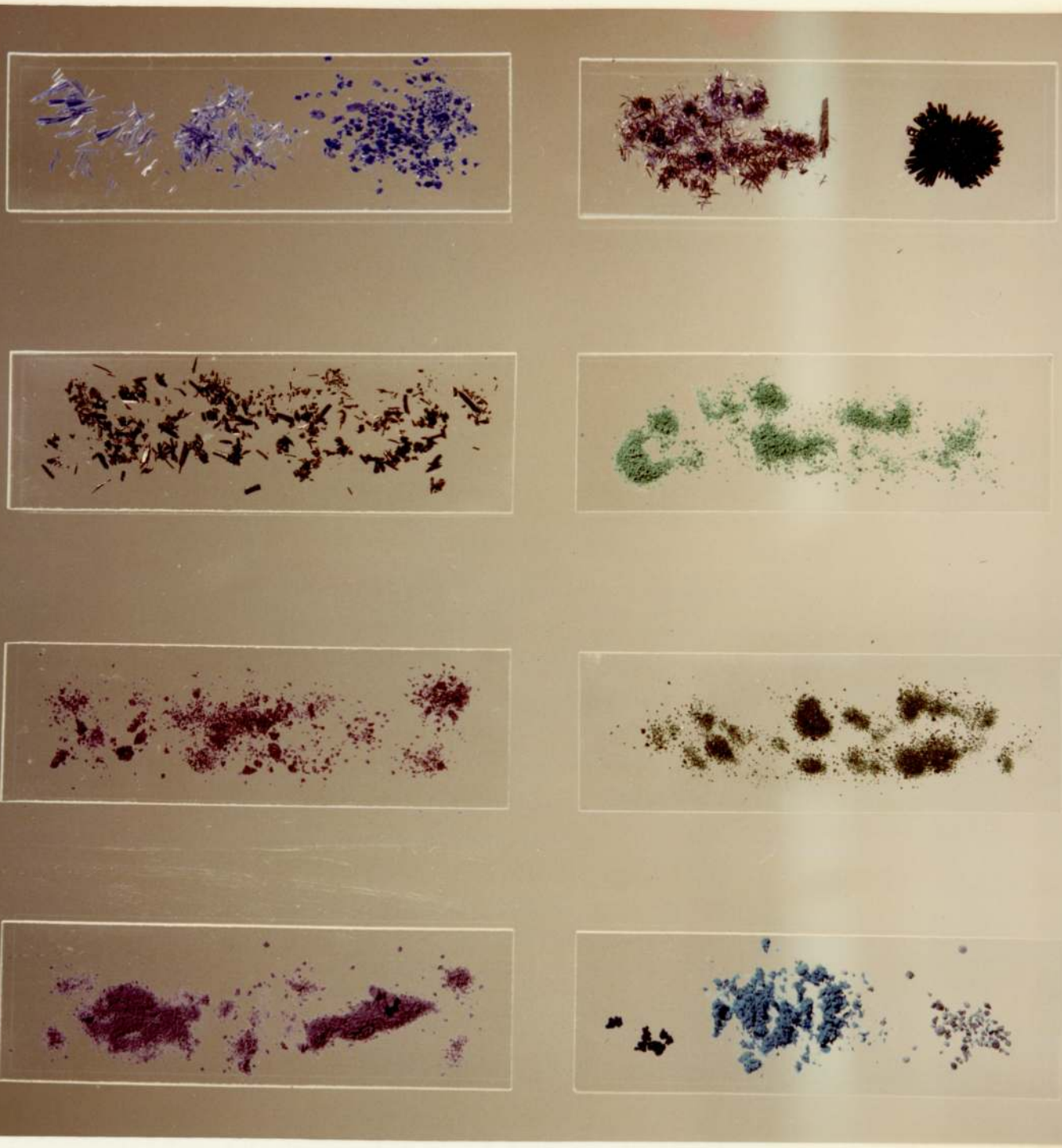


PLATE 2

Complexes of dl-phenylpropandamine.	Figures 9 and 10
Complexes of dl-N-methylephedrine.	Figures 11 and 12
Complexes of l-phenylephrine	Figures 13 and 14
Complex of d-methylamphetamine	Figure 15
Complexes of amphetamine	Figure 16

Key to Figures page 66.



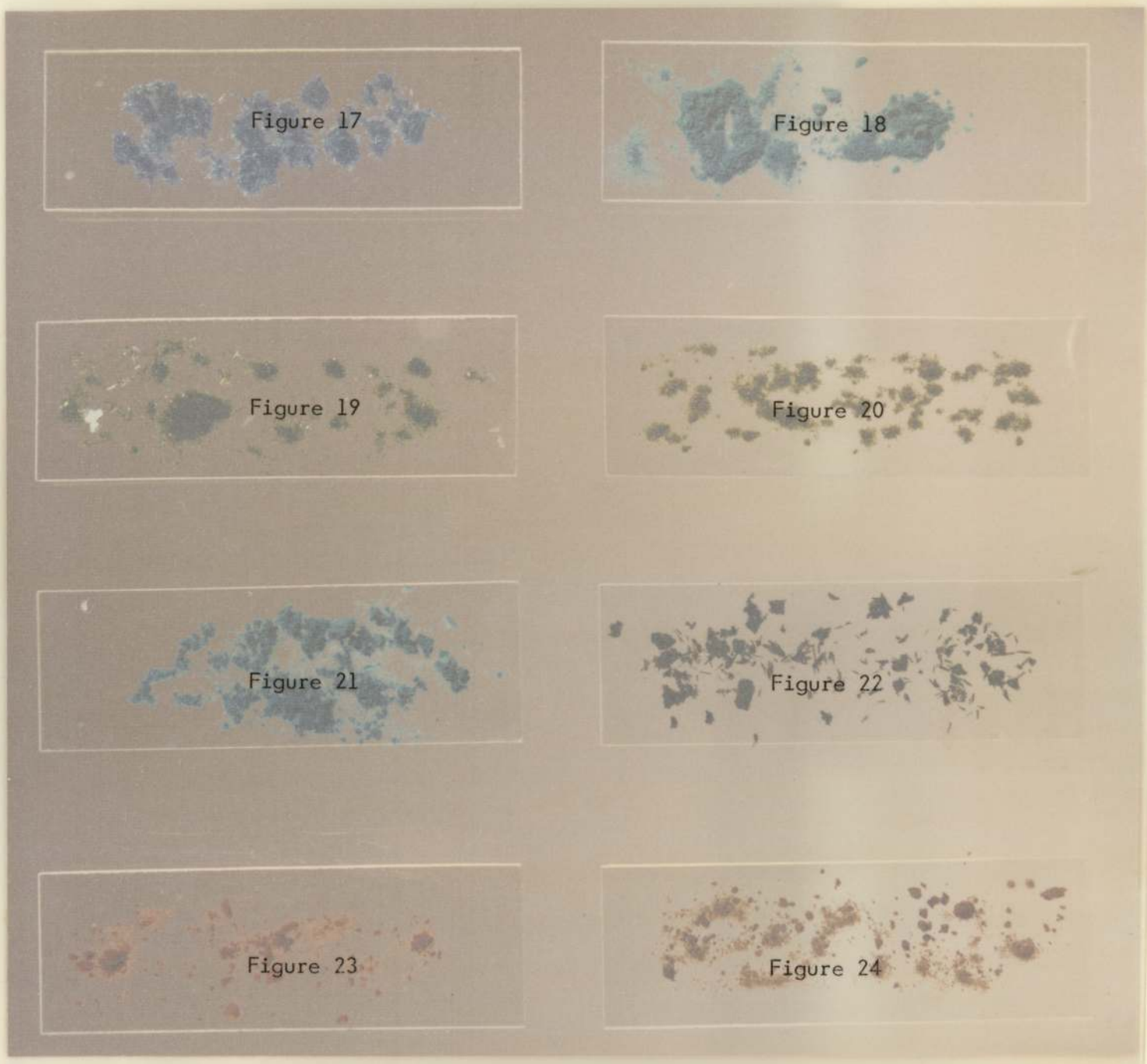


PLATE 3

Complexes of β-phenylethylamine	Figures 17,18,19,20 and 22
Complex of β-phenylethylamine	Figure 21
Complex of chlorpromazine	Figure 23
Complex of trifluoperazine	Figure 24

Key to Figure page 66.

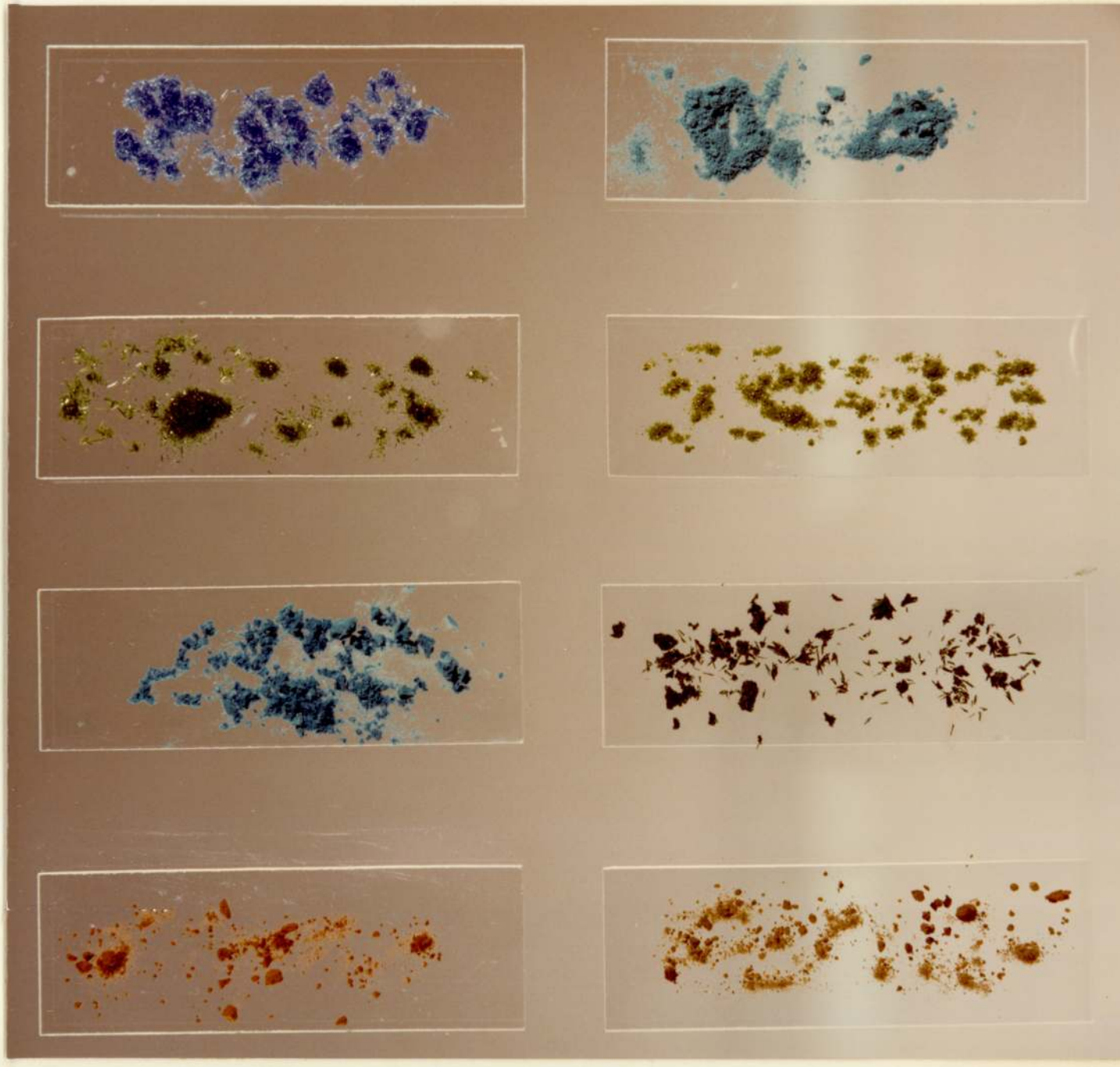


PLATE 4

Figure 25

Complex of dl-phenylpropandamine

CHAPTER FOUR

DISCUSSION

PART I

COMPLEXES OF SELECTED SYMPATHOMIMETIC AMINES

4.2.0. Complexes of d-pseudoephedrine.

INFRARED SPECTRA. The N-H stretching vibrations [78] and OH stretching vibrations are observed in the infrared region above 3000 cm^{-1}.[79] Assignment of bands in the spectrum of d-pseudoephedrine in this region gives rise to problems. However, it is known in general, that N-H bands although weaker in intensity than O-H bands are sharper[79]. The spectrum of d-pseudoephedrine in chloroform was traced to aid in the determination of the positions of the N-H and O-H bands. Table 4.2.1. The band at 3600 cm^{-1} present in the spectrum of d-pseudoephedrine in chloroform but absent in the spectrum of the pure substance is due to unassociated OH. The infrared spectrum of the pure substance, Figure 4.2.1(i) showed a fairly sharp band of medium intensity at 3222 cm^{-1} and a broad band at 3090-2700 cm^{-1}. After investigating the spectrum of d-pseudoephedrine in chloroform the former band was assigned to N-H stretching vibrations and the latter band to associated O-H stretching vibrations.

In discussing the infrared spectra of the complexes in general, the main regions investigated were (i) the region above 3000 cm^{-1}, which would give relevant information on coordination of copper to the nitrogen and oxygen atoms and (ii) the region below 600 cm^{-1} which would give information on coordination of copper to chlorine, nitrogen and oxygen atoms.

Copper-chlorine stretching vibrations have generally been assigned in the region 328-222 cm^{-1} [80]. There is a certain amount of overlap of terminal and bridging ν(Cu-Cl), and terminal ν(Cu-Cl) has been assigned above the upper limit of this region [81].

Copper-nitrogen and copper-oxygen stretching vibrations occur in the far infrared region below 600 cm^{-1} [82]

4.2.1 Bis (d-pseudophedrinato)copper(II) $(C_{10}H_{14}NO)_2Cu$ (reddish violet) The band at 3100 cm^{-1} in the spectrum of the complex is assigned to the N-H stretching vibration. On coordination to the copper atom it has been shifted by 222 cm^{-1} to lower wavenumber. This band has increased in intensity on coordination.

No bands are at present in the region above 300 cm^{-1} that can be assigned to H_2O or the free hydroxyl group. This suggests the absence of water, associated hydroxyl groups and unassociated hydroxyl groups in the complex. On the formation of the chelate ring, d -pseudophedrine becomes deprotonated losing the hydroxyl proton and the copper forms coordinate links with the oxygen and nitrogen atoms.

A possible scheme for the formation of the chelate is represented below in equation 1.

Analytical data also support the loss of a proton from d-pseudophedrine. Table 3.2.1.

Possible scheme for the formation of the chelate equation 1.

Analytical data also support the loss of a proton from d-pseudoephedrine.

Table 3.2.1.

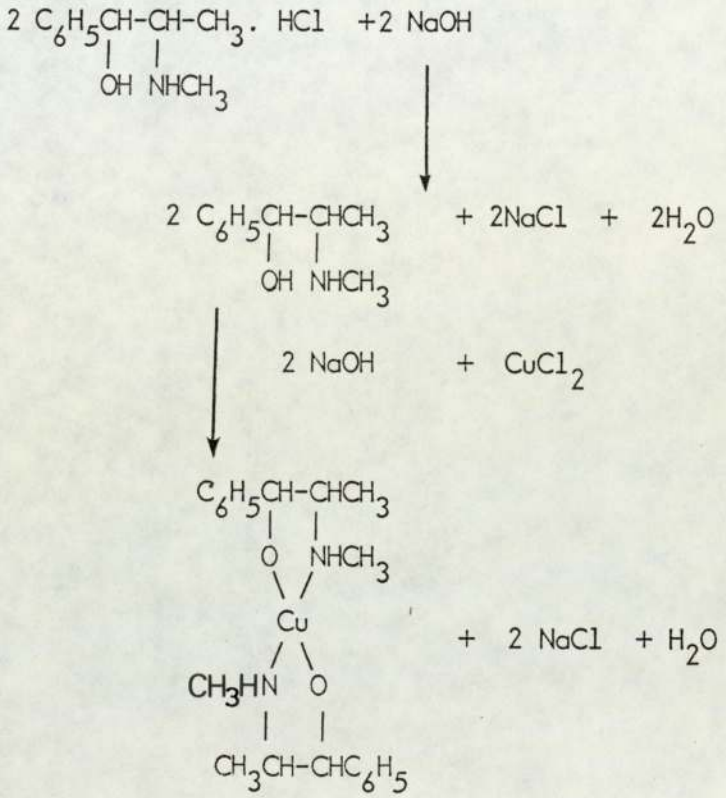


Figure 4.2.1(a)

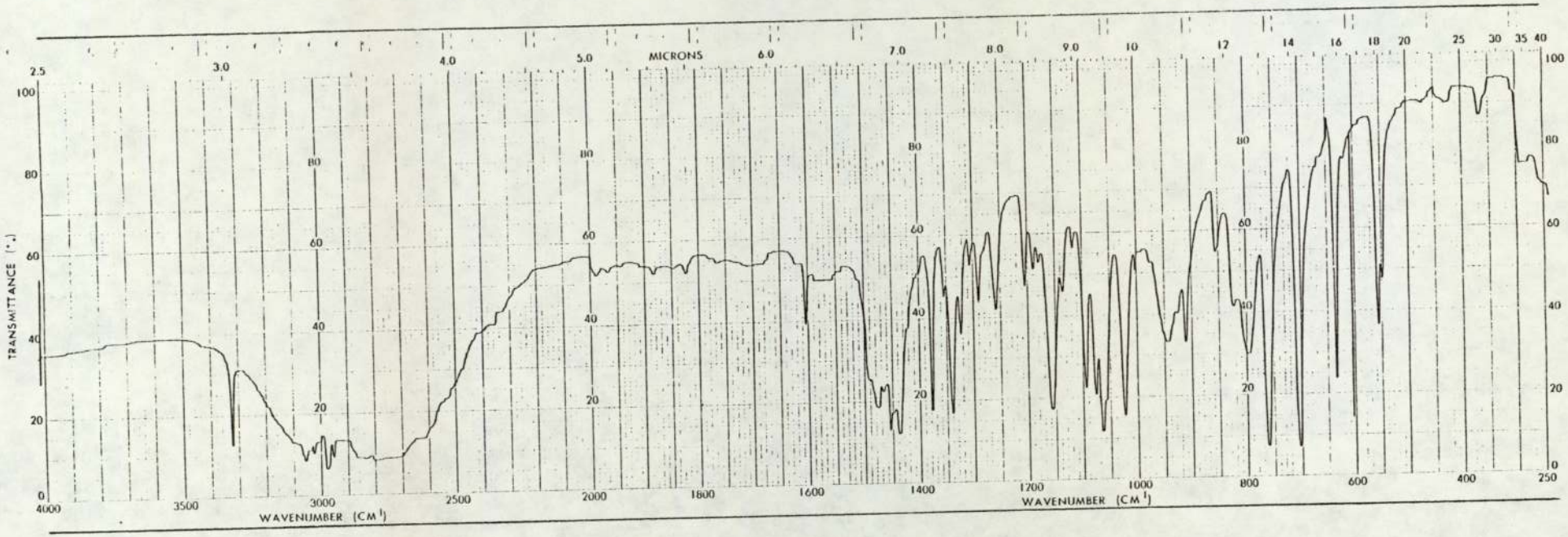


Figure 4.2.1(i)

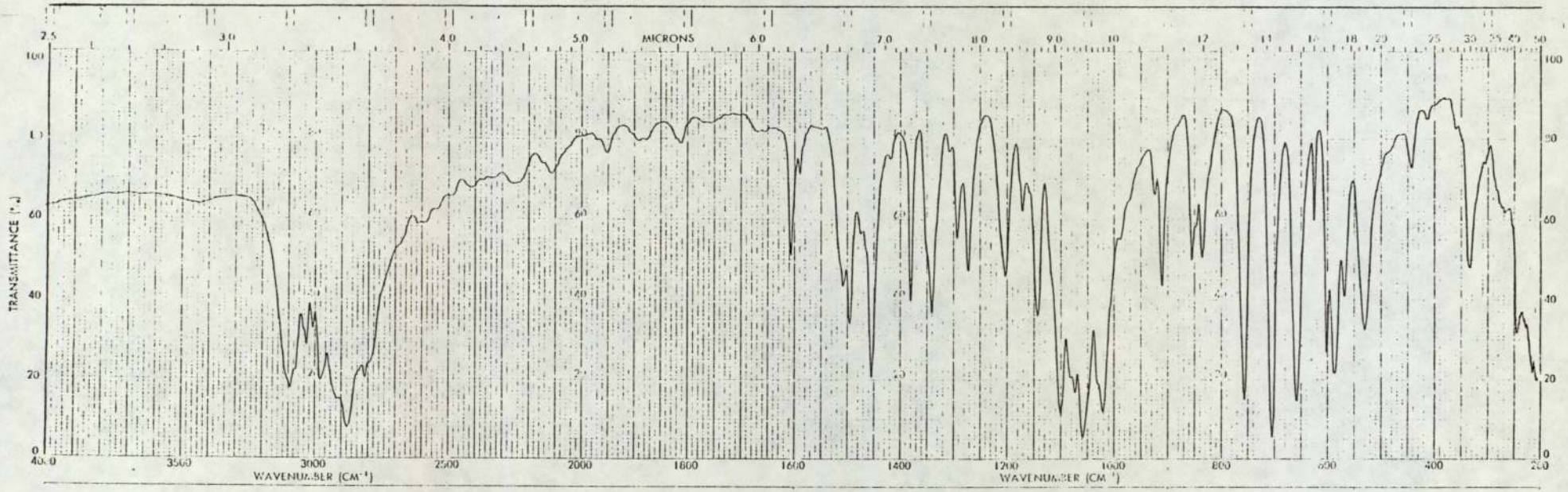


Figure 4.2.1(II)

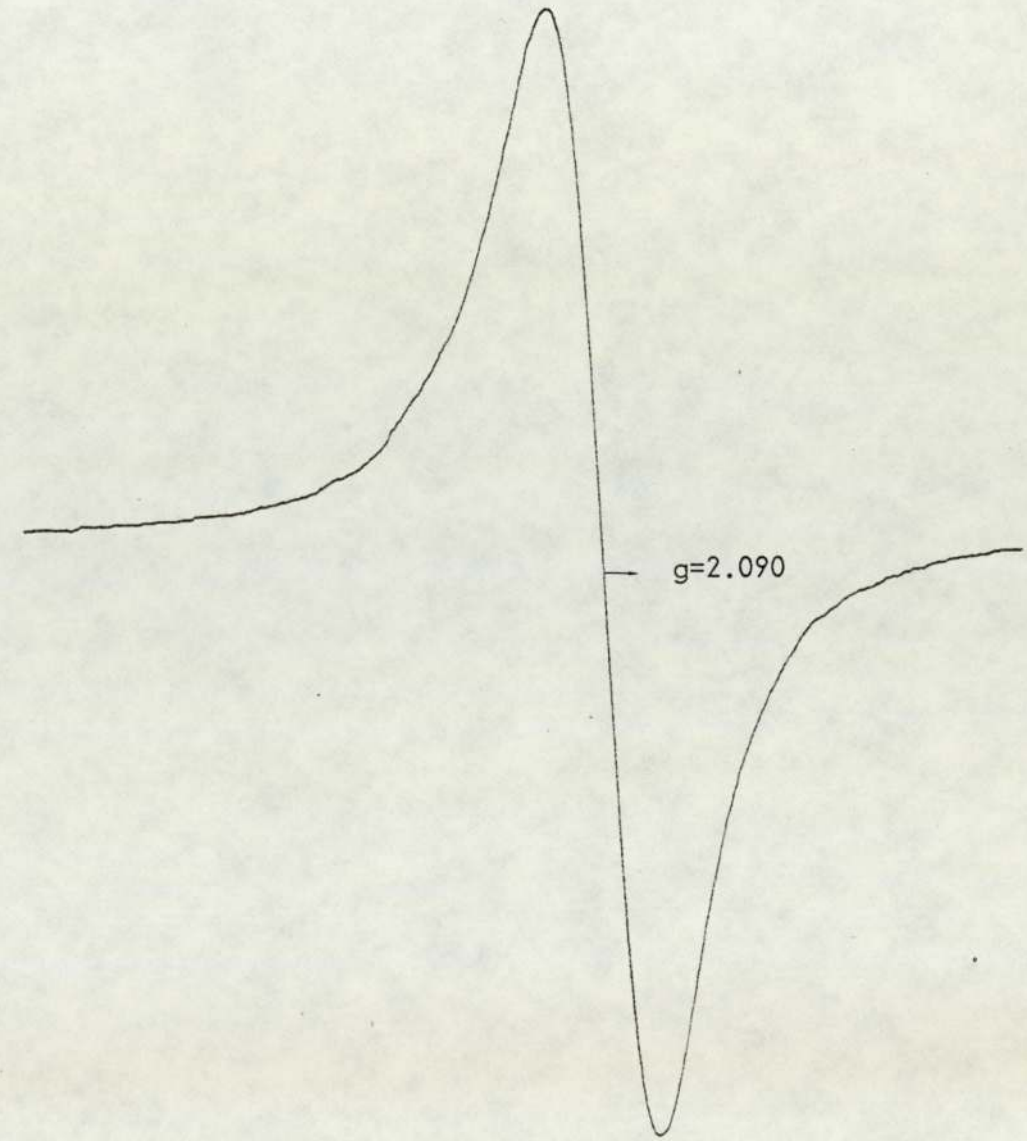


Figure 4.2.1(iii)

This complex was also synthesized using the stable isotopes of 63 Cu and 65 Cu (section 3.2.20) Table 4.2.1. shows the relative band shifts observed when using the two isotopes. In general shifts between 1-2 cm^{-1} were observed in the far infrared region where copper ligand frequencies are located. Coordination through the oxygen atom is indicated by the strong band at 336 cm^{-1} 358 cm^{-1} (shoulder). The formation of a bond between copper and nitrogen is indicated by the strong band at 530 cm^{-1}.

E.S.R SPECTRUM. The isotropic spectrum Figure 4.2.1.(iii) yielding an average g-value of 2.090. (Table 4.2.1.)was very broad and could not give any useful information on the electronic ground state present in the complex. The most common reason for observing an electronic isotropic e.s.r. spectrum is through extensive exchange coupling between grossly misaligned local copper (II) ions. [85,86].

MAGNETIC SUSCEPTIBILITY The measurement of magnetic susceptibility giving a value of μ_{eff} as 1.87 B.M. [87] does not indicate antiferromagnetic interactions. It is possible that spin-spin relaxation is occurring, where spins in the neighbouring molecules interact and the interaction being smaller than kT. influences the line shape of the spectrum. This would have been avoided if an isomorphous complex with zinc could have been prepared and the e.s.r isomorphous spectrum traced. D-pseudo-ephedrine did not appear to have any affinity for Zn(II). Copper(II) doped zinc complexes have been prepared and their e.s.r. spectra traced. These spectra show fine strucure giving more than one g-value [88].

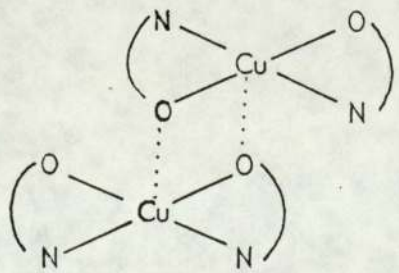
DIFFUSE REFLECTANCE SPECTRUM. The diffuse reflectance spectrum shows

bands at 20 000 and 15 500cm^{-1} (shoulder) which are consistent with an approximately trans square planar arrangement of ligands.

In general the diffuse reflectance spectrum cannot always distinguish between a square-coplanar stereochemistry, tetrahedral stereochemistry or distorted square pyramidal stereochemistry [86] and thus cannot be used as a sole criterion for determining stereochemistry.

Sometimes a simple size factor may prevent the formation of a certain stereochemistry. If large or bulky ligands are attached to the atom involved in coordination to the metal certain stereochemistries of the metal are prevented for example the approximately tetrahedral stereochemistry in the dipyromethene complex [91] is considered to arise from the presence of a bulky ligand which prevents a square-coplanar stereochemistry. Other cases of distorted tetrahedral coordination occur in some bis(salicylaldiminato)complexes where there are bulky groups attached to the coordinating atom.

It is possible that in four-coordinate complexes containing chelating ligands, dimerization may occur such that each copper atom becomes 5-coordinate. An example of this is the β-form of bis(8-quinolinolato) copper (II), represented schematically below.



With the availability of four donor atoms for each copper atom then the stereochemistries possible are square planar distorted tetrahedral and compressed tetrahedral.

The magnetic moment of 1.82 B.M. [92] suggests strong covalent bands and does not support the idea of the formation of a dimer in which the copper atoms are coordinated in the fifth position such as represented by the above structure.

Bailey et al [64] reported on a complex synthesized by the addition of ethanol to an aqueous solution of copper (II) sulphate and an excess of d-pseudoephedrine in the presence of base.

No empirical formula was given for the complex which they investigated by X-ray single crystal analysis. They reported that the stereochemistry of the complex was such that the d-pseudoephedrine ligands have a trans configuration but are coordinated around the copper tetrahedrally, the copper atom being distorted away from a planar arrangement. They concluded that the distortion away from planarity was a consequence of crystal packing requirements and of hydrogen bonding in the lattice. They reported that two hydrogen-bonded systems were present in the crystal. The non-chelated d-pseudoephedrine molecules comprised one scheme with intramolecular hydrogen bonds, whilst further intermolecular hydrogen bonding formed chains of molecules. Also in the crystal lattice they reported that present was an independent network of symmetry-related coordinated d-pseudoephedrine molecules linked through water molecules which were mutually hydrogen bonded.

In the complex synthesized in this work a different means of preparation was used. (Section 3.2.1) Elemental analytical data and infrared data did not indicate the presence of water in the complex and it is thus likely that the complex isolated by Bailey et al was not identical to the complex prepared (Section 3.2.1).

THERMOGRAVIMETRIC ANALYSIS. Initially pyrolysis of this complex and all the other complexes werecarried out in air. The results obtained did not yield any useful information and it was thought that oxidation could be taking place and thus pyrolysis was subsequently carried out in an atomosphere of nitrogen. The results obtained (Figure 4.2.1(iv) showed that breakdown once it had started to occur at-181, occurred within a very short time interval at the heating rate used (30 degrees per minute).

The proposed structure for this complex is represented in Figure 4.2.1(b)

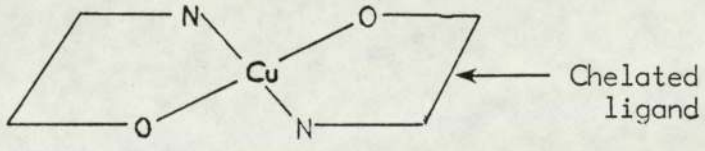


Figure 4.2.1 (b)

X-RAY ANALYSIS. Single crystal x-ray analysis data has been collected for this complex but at this time the results obtained have not been analysed. The unit cell dimensions have been found and the density of the crystal determined. The results of x-ray analysis would give the correct crystal and molecular structure of the complex.

Unit cell dimensions a = 19.49A, b = 19.47A, c = 13.92A and β=120°, d = 1.258

Thermogravimetric curve for $Cu(C_{10}H_{14}N))_2$

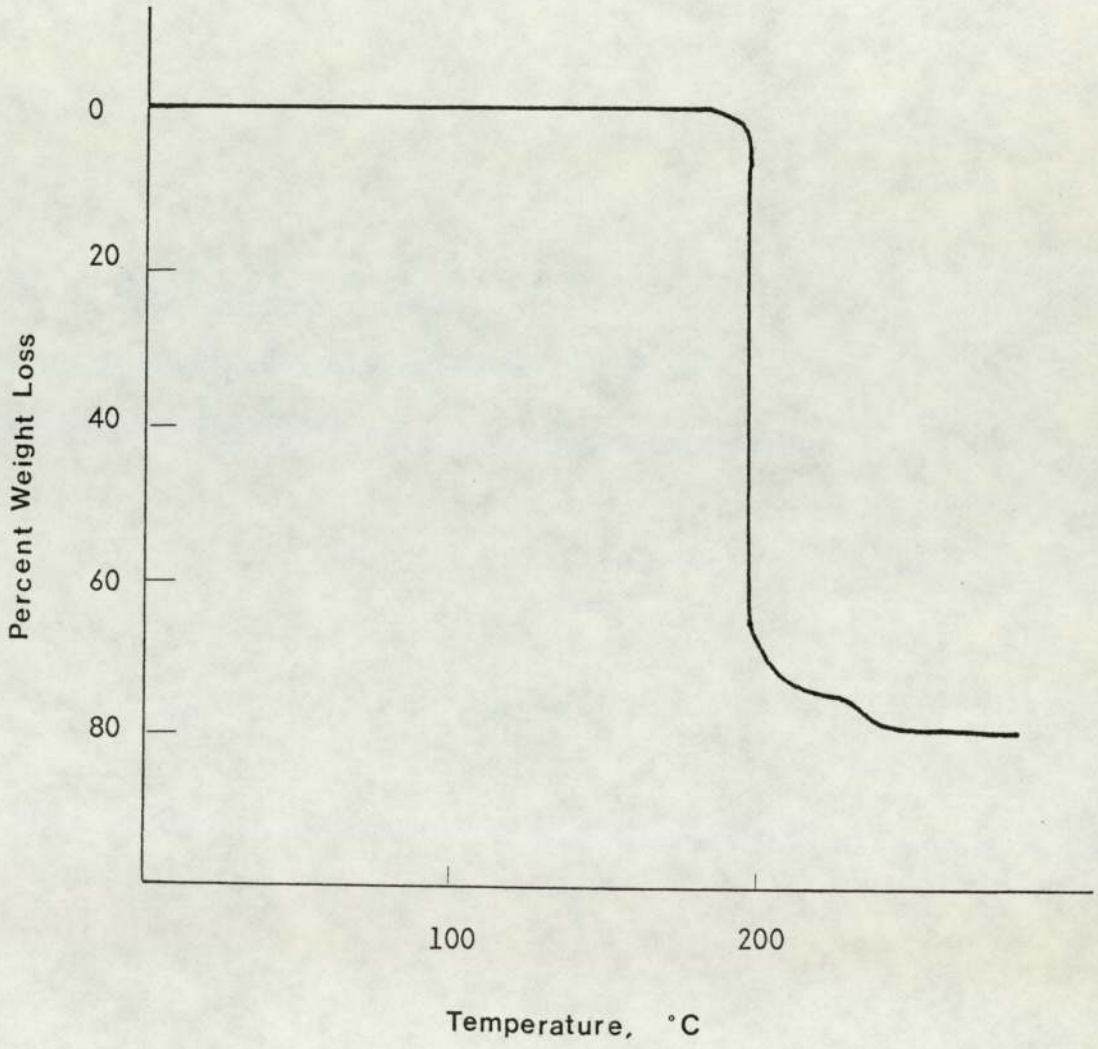


Figure 4.2.1. (iv)

4.2.2. Di-μ-chlorobis(d-pseudoephedrinato)copper(II) $Cu(C_{10}H_{14}NO)Cl_2$

INFRARED SPECTRUM. The infrared spectrum Figure 4.2.2(i) of the complex, shows a sharp band at 3306 cm^{-1} which has been assigned to ν(N-H). On coordination to copper the NH stretching vibration has only shifted slightly. The absence of large shifts of the NH stretching frequency on coordination implies that the interaction with Cu(II) may be only slight, although the intensity has greatly increased relative to other bands. This has been observed in other complexes [99] and is probably due to the greater dipole moment of the N-H band. The increase in intensity could be explained because of the coordinated NH group or of the greater electron-withdrawing power of nitrogen due to coordination of the copper.

The absence of a band that can be assigned to OH in the region above 3000 cm^{-1} indicates once again the loss of the hydroxyl proton on chelation. A possible scheme for this is represented in equation 3. The presence of broad bands at 3500 cm^{-1} and 1640cm^{-1} in the spectra traced in the KBr disc but absent in nujol medium are almost certainly due to water in the KBr disc.

Because of the ease of preparation of this complex, complexes were synthesized using the stable isotopes ^{63}Cu and ^{65}Cu Figure 4.2.2(ii) shows the spectra of these complexes traced in polyethylene. Table 4.2.1 shows the relative band shifts on isotopic substitution. The shifts range from 1-5 cm^{-1}. A band at 465 cm^{-1} is assigned to ν(Cu-N.) Bands at 343 and 370 cm^{-1} (shoulder) are assigned to ν(Cu-O.) The band at 290 cm^{-1} (shoulder 276 cm^{-1}) is assigned to ν(Cu-Cl.)

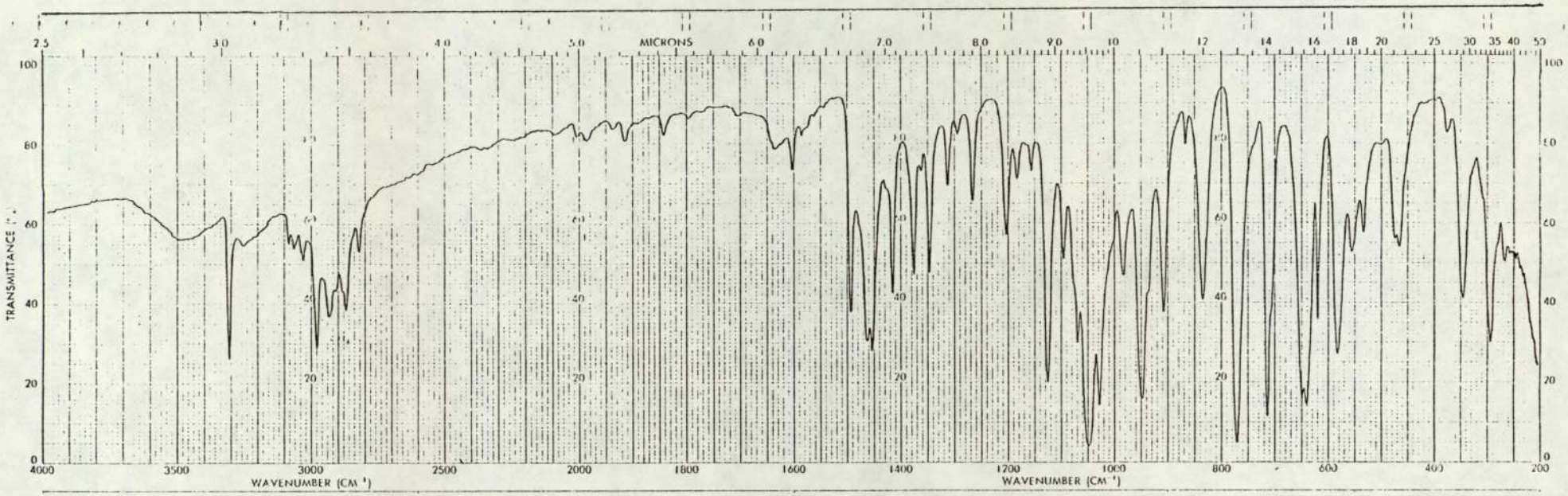


Figure 4.2.2 (i)

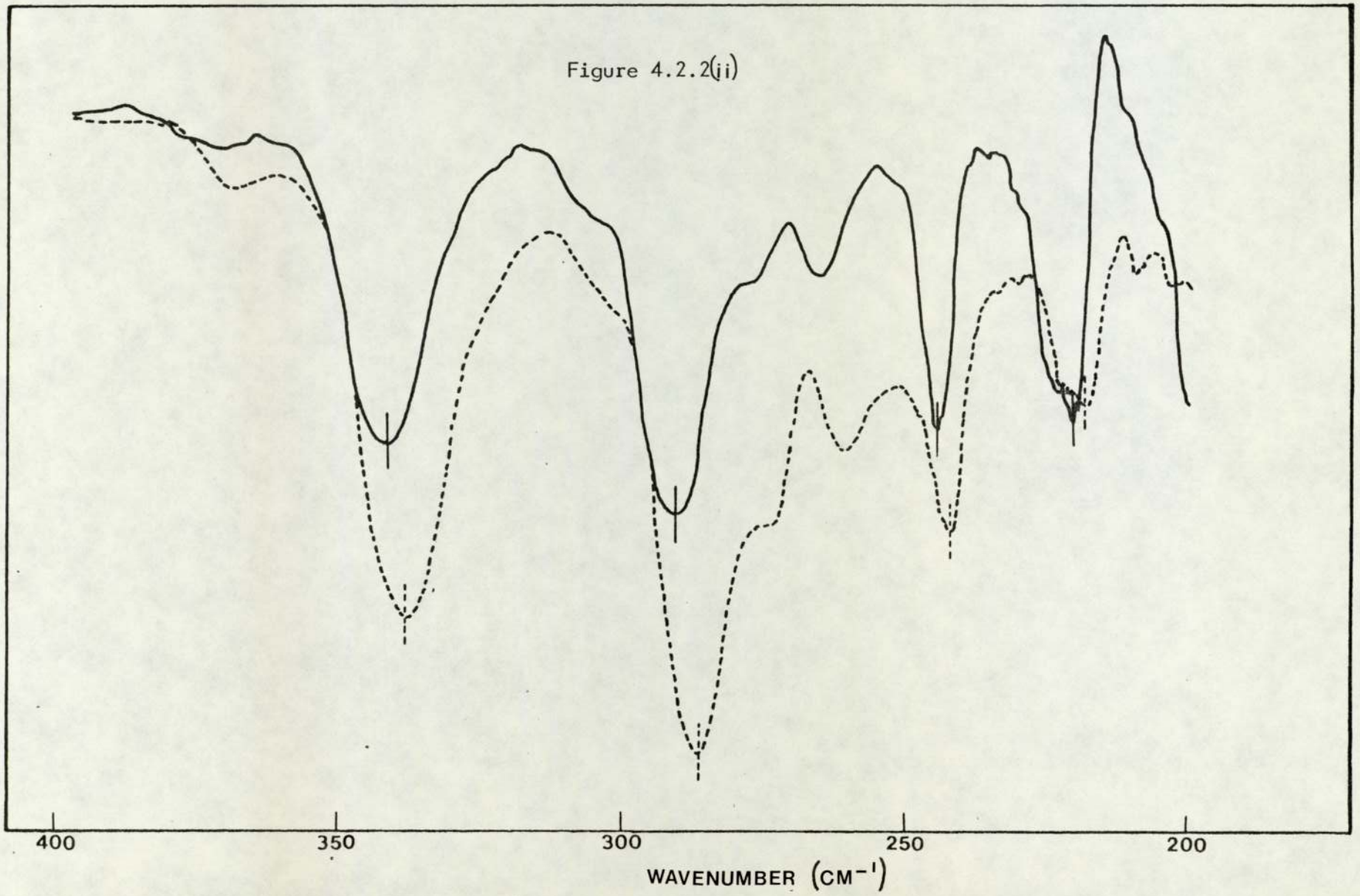


Figure 4.2.2(ii)

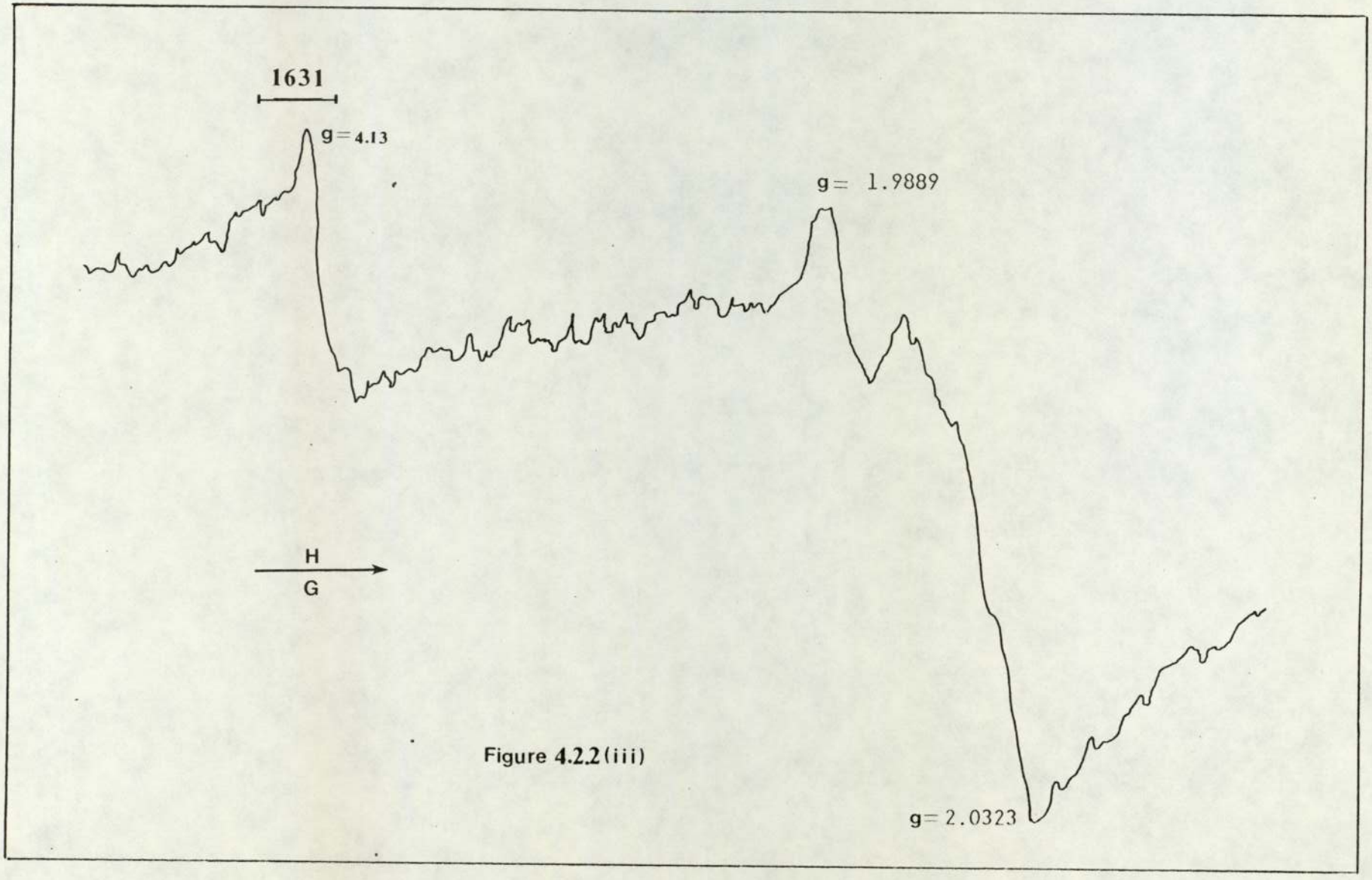


Figure 4.2.2(iii)

E.S.R SPECTRUM. The e.s.r. spectrum, Figure 4.2.2(iii) is rather interesting in that both low field and high field spectra are observed. These characteristic e.s.r. spectra have been used as a means of recognising polynuclear systems [100]. The structure of the dimer Bis [ethylenediaminebis(phenoxo)copper (II)]-phenol ($\frac{1}{2}$) was determined by x-ray crystal analysis, the magnetic susceptibility measured and e.s.r. spectrum traced. The e.s.r. spectrum showed low and high field spectra. The main g-value being 2.09 and the low field g-value, 4.25g.

The e.s.r. spectrum of this complex. Figure 4.2.2(iii) showed 3 g-values, the low field value, g = 4.13 at 1631 g and the main g-values of the anisotropic spectrum g = 1.989 and g = 2.0323. The lowest g-value~2.0 is indicative of a d_{z^2} ground state which is consistent with copper (II) in a trigonal-bipyramidal environment.

DIFFUSE REFLECTANCE SPECTRUM. The spectrum shows bands at 27 000 16 000 and 12 700 cm^{-1}. The band at 27 000cm^{-1} is probably a charge transfer band [101]. The latter bands are consistent with d_{z^2} ground state with an effective symmetry of D_{2h} for the copper (II) ion or a $d_{x^2-y^2}$ ground state with an effective symmetry of D_{4h}.

MAGNETIC SUSCEPTIBILITY. The room temperature magnetic moment of 1.70 B.M. supports a dimeric structure. The unpaired spins on the adjacent copper (II) ions in the complex are possibly coupled by a superexchange mechanism involving bridged oxygen or chlorine atoms.

Possible structures for the complex are represented in Figure 4.2.2(iv). For the copper (II) ion to achieve a coordination number of four

dimerization must take place. For five coordination to be achieved for each copper (II) ion, a situation in which the dimers are stacked such that copper (II) ions in one plane interact with the oxygen atom in the plane above is proposed. The insolubility of the complex in all of the common organic solvents would agree with this proposal.

Copper (II) complexes with N-dialkylamino $Cu(R_2N\ OH_2OH_2O)\ X_2$ have been synthesized.[101a] These complexes were dimeric and had structures similar to above.

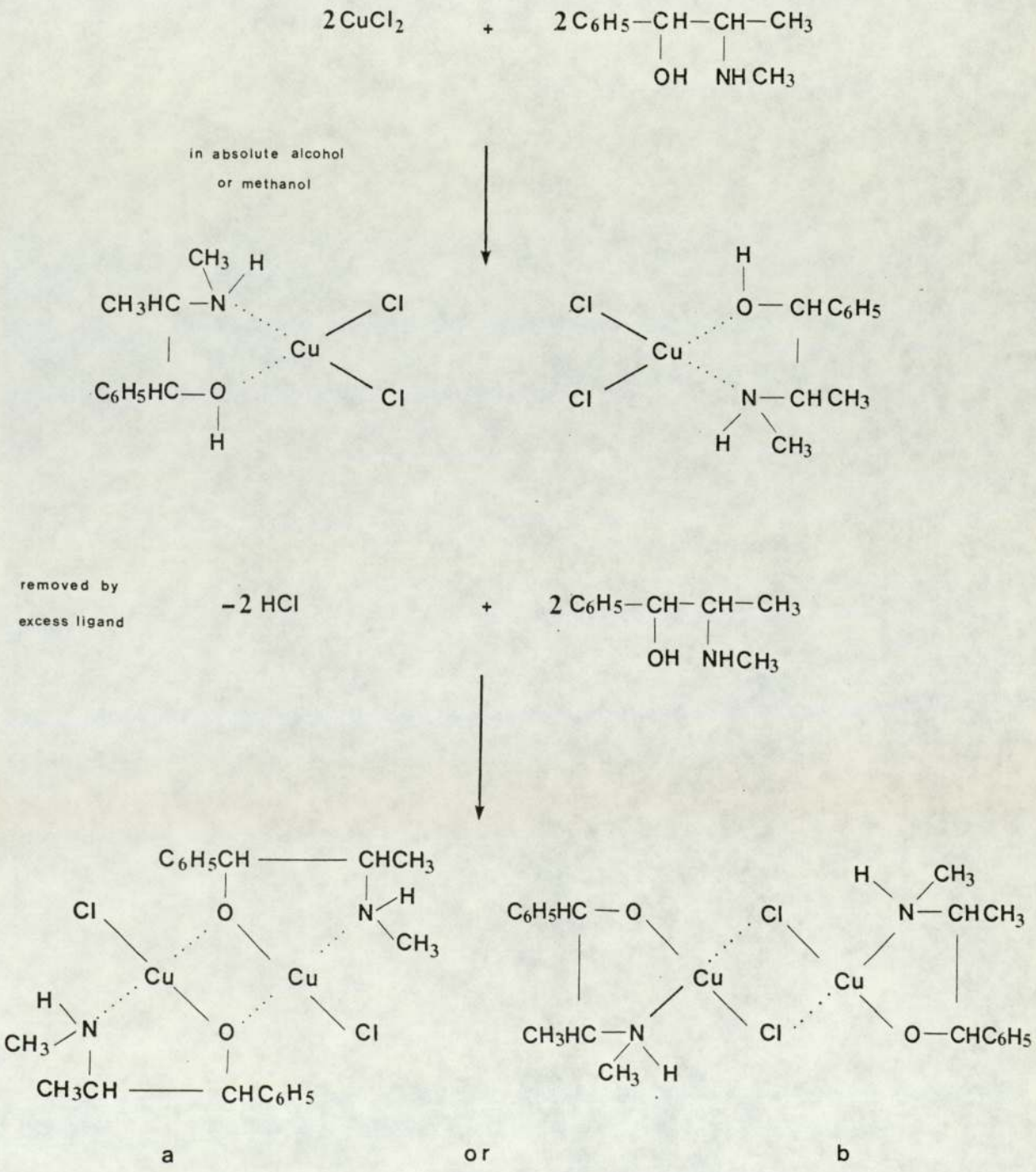
For the complex of Cu(II) elemental analysis indicates a ratio of 1 copper atom to 1 ligand.

Dimeric complexes reported in the literature have a square planar configuration such as observed for the binuclear complexes of diamine alcohols, or a square pyramidal structure [96]. These complexes are reported to have a $d_{x^2-y^2}$ ground state.

Forster and Ballhausen treated the electronic structure of copper (II) acetate in terms of molecular orbital theory in which they assumed large overlap between $3d_z$ orbitals so that the antibonding level of the 3d molecular orbitals have a higher energy than that of the molecular orbitals from $3d_{x^2-y^2}$. This suggests a strong σ bond ($3d_{z^2}-3d_{z^2}$) between copper (II) ions in the pair instead of the weak δ-bond proposed by Figgis [103]. Forster and Ballhausen however, emphasised that the proposed molecular orbital treatment is tentative. The complete explanation of the nature of the copper-copper bond is still an interesting problem.

Possible scheme for the formation of the copper (II) chelates of d-pseudoephedrine, l-ephedrine, phenylpropanolamine and dl-N-methylephedrine.

Figure 4.2.2 (iv)

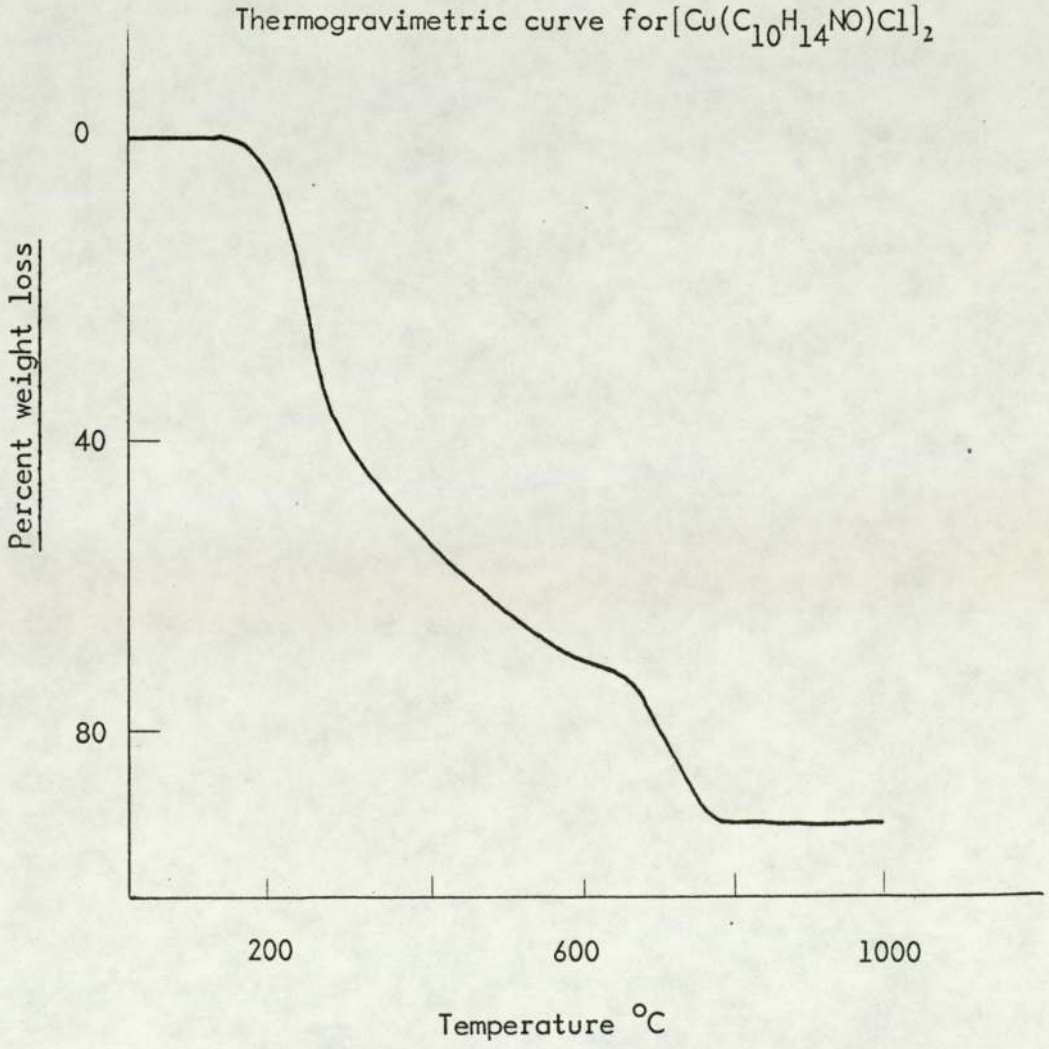


The g values for the complex under investigation together with the diffuse reflectance spectrum are consistent with a d_{z^2} ground state. If however the g values do not represent the local copper environment then the most useful information obtainable from the e.s.r. spectrum is the existence of a dimeric structure indicated by the low field spectrum.

THERMOGRAVIMETRIC ANALYSIS. The result of the pyrolysis under an atmosphere of nitrogen is shown in Figure 4.2.2.(v). The complex started to decompose at 139° and decomposition was complete at 739°.

Figure 4.2.2. (v)

Thermogravimetric curve for $[Cu(C_{10}H_{14}NO)Cl]_2$



4.2.3 $\left[\{Cu(C_{10}H_{15}NO)(C_{10}H_{14}NO)\}\right]_2 Cl_2$ Blue

INFRARED SPECTRUM. In general the spectrum of this complex was poorly resolved (Figure 4.2.3i). Sometimes high molecular weight compounds give spectra which are poorly resolved. The high molecular weight (~857) of this complex could account for the appearance of its spectrum. A sharp band at 3685 cm^{-1} in the infrared spectrum is assigned to OH in a bridge between two copper atoms. The OH group is known to form a bridge between two metals [90,93]. Sharp bands observed between 3690 and 3500 cm^{-1} have been assigned to the bridging OH group.

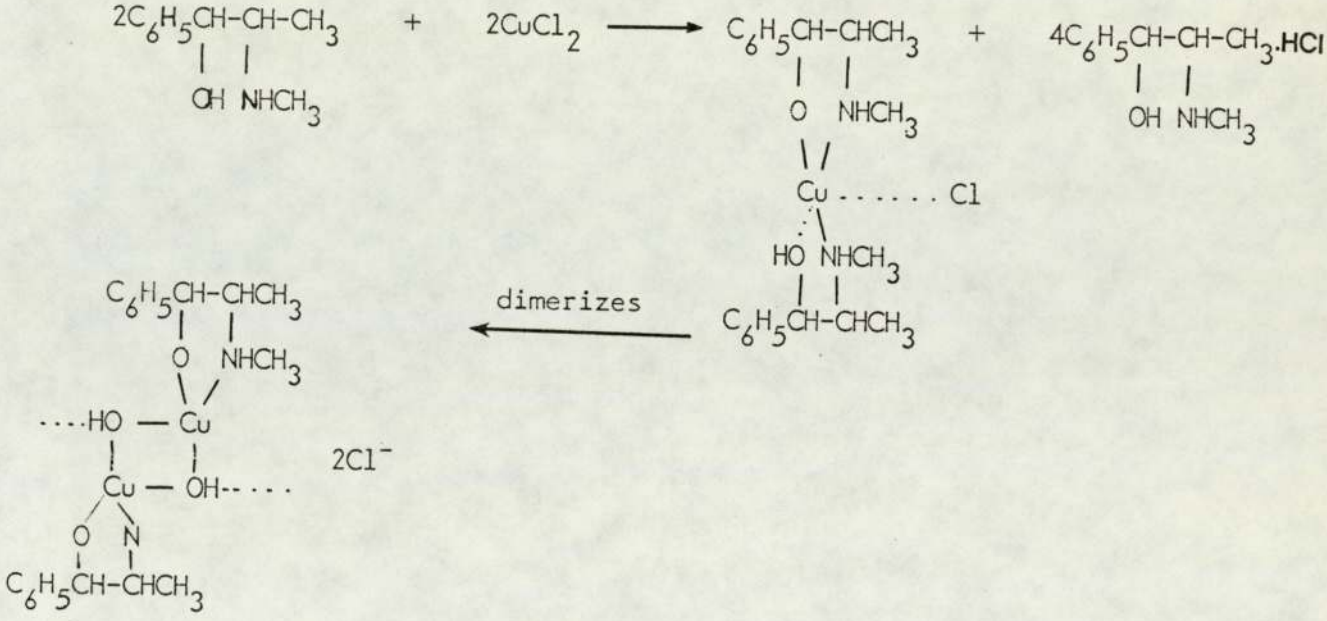
The OH groups forming the bridges in the complex are the hydroxyl groups of half of the d-pseudoephedrine ligands present in the complex.

A strong band at 585 cm^{-1} is assigned to (Cu-O-Cu) in common with other well documented examples [90] e.g. (bipy) Cu $(OH)_2Cu(bipy)(ClO_4)_2$ and (bipy)$Cu(OH)_2Cu$(bipy) SO_4 $5H_2O$. Also substituted hydroxo-bridged dimers have been reported.

The band at 3100 cm^{-1} is assigned to ν(N-H). This bond has been lowered due to coordination of the nitrogen atom to copper. The absence of a band in the spectrum that can be assigned to the free OH group together with the facts that (i) in the region above 3000 cm^{-1} except for the presence of the band at 3685 cm^{-1} assigned to the OH group

between copper atoms and(ii)a slight shift of ~ 10 cm^{-1} of the band assigned to ν (N-H) the appearance of the spectrum (Figure 4.2.3(i)) is identical to the spectrum of $(C_{10}H_{14}NO)_2$ Cu (Figure 4.2.1(ii)) suggest that chelate rings have been formed in the complex by d-pseudoephedrine ligands that have been deprotonated in a manner analogous to the formation of the violet chelate $(C_{10}H_{14}NO)_2Cu$.

A possible scheme for this reaction is presented in equation 2.



The d-pseudoephedrine hydrochloride formed would remain in solution. In preparing a similar complex using the isomer, l-ephedrine, l-ephedrine hydrochloride grew out of solution which was isolated and identified by means of infrared analysis. L-ephedrine hydrochloride is less soluble (1 in 17) than d-speudoephedrine hydrochloride (1 in 4) which would account for this observation.

Evidence for the existence of a dimeric structure or polymeric structure rests primarily on the fact that -OH- bridges between two copper atoms

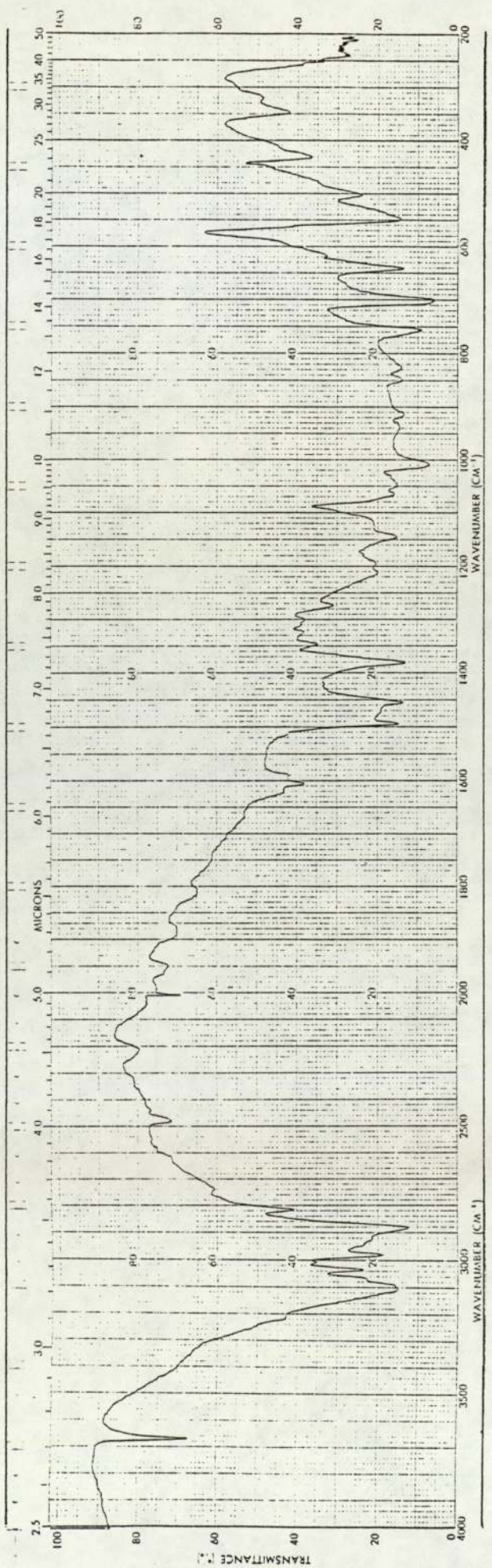


Figure 4.2.3.(i)

exist in the complex. These bridges were identified, as explained from the infrared spectrum.

The far infrared region shows a strong band at 360 cm^{-1} which is assigned to ν(Cu-O) where the oxygen donor atom involved in bonding forms part of a chelate ring. A band at 440 cm^{-1} and a split band at 264 and 246 are assigned to ν(Cu-N).

The infrared spectrum shows no positive evidence of Cu-Cl linkage, but it is possible that the band at 230 cm^{-1} could be assigned to ν(Cu-Cl) if the Cu-Cl was terminal. On the other hand Cu-Cl is known to form an infinite chain structure of dimers in which the Cl atoms act as bridges between two copper atoms; $CuCl_2 . 2H_2O$ being a simple example. Bridging Cu-Cl stretching frequencies that have been observed as far down as 174 cm^{-1} are in general lower than terminal Cu-Cl stretching frequencies, and with the particular spectrophotometer employed spectra were traced only as far down as 200 cm^{-1}.

The possibility of chlorine forming bridges between the dimeric copper units cannot therefore be completely ruled out.

The molar conductance of this complex in solution could not be measured because of the instability of the complex in solution as shown by the visible absorption spectra. The diffuse reflectance spectra shows a broad band at 14 500cm^{-1} with a shoulder at 12 500cm^{-1} and a band at 27 100. The solution spectrum of the complex shows a new band with a maximum at 15 000 cm^{-1} together with the band at 27 100 which has increased in intensity. The diffuse reflectance spectrum does not conflict with the proposal that Cu(II) has a square-based pyramidal

stereochemistry [90,95]. It is probable that the stereochemistry of the Cu(II) is distorted, [90] where a compressed tetrahedron exists and a 5th bond is formed by chlorine above the level of the other four bonds.

E.S.R. SPECTRUM. The observed E.S.R. spectrum was isotropic and broad and it is possible that spin-spin relaxation is present in the complex.

There are several reasons why an isotropic spectrum is observed in practice for a complex [86]. The most common reason is the presence of grossly misaligned tetragonal axes in the complex; for example $Cu\ dien_2\ (NO_3)_2$

If the spectrum is broad (~ 500 gauss) then it is possible that spin-spin relaxation is occurring in neighbouring molecules which influences the line shape. This happens when the interaction is smaller than kT. If the interaction is greater than kT ferromagnetic or antiferromagnetic interactions result which can be detected by bulk magnetic susceptibility measurements.

MAGNETIC SUSCEPTIBILITY. Magnetic susceptibility measurements of the powdered sample gave a magnetic moment of 1.77 B.M. at room temperature which at first would suggest that antiferromagnetic interactions are not present. The copper (II) ion ($3d^9$) has one unpaired electron in the 3d shell, and its compounds were considered to have magnetic moments close to the spin-only value, 1.73 B.M. irrespective of the bond type involved. In fact the observed values of magnetic moment for copper (II) compounds with ionic or rather weak covalent bonds are 1.9-2.2 B.M.,

and 1.72-1.82 B.M. for the compounds with strong covalent bonds.[92]

The observed magnetic moment of the complex thus lies in the region expected for copper (II) ions physically well separated from each other (> 5Å). However, recently a complex was isolated [96] $[\{Cu(OC_6H_5)_2(en)_2\}]. 2C_6H_5OH$ which is a dimer; the distance between the copper (II) ions being 3.215Å. The magnetic moment at room temperature was reported as ranging from 1.7-1.8 B.M. The copper atoms were reported to be five coordinate with a distorted square pyramidal stereochemistry. X-ray investigation showed that the complex had bridging phenoxo groups. Several mechanisms have been proposed for the magnetic interactions in binuclear copper (II) complexes. [97,98]. It was proposed by the authors that the structure of their complex could be represented as:

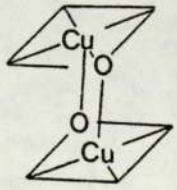


Figure 4.2.3 (a)

As such they concluded that with this type of idealised geometry it was not surprising that the complex exhibited a normal magentic moment probably due to incorrect orientation of the metal orbitals to interact with the oxygen p orbitals or themselves. Along with geometrical factors dynamic electrons exchange processess between the copper centres could influence the paramagnetism of the molecule.

THERMOGRAVIMETRIC ANALYSIS. The result of pyrolysis of this complex under nitrogen atmosphere is shown in Figure 4.2.3(ii). The complex decomposes in two stages. Initially 3 ligands are lost and then the fourth.

Figure 4.2.3 (ii)

Thermogravimetric curve for $Cu(C_{10}H_{15}NO)(C_{10}H_{14}NO)_2Cl_2$

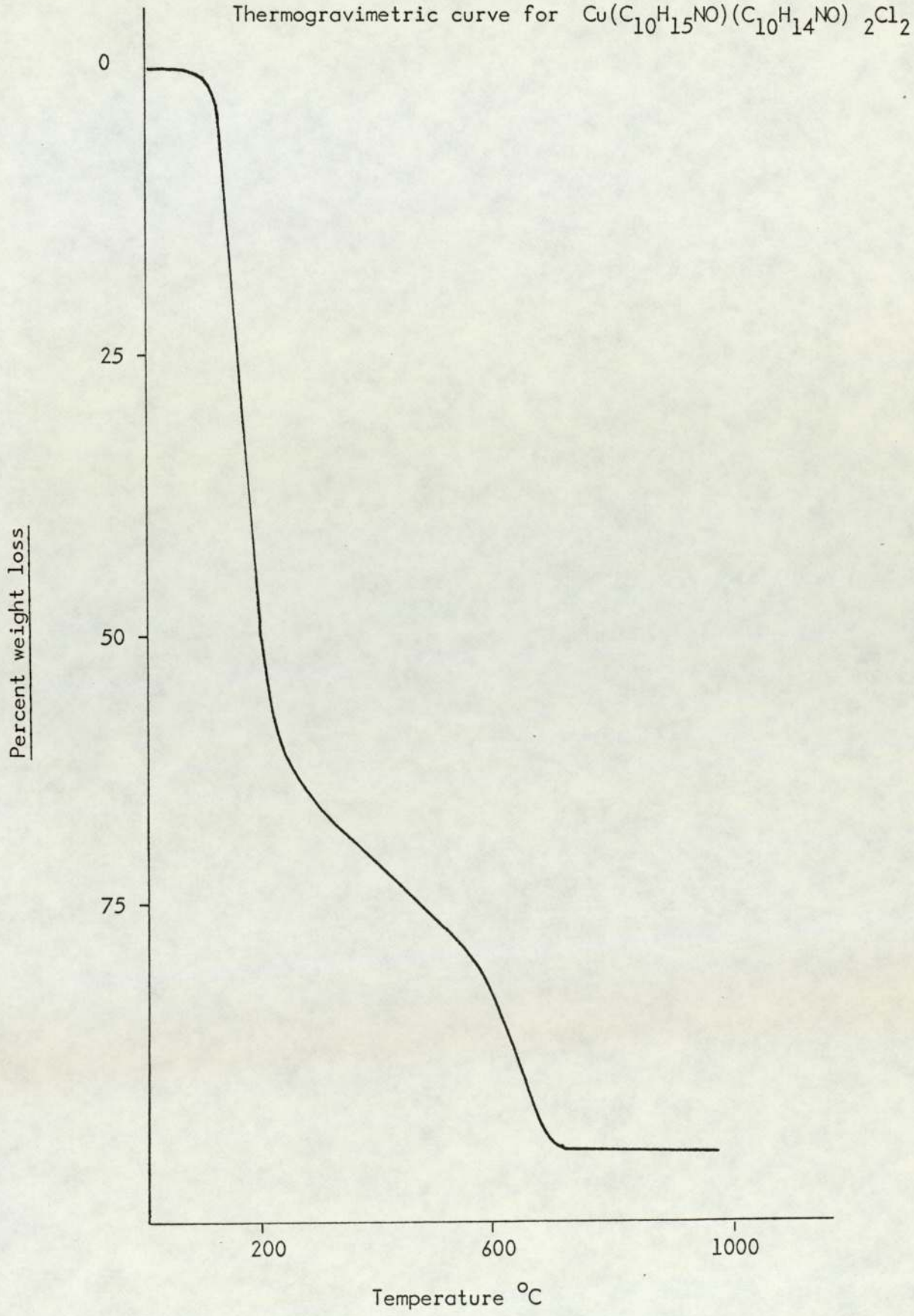


Table 4.2.1(i) IR spectra of d-pseudoephedrine, d-pseudoephedrine hydrochloride and its complexes

$C_{10}H_{15}NO$	$C_{10}H_{15}NO.\ HCl$	Tentative assignments cm^{-1}
3322		ν N-H
3080-2700br	3270s	ν O-H hydrogen bonded O-H
	2700	νNH_2

$Cu(C_{10}H_{14}NO)_2$	$(C_{10}H_{14}NO)CuCl$	Tentative assignments cm^{-1}
3090	3306	ν N-H
530	465	ν Cu-N
358sh	370sh	ν Cu-O
336,334s	343,338s	
	290 286s	ν Cu-Cl
275	276, 275 265, 261	ν Cu-N

$\left[\left\{Cu(C_{10}H_{15}NO)(C_{10}H_{14}NO)\right\}\right]_2Cl_2$	Tentative assignments cm^{-1}
3865	ν O-H
3100	ν N-H
545	Cu⟨O⟩Cu
440	Cu-N
350	Cu-O
264	
246	Cu-N
230	Cu-Cl

abbreviations, br = broad, m = medium, sh = shoulder, s. = strong, w = weak
v.s = very strong

Table 4.2.1 (ii)

Electronic and Magnetic Data for complexes of d-pseudoephedrine			
$Cu(C_{10}H_{14}NO)_2$			
Diffuse Reflectance Spectra $\tilde{\nu}_{max.}$ cm^{-1}	$m\mu$	E.S.R. Data g	Magnetic Moment BM
20 500	488	2.090	1.87
16 500	606		
$Cu(C_{10}H_{14}NO)Cl_2$			
27 100	369	2.010	1.70
16 000	625	2.323	
12 700	787	1.948	
$(C_{10}H_{15}NO)C_{10}H_{14}NO)_2Cl_2$			
14 500	690	2.123	1.77
12 500	800		

Complexes of l-ephedrine

4.2.4. Bis(l-ephedrinato)Copper (II) $(C_{10}H_{14}NO)_2$ Cu. Violet

INFRARED SPECTRUM. The infrared spectrum of the free base Figure 4.2.4(i) shows the presence of water or associated OH groups in the form of a broad band, 2880-2400 cm^{-1}. A band with a maximum at 3310 cm^{-1} is assigned to ν(N-H).

The spectrum of the complex before recrystallisation Figure 4.2.4(ii) showed the presence of water; broad band with a maximum at 3450 cm^{-1} and 1650 cm^{-1}. After recrystallisation twice from petroleum ether, Figure 4.2.4(iii) these two bands were absent. A strong band at 3100 cm^{-1} is assigned to ν(N-H). As in the case of the violet chelate isomer of d-(ψ)-ephedrine there is no band present that can be assigned to ν(O-H). In fact the spectra of the complexes in the region above 3000 cm^{-1} are identical.

A band split at 448 and 430 cm^{-1} is assigned to ^{IV}Cu-N and a band split at 396 and 373 cm^{-1} is assigned to ^{IV}Cu-O.

E.S.R. SPECTRUM. The e.s.r. spectrum giving an average g-value of 2.090 is isotropic and broad and as such cannot give any information about the structure of the complex.[86]

DIFFUSE REFLECTANCE SPECTRUM. The diffuse reflectance spectrum shows bands at 19 700 and 14 500 cm^{-1}. It is very similar to the spectrum obtained for its isomer d-pseudoephedrine. This suggests that the complexes have similar structure.

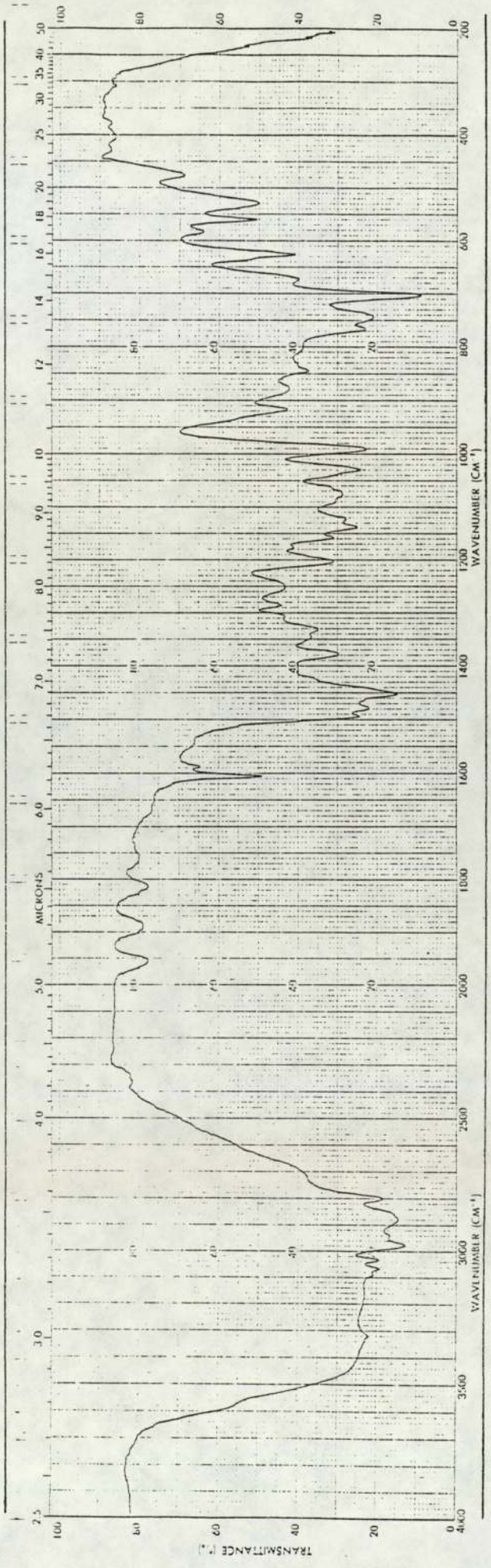


Figure 4.2.4 (i)

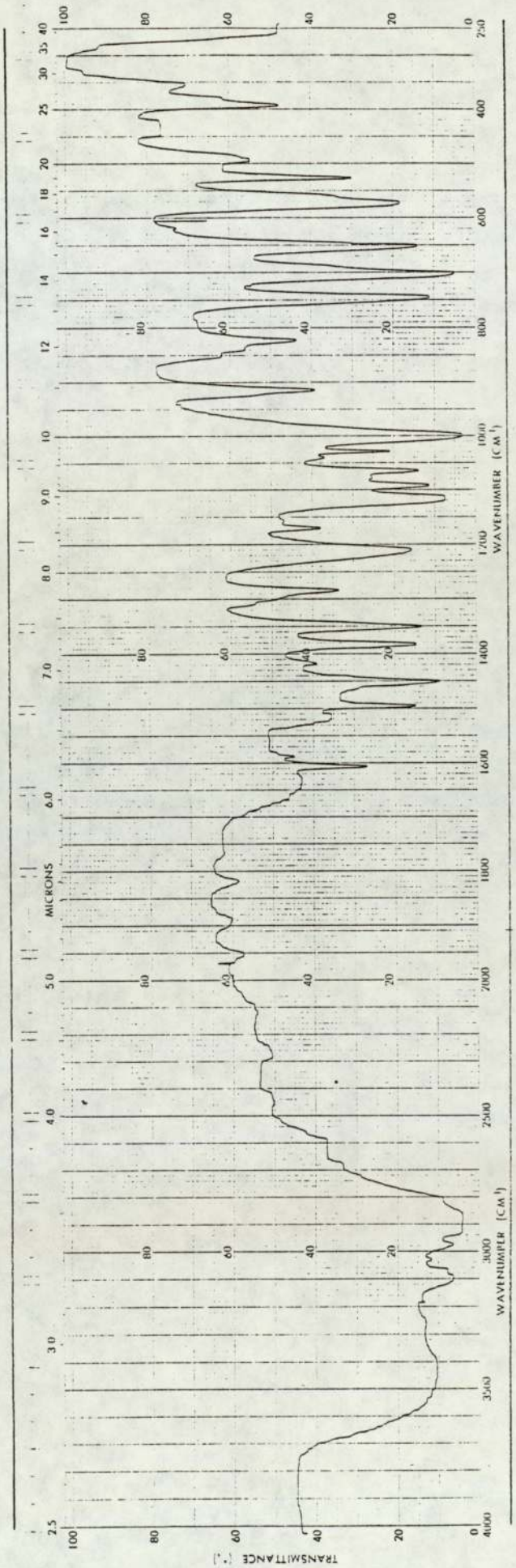


Figure 4.2.4 (ii)

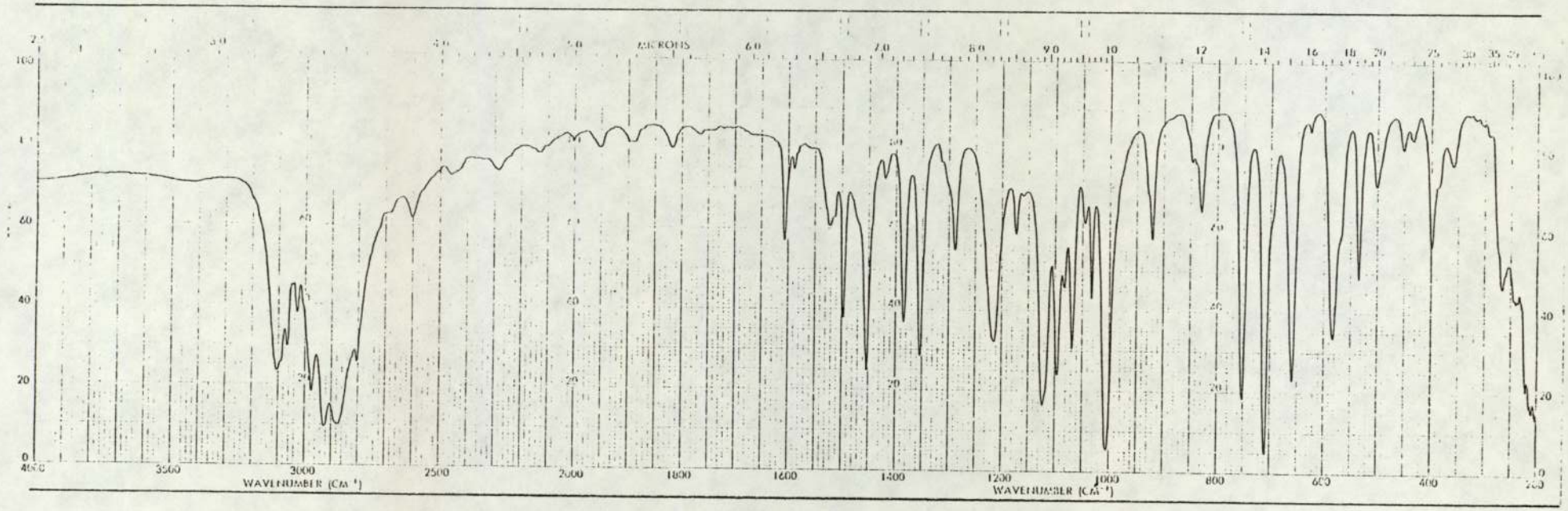


Figure 4.2.4 (iii)

MAGNETIC SUSCEPTIBILITY. The magnetic moment of 1.82 B.M. suggests strong covalent bonds in the chelate and does not support the idea of formation of a dimer in which the copper atoms are coordinated in the fifth position of a square based pyramid. See section 4.2.1. Thus assuming that the complex does not dimerise, with the availability of four donor atoms for each copper atom then the possible stereochemistries are square planar, distorted tetrahedral and compressed tetrahedral.

The number of bands in the far infrared region of the spectrum indicate a symmetrical structure for the complex. Thus if the copper atom is in a square planar environment the ligands could be coordinated in the trans position.

The diffuse reflectance spectrum cannot always be used as a single criterion in establishing the electronic ground state of the complex. Bannister and Cotton [104] said that no great spectral change would be expected if the structure of a complex was a compressed tetrahedron or was square planar.

THERMOGRAVIMETRIC ANALYSIS. The results obtained for this complex were similar to the results obtained for the d-pseudoephedrine chelate, $Cu(C_{10}H_{14}NO)_2$. The complex started to decompose at -133° and the ligands were then lost within a short interval of temperature.

4.2.5

Di-μ-chlorobis(l-ephedrinato) copper (II) $[Cu(C_{10}H_{14}NO)Cl]_2$ green

INFRARED SPECTRUM. The infrared spectrum showed a sharp band at 3260 cm^{-1} which is assigned to the N-H stretching vibration. No band is observed in the region above 3000 cm^{-1} that can be assigned to O-H stretching

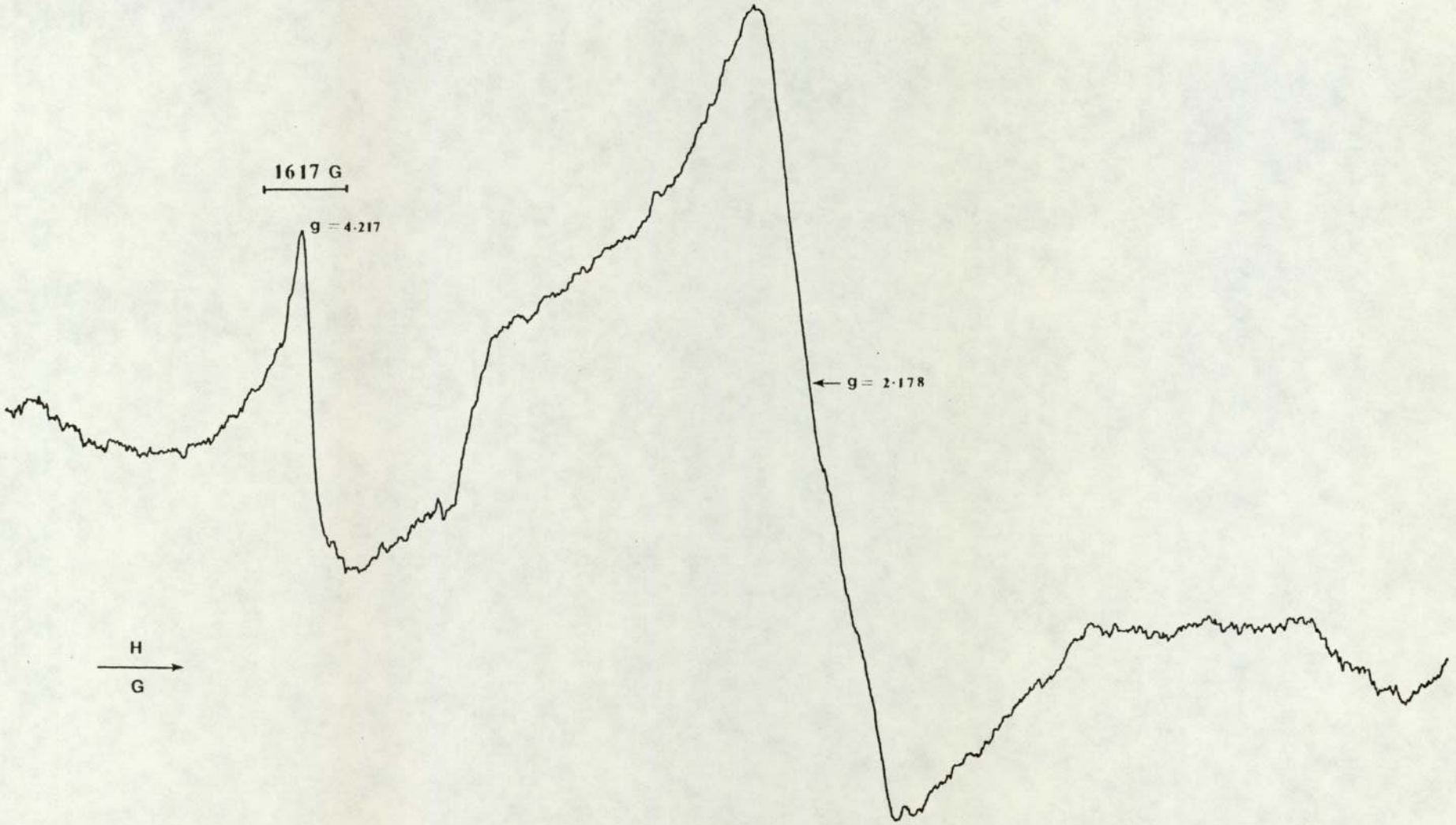


Figure 4.2.5

vibrations or water. This suggests the loss of the proton from the hydroxyl group of l-ephedrine and coordination through oxygen. In the far infrared region a band at 425 cm^{-1} is assigned to Cu-N. A broad band at 280 cm^{-1} is assigned to Cu-Cl and a band split at 245 and 228 cm^{-1} is assigned to Cu-O. The i.r spectrum suggests that oxygen, nitrogen and chlorine are coordinated to copper.

E.S.R. SPECTRUM. The e.s.r. spectrum shows low and high field spectra characteristic of binuclear complexes. Figure 4.2.5.

The observed g-values were 2.178 at high field and 4.217 at low field.

DIFFUSE REFLECTANCE SPECTRUM. A charge transfer band was observed at 27200 cm^{-1} and bands at 15000 and 13000 cm^{-1} which are consistent with a square planar stereochemistry or distorted tetrahedron.

MAGNETIC SUSCEPTIBILITY. The magnetic susceptibility measured at room temperature gave a value of 1.57 B.M. implying that there were interactions between the copper centres. This interaction could occur through the bridging chloride ligands, structure a, section 4.2.2.

The stereochemistry of the copper (II) ion that is consistent with the information is trans square planar. The e.s.r. spectrum is very similar to that of binuclear copper (II) acetate monohydrate and the complex by comparison probably has the same ground state.

This complex was very soluble in common organic solvents, unlike the d-pseudoephedrine complex with a similar empirical formula. The physical

data obtained for this l-ephedrine complex did not suggest the possibility of a d_{z^2} ground state for copper (II).

THERMOGRAVIMETRIC ANALYSIS. The complex began to decompose at - 94° and decomposition was complete at - 476°

4.2.6 $\left[\{Cu(C_{10}H_{15}NO)(C_{10}H_{14}NO)\}_2\right]Cl_2\ 2H_2O$ Blue

INFRARED SPECTRUM. The infrared spectrum of this complex of l - ephedrine has very similar features to the spectrum of the analogous isomer. A band at 3650 cm^{-1} is assigned to (O-H) in a bridge between two copper atoms. A band at 3130 cm^{-1} is assigned to ν(N-H). In addition to these bands in this region there is an additional broad band with a maximum at 3360 cm^{-1} which has been assigned to coordinated water. Water in inorganic complexes may be classified as lattice or coordinated water [84], but there is no definite borderline between the two. The term lattice water describes water trapped in the crystalline state either by weak hydrogen bonds to the anion or by weak ionic bonds to the metal or both. Coordinated water is water that is bonded to the metal through partially covalent bonds.

The strong band at 545 cm^{-1} is assigned to ν Cu$\diagup^{O}\diagdown$Cu. A main band at 440 cm^{-1} is assigned to νCu-N.

The strong band at 360 cm^{-1} is assigned to νCu-O in the chelate ring.

A similar structure is thought to exist as in the d-pseudoephedrine complex. $\left[\{Cu(C_{10}H_{15}NO)(C_{10}H_{14}NO)\}_2\right]Cl_2$ but the water molecule probably takes the fifth position of a distorted square pyramid that dimerises

in the solid state.

E.S.R. SPECTRUM. The e.s.r. spectrum shows isotropy Figure 4.2.6. giving a g-value of 2.109, and therefore does not give any positive evidence for any particular electronic ground state of the copper. A copper doped zinc complex was prepared but the analytical data showed that it had a different empirical formula although the infrared spectrum was very similar, but better resolved. In the region above 3000 cm^{-1} the spectrum of the copper doped zinc complex and the spectrum of the neat copper complex were identical, but in the far infrared region there were great differences

DIFFUSE REFLECTANCE SPECTRUM. The spectrum of this complex shows a broad band at 14000 cm^{-1}. It is probable that this envelope contains more than one transition. The band at 27 200 cm^{-1} could be a charge transfer band. In solution the band at 14 000 cm^{-1} decreases greatly in intensity and a new band appears at 26 100 cm^{-1} showing that the complex is unstable in solution giving a new complex, this would be consistent with the breakdown of a dimeric structure.

The diffuse reflectance spectrum is consistent with a distorted square planar structure. The water is probably coordinated weakly in the sixth position, above the plane, but in the limits the complex could show tetragonal distortion and for all purposes the complex could be considered to have a distorted square planar structure. See section 4.2.3.

THERMOGRAVIMETRIC ANALYSIS. The results show initially the loss of water then the complex loses its ligands in two stages. Three ligands are lost

at first and then the fourth ligand is lost leaving CuCl. Decomposition began at approximately 94° and was complete at approximately 714°.

In fact except for the loss of water the shape of this curve is identical to the curve obtained for the d-pseudoephedrine complex:

$[\{Cu(C_{10}H_{15}N)(C_{10}H_{14}NO)\}]_2Cl_2$

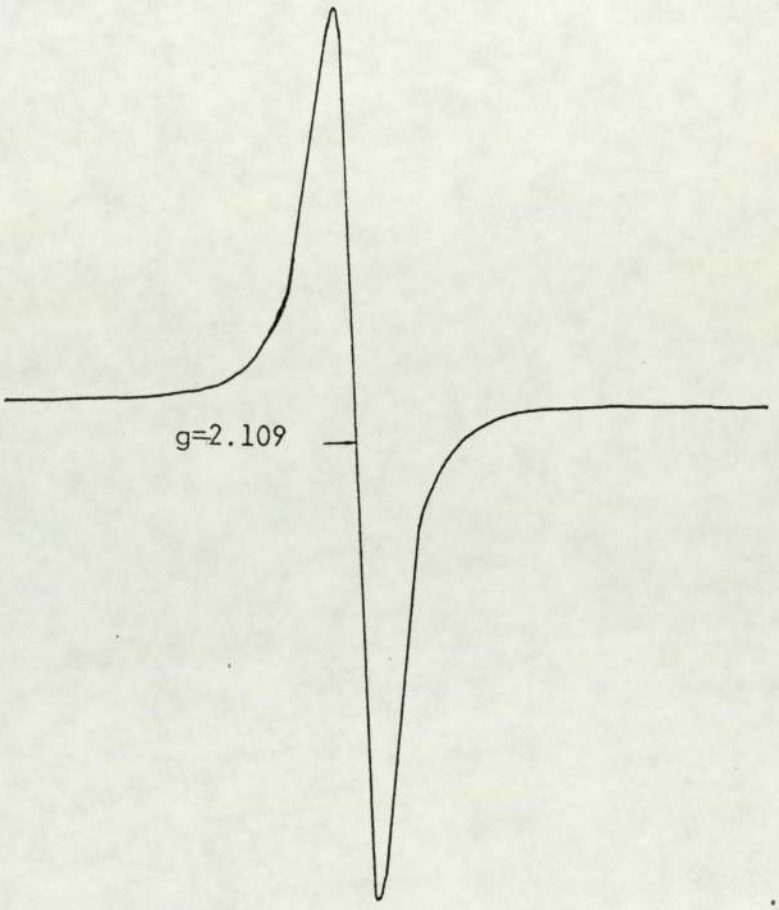


Figure 4.2.6

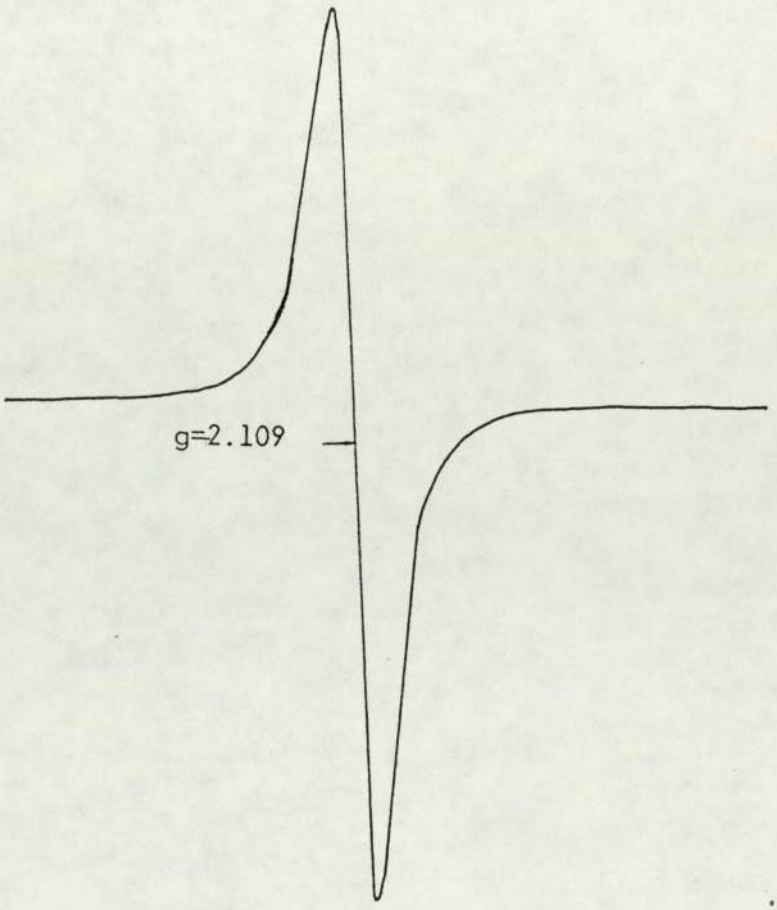


Figure 4.2.6

Table 4.2.4 (i) IR spectra of l-ephedrine, l-ephedrine hydrochloride and its complexes

$C_{10}H_{15}NO$	$C_{10}H_{15}NO$ HCl	Tentative assignments cm^{-1}
3620 sh	3325	unassociated ν O-H
2880-2400br		νO-HνN-H
	2760	νNH_2

$Cu(C_{10}H_{14}NO)_2$	$Cu(C_{10}H_{14}NO)Cl_2$	Tentative assignments cm^{-1}
3100		νN-H
448	425	Cu-N
430		
396	245	Cu-O
373		
	280s,br	Cu-Cl
264	246	
228	228	

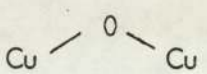
$[\{CuC_{10}H_{15}NO)\ (C_{10}H_{14}NO)\}_2Cl_2 2H_2O]$	Tentative assignments cm^{-1}
3650	νO-H
3360	H_2O
3130	νN-H
545	Cu  Cu
360	Cu-O
310	Cu-Cl
250	
440	Cu-N

Table 4.2.4 (ii)

Electronic and Magnetic Data for complexes of l-ephedrine

Diffuse Reflectance Spectra $\tilde{\nu}_{max}$ cm^{-1}	$m\mu$	E.S.R Data g	Magnetic Moment BM
$Cu(C_{10}H_{14}NO)_2$			
19 700	508	2.090	1.82
14 500	690		
$[Cu(C_{10}H_{14}NO)Cl]_2$			
27 200	368	2.015	1.57
15 000	667	2.178	
13 000	769		
$[\{Cu(C_{10}H_{15}NO)(C_{10}H_{14}NO)\}]_2 Cl_2 2H_2O$			
14 000	714	2.109	1.88
12 900	775		

Complexes of dl-phenylpropanolamine (dl-norephedrine)

INFRARED SPECTRUM. The spectrum of the pure substance as well as being traced as a mull in nujol using CsI plates and using a KBr-disc, was traced in chloroform solution to determine the positions of NH_2 and O-H stretching vibrations. The band at 3600 cm^{-1} in the spectrum of the ligand in chloroform is due to unassociated OH groups. The relatively broad band between 3540 and 3000 cm^{-1} is due to associated OH, characteristic of hydrogen-bonded hydroxyl groups. In the spectrum of the free base traced in KBr and nujol the bands at 3340 and 3280 are assigned to (NH_2) and are typical of bands for a free amine group. [79]

4.2.7(i) Bis(dl-norephedrinato)copper(II) trihydrate $Cu(C_9H_{12}NO)_2\ 3H_2O$
Royal Blue

INFRARED SPECTRUM. The spectrum of this complex shows a very broad band centred between 3500 and 3000cm^{-1}. The position of this band renders this region uniformative concerning possible oxygen and nitrogen links to copper.

The far infrared spectrum is similar to the spectra of the d-pseudoephedrine complex $C_{10}H_{14}NO)_2Cu$ in appearance of band shape but in general the

bands that are assigned to Cu-O and Cu-N stretching vibrations occur at lower wavenumbers.

Cu-O bands are assigned at 365 cm^{-1} for the oxygen coordinated to copper in the chelate ring and at 222cm^{-1} for the oxygen of water coordinated to copper. This band is of medium intensity.

Bands at 310 cm^{-1} and 280 cm^{-1} are assigned to Cu-N stretching vibrations

E.S.R. SPECTRUM. The spectrum observed. Figure 4.2.7 is a typical axial spectrum observed when there is reasonable alignment of the principal symmetry axes within the crystal.

This type of spectrum [105] is observed with elengated tetragonal-octahedral, square-coplanar or square-based pyramidal stereochemistries, the g-values are related by the expression:

$$G = g_{\parallel} - 2/g_{\perp} - 2 \simeq 4$$

If $G > 4.0$ then the local tetragonal axes are aligned parallel or only slightly misaligned, if $G < 4.0$ then significant exchange coupling [106] is present and the alignment of tetragonal axes is poor.

Sometimes a complex with rhombic symmetry with slight misalignement of the "tetragonal" axes can also give axial spectra.

If the lowest g-value is greater than 2.04, this implies a $d_{x^2-y^2}$ or less commonly a d_{xy} ground state.

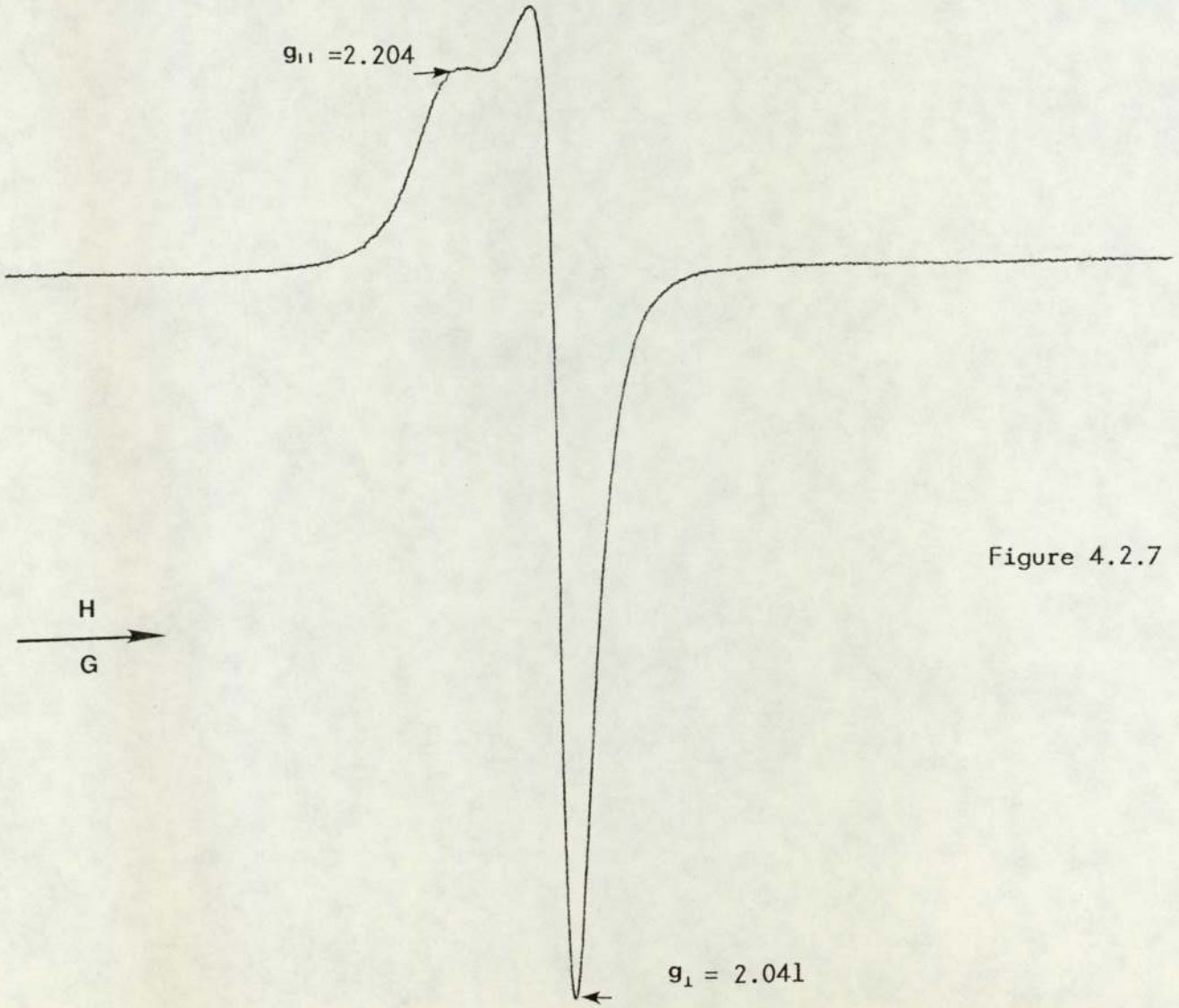


Figure 4.2.7 (i)

If the lowest g-value is less than 2.03 this implies a d_{z^2} ground state. The value of G has no significance in this case.

The g-values for this complex, $g_{\parallel} = 2.204$ and $g_{\perp} = 2.041$ and $G = 4.9$ indicate that exchange if it does occur is small and the observed g values significant.

The E.S.R. data is consistent with a square coplanar or square-based pyramidal ground state of the copper (II) ion.

MAGNETIC SUSCEPTIBILITY. The room temperature magnetic moment $\mu_{eff} = 1.86$ B.M. did not suggest that the complex was a dimer or that exchange coupling was present.

DIFFUSE REFLECTANCE SPECTRUM. The spectrum showed a broad absorption with a maximum at 17500 cm^{-1} which is consistent with a square-based pyramidal stereochemistry the copper ion having a $d_{x^2-y^2}$ ground state.

THERMOGRAVIMETRIC ANALYSIS. The complex began to decompose at 94° and finished decomposing at 226°. Initially water was lost. After the loss of water, under the conditions employed the compound decomposed over a narrow range of temperature. Three moles of water were lost

The x-ray crystal structure of this compound has been determined and the physical data of this work are in agreement with the structure determined. Shown below.

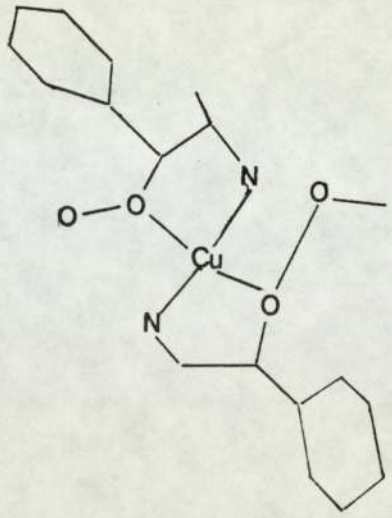


Figure 4.2.7a

4.2.7 (ii) Bis (dl-norephedrinato) copper(II) $(C_9H_{12}NO)_2Cu.\ CH_3OH$

This complex was unstable when removed from methanol vapour. Rapid elemental analysis indicated the presence of methanol. Table 3.2.7 Methanol was thought to be an integral part of the structure since once the complex was left in an unsealed vessel the crystals gradually Figure 25 changed in colour and appearance. Figure 10 Plate 2 shows the crystals before the loss of methanol and Figure 9 Plate 2 shows the crystals after methanol loss. Analysis of the crystals after loss of methanol showed that they had gained 3 moles of water.

Because of the instability of this complex it was difficult to obtain many physical measurements.

INFRARED SPECTRUM. Although the infrared spectrum was traced the assignments made must be thought of as being tentative as it is probable that the spectrum was intermediate between the two complexes. The

general appearance of this spectrum was quite similar to the spectrum of $(C_9H_{12}NO)_2Cu.\ 3H_2O$. (4.2.7i) but there were obvious differences in the region greater than 3000 cm^{-1} and less than 600 cm^{-1}. Many of the bands were split.

A sharp band is observed at 3650 cm^{-1} in this complex. This would be consistent with the hydroxyl group of methanol forming a bridge between two copper atoms. As mentioned previously the OH group [90] and OR group where R is an alkyl group are known to form bridges between two copper atoms.

A broad band is observed in the region greater than 3000 cm^{-1} which makes it difficult to assign bands. A fairly broad band centered at 3300 cm^{-1} that is split is assigned to NH_2 stretching vibrations. It is possible that NH_2 is coordinated to copper, but due to the uncertainty of assignment, the far infrared region is more informative about coordination of copper to oxygen and nitrogen.

A band at 580 cm^{-1} is assigned to $Cu\diagup^{O}\diagdown Cu$. Stretching vibrations

A strong band at 390cm^{-1} is assigned to νCu-O and a split band at 370 and 355cm^{-1} is assigned to νCu-N.

The visible spectrum of this complex was traced in methanol. A very broad band with maxima at 20 000 and 17 000 cm^{-1} (main band) was observed. This spectrum is consistent with a square-based pyramidal stereochemistry.

E.S.R. The e.s.r. spectrum Figure 4.2.7(ii) was measured giving g-values,

g_{11} = 2.205 and $g_{\perp}$ = 2.046, and G = 4.49. The observed g values giving G = 4.49 imply that the g values reflect the local environment of the copper (II) ion. The local tetragonal axes are aligned parallel or are only slightly misaligned. The ground state implied is $d_{x^2} - {}_{Y^2}$.

THERMOGRAVIMETRIC ANALYSIS. Similar results were obtained to the results from the d-pseudoephedrine chelate $(C_{10}H_{14}NO)_2Cu$. Decomposition began at approximately 80°. There was no definable step for the loss of methanol which possibly occured before heating. The shape of the curve was similar to that of the trihydrate form of the complex without a stage for the loss of water. Decomposition was complete at-494°.

The results of the data from elemental analysis and physical measurements suggest that a likely structural representation of the complex is a bridged dimer consisting of a square-based pyramid with two oxygen and two nitrogen atoms at the corners. Above this plane the CH_3OH molecule is coordinated. The infrared spectrum suggests that the OH forms a bridged between two units. With such a formulation it is probable that a chain of dimers exist i.e. a polymer.

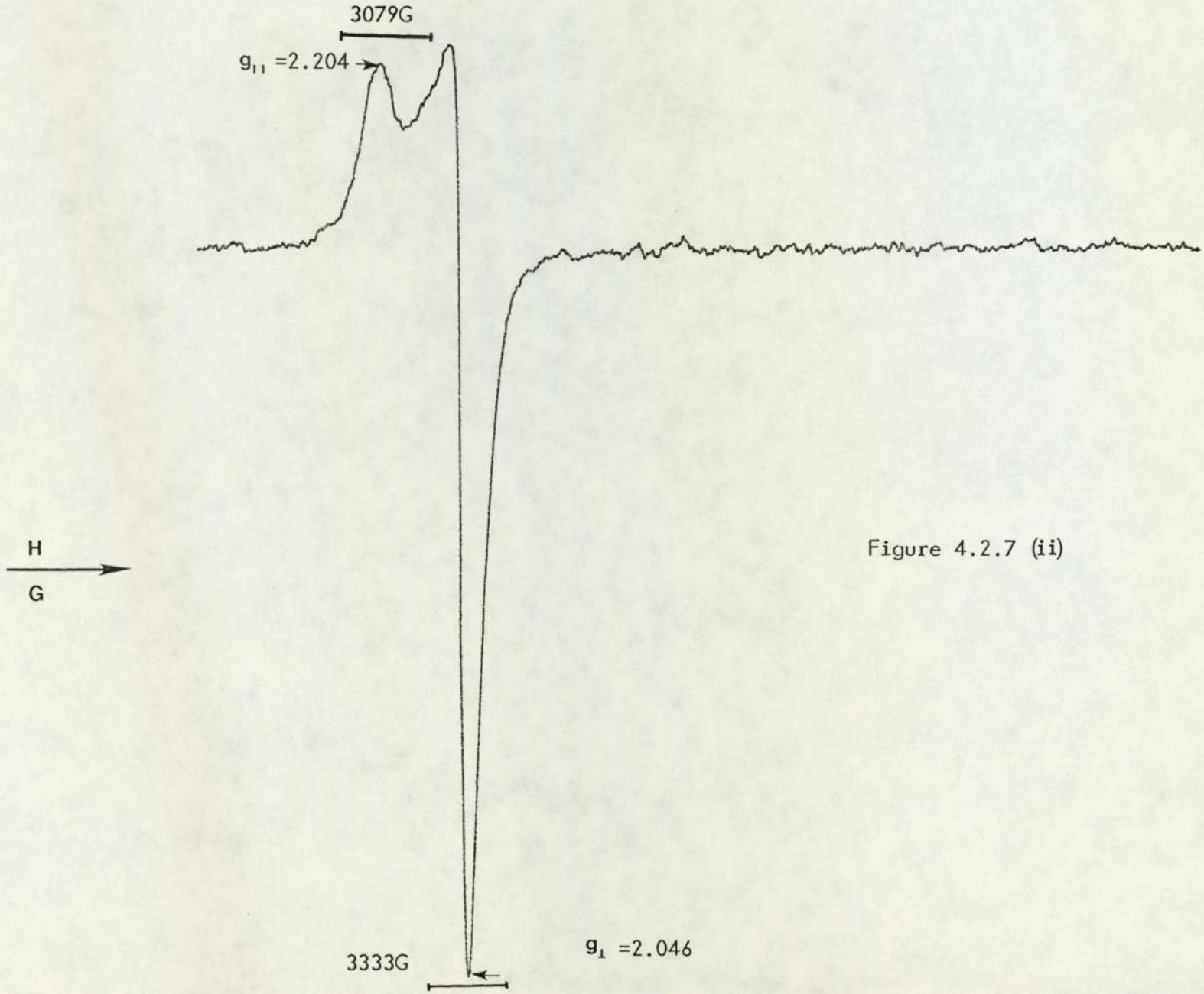


Figure 4.2.7 (ii)

4.2.8 Di- μ-chlorobis(dl-norephedrinato) copper (II) $[(C_9H_{12}NO)CuCl]_2$

Green

INFRARED SPECTRUM. The infrared spectrum showed a doublet at 3290 and 3235 cm^{-1} characteristic of NH_2 stretching vibrations. These bands are shifted to lower wavenumber relative to the free base dl-phenyl propanolamine on coordination to the metal. There is no band present that can be assigned to the hydroxyl group which suggests that the OH group as an entity is not present in the complex. It is possible as in the case of di-μ-chlorobis(d-pseudoephedrinato) copper (II) with a similar formula that the hydroxyl proton is lost and copper is coordinated in a chelate ring to oxygen and nitrogen.

The far infrared spectrum shows a strong absorbtion at 374 cm^{-1} which is assigned to νCu-O. A strong absorption at 330 cm^{-1} is assigned to νCuCl and a band split at 250 and 230 cm^{-1} are assigned to νCu-N.

A scheme for the formation of this complex has been described in section 4.2.2 where R = H.

Although the copper chlorine stretching frequency is high it lies within the range observed for bridging νCu-Cl. Alternatively if the correct representation for the complex was b) then the νCu-Cl would be terminal.

DIFFUSE REFLECTANCE SPECTRUM. A band was observed at 26 200cm^{-1} which was almost certainly a charge transition band and at 16 000 cm^{-1}. This band is consistent with $d_{x^2-y^2}$ ground state for copper.

E.S.R. Spectrum for di- μ-chlorobis(dl-norephedrinato) copper(II)

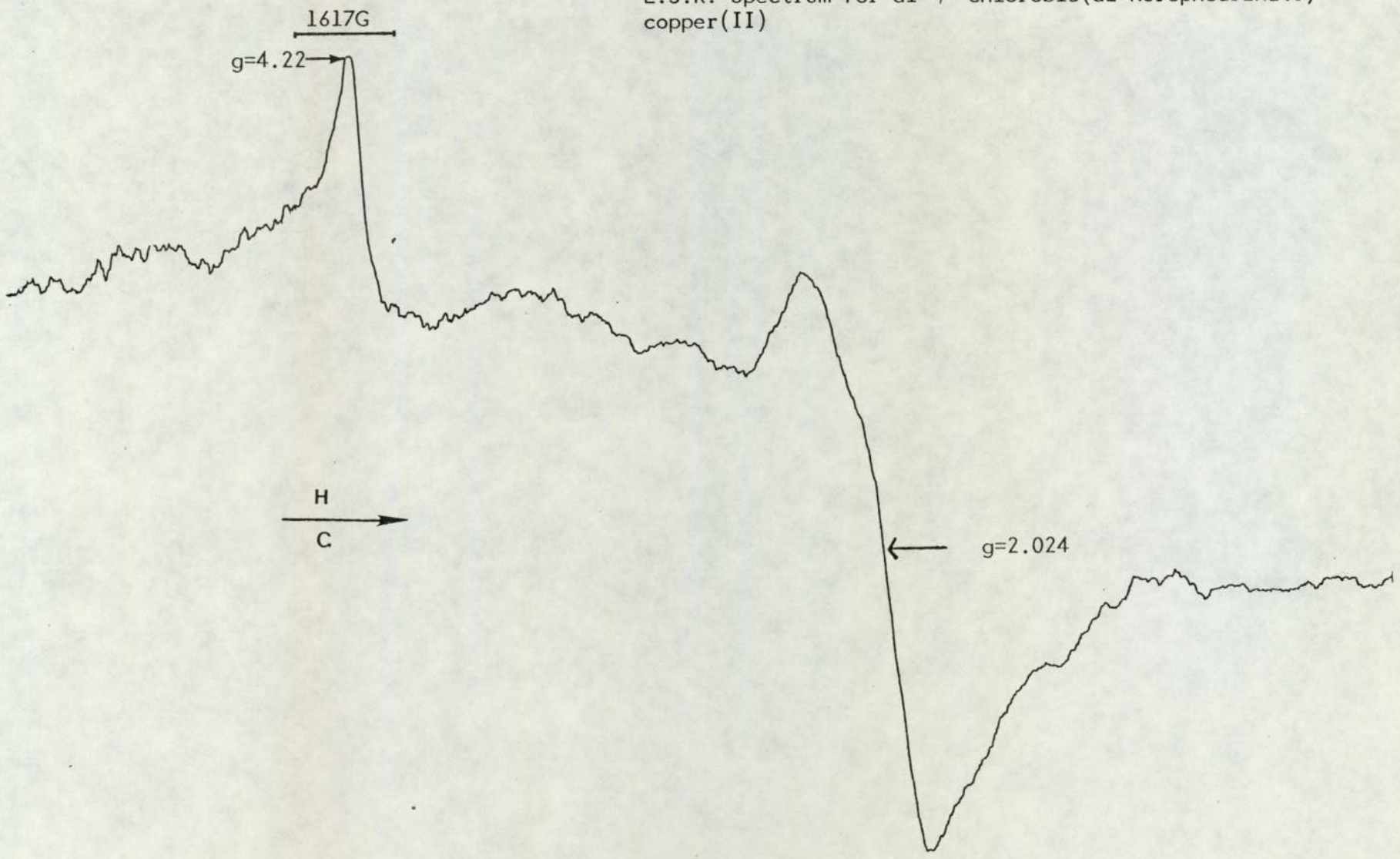


Figure 4.2.8(i)

E.S.R. SPECTRUM. Low field and high field signals are observed which imply a similar structure to that found in binuclear copper acetate monohydrate. The presence of a low field signal g = 4.22 at 1617G indicates a dimeric structure. The main field signal is isotropically broad indicating that exchange coupling is present in this complex.

MAGNETIC SUSCEPTIBILITY. The room temperature magnetic susceptibility measurements gave a value of 0.448 BM which is indicative of exchange coupling between copper centres in close proximity.

Such a low value indicated that a super-exchange mechanism existed where chlorine bridge or oxygen could be involved in the interaction. Sometimes this type of magnetic interaction between copper ions in a complex is greater than when direct interaction is present. It is possible that this complex possess both types of magnetic interaction.

The presence of a dimeric species was also indicated by the insolubility of this complex in all the common organic solvents.

The magnetic susceptibility at different temperatures from room temperature down to 93K was measured to investigate the variation of μ_{eff} with temperature. The result of this study is shown in Figure 4.2.8(i). The curve showed hysteresis, which was probably due to difficulty in achieving thermal equilibrium between the cold chamber and the sample. Achieving thermal equilibrium is often a slow process.

Figure 4.2.8 (ii)

Graph of μeff against absolute temperature for di- μ-chlorobis(dl-norephedrinato)copper(II)

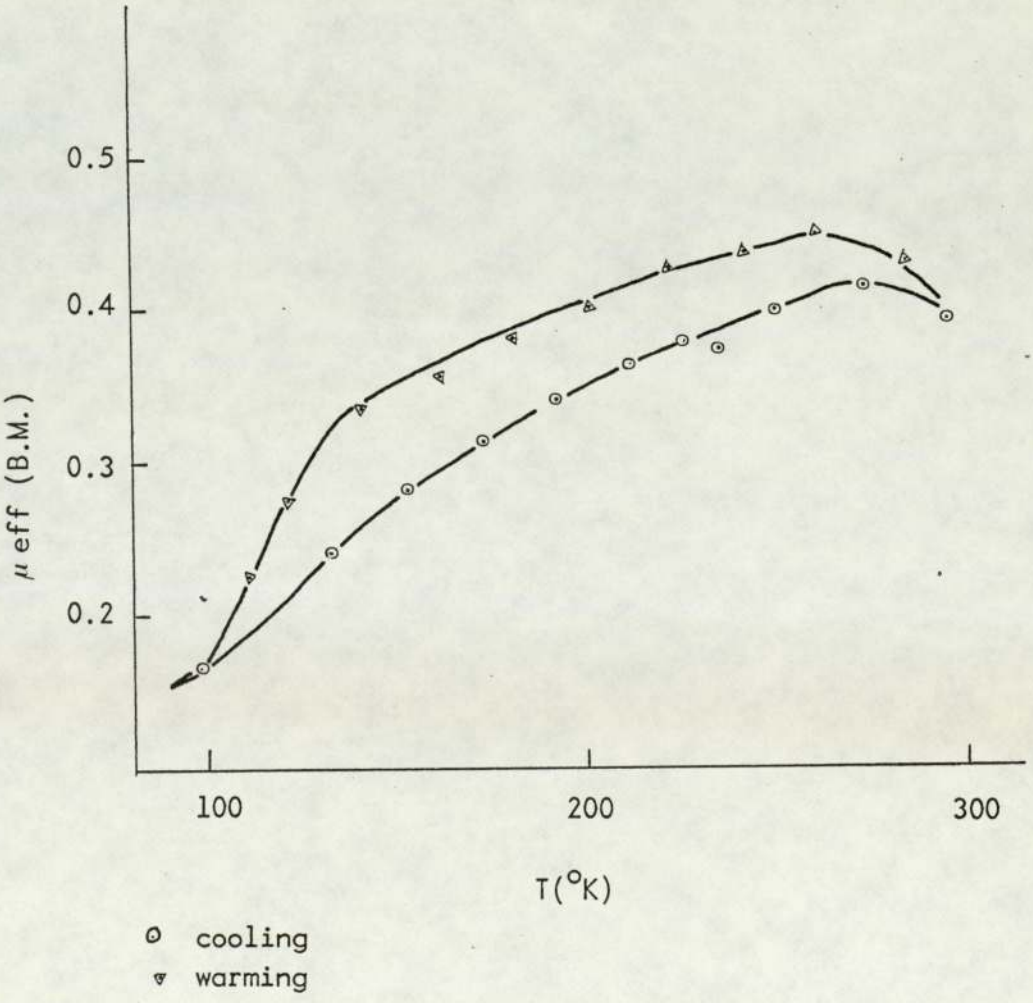


Table 4.2.7.i IR spectra of dl-phenylpropanolamine, dl-phenylpropanolamine hydrochloride and its complexes

$C_9H_{13}NO_2$	$C_9H_{13}NO_2HCl$	Tentative assignments
3660	3500	Unassociated νO-H
3240-3000br		associated νO-H
3340m 3280		νNH_2
	3040	νNH_3^+

$(C_9H_{12}NO)_2Cu.\ CH_3OH$	$(C_9H_{12}NO)_2Cu.3H_2O$	Tentative assignments cm^{-1}
3650	3500-3000	νO-H associated O-H
3300	3350w	νN-H
580		Cu-O-Cu
390v.s.	365	νCu-O
370	310	
335	280	νCu-N
	222	νCu-O

$[Cu(C_9H_{12}NO)Cl]_2$	Tentative assignments cm^{-1}
3290 3235 3150	νNH_2
374 330	Cu-O Cu-Cl
250 230	Cu-N

Table 4.2.7iiElectronic and Magnetic Data for complexes of

dl - phenylpropanolamine

$Cu\ (C_9H_{12}NO)_2 3H_2O$

Diffuse Reflectance Spectra cm^{-1}	max $m\mu$	E.S.R. Data		Magnetic Moment B.M.
17 500	571	g	2.041	1.86
		g	2.204	
		G	4.95	
	$Cu(C_9H_{12}NO)_2CH_3OH$			
20 000	500	g	1.975	
17 000	588	g	2.114	
		G	4.50	
	$[Cu(C_9H_{13}NO)Cl]_2$			
		low field:		
26 200	38		4.22	0.448
16 000	606			

Complexes of dl-N-Methylephedrine

INFRARED SPECTRA The infrared spectrum of the free base dl-N-Methylephedrine is not very informative in the region above 3000 cm^{-1}. A broad band, 3200 - 2700 cm^{-1} is assigned to associated OH groups of dl-N-Methylephedrine. No N-H bond is present in the compound and therefore no evidence for coordination to nitrogen is expected in this region of the infrared spectrum.

4.2.9 $[(C_{11}H_{16}NO)Cu(C_{11}H_{17}NO)OH]_2\ 8H_2O$ VIOLET

The infrared spectrum of the complex shows a broad band 3500 - 3200 cm^{-1} which is due to coordinated water[84] and possibly hydrogen bonded OH groups. A band at 1660cm^{-1} is due to lattice or coordinated water.

In the far infrared region a band at 395 cm^{-1} is assigned to νCu - O, sharp bands at 310 and 280 cm^{-1} are assigned to coordinated water; bands at 245 and 226 cm^{-1} are tentatively assigned to νCu - N.

The infrared spectrum suggests that oxygen is bonded to copper. Evidence for Cu - N is not so convincing. The presence of two methyl groups coordinated to the nitrogen atom would make it difficult for nitrogen to coordinate to copper. However in view of the fact that the complex was formed under conditions similar to that of the chelates of d-pseudoephedrine, l - ephedrine, dl-phenylpropanolmine and l-phenylephrine and was violet in colour the formation of a chelate ring with perhaps weak coordination of copper to nitrogen would be possible.

Elemental analysis shows that water is in the complex and the I.R. confirms the presence of lattice water. A peak at 1660 cm^{-1} is typical of lattice water.

The infrared spectra before and after recrystallisation were identical, although the data from elemental analysis indicated that after recrystallisation from a mixture of acetone and water, the number of water molecules had increased. If however the water was coordinated to other water molecules by hydrogen bonding in the crystal lattice then the overall infrared spectrum would not distinguish between the two compounds.

DIFFUSE REFLECTANCE SPECTRUM. Bands were observed at 21 300 and 18 000 cm^{-1}. The intense colour of this complex could be due to a change transfer band. The band at 21 300 cm^{-1} is assigned to a charge transfer transition and the band observed at 18 000 cm^{-1} is consistent with copper in an elongated tetragonal - octahedral environment, in which the copper is in a square plane with two oxygen atoms from water above and below the plane.

E.S.R. SPECTRUM. A broad isotropic spectrum giving an average g-value of 2.05 g was observed. This was probably due to extensive exchange coupling between grossly misaligned local copper (II) ions. As such no information on the ground state of copper (II) in the complex could be obtained. A similar result was obtained for the other complexes of this series.

MAGNETIC SUSCEPTIBILITY. The measurement of the magnetic susceptibility giving a magnetic moment of 1.53 BM was consistent with exchange coupling between copper centres and indicated a polynuclear species. It is possible that chains of dimers linked through hydrogen bonding could exist such as represented below. The infrared spectrum did not indicate the presence of bridging hydroxo groups in the complex so it is likely that exchange coupling occurs via the oxygen atoms of the chelated dimer.

THERMOGRAVIMETRIC ANALYSIS. This complex was thermally unstable. It began to decompose at ~ 37°. Initially the complex lost 10 moles of water. Decomposition occured within a narrow interval of temperature.

4.2.10 Di - μ - chlorobis(dl-N-Methylephedrinato) copper (II)

$C_{11}H_{16}NO\ CuCl$ Green

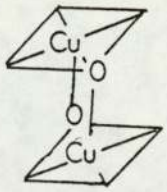
INFRARED SPECTRUM. The spectrum showed no bands in the region greater than 3000 cm^{-1}, indicating the absence of water in the complex. With no OH band present a chelate ring formed through coordination of copper to oxygen and nitrogen seems possible, according to equation 3, section 4.2.2, thus fitting in with the series of compounds with the same empirical formula.

Coordination to nitrogen is suggested by bands at 260 and 220 cm^{-1} and coordination of oxygen is suggested by the band at 435 cm^{-1}. A band at 243 cm^{-1} is assigned to νCu - Cl. This band occurs in the region that contains bridging and terminal Cu - Cl stretching vibrations and it can only be tentatively assigned to bridging Cu - Cl.

E.S.R. SPECTRUM. The E.S.R. Spectrum of this complex is shown in Figure 4.2.10. The main line gave a g-value = 2.203 and a weak line at low field gave a g value = 4.14, together with hyperfine structure, indicating interaction of the electron with the nuclear spin of atoms of the ligand. The appearance of the spectrum supports the idea of a dimeric complex.

MAGNETIC SUSCEPTIBILITY. The magnetic susceptibility measurement gave a room temperature magnetic moment of 1.85 B.M. which lies within the range 1.8 - 2.0 B.M. normally found for copper (II) complexes in the absence of any ferromagnetic coupling.

It has been observed by some authors that binuclear systems having the geometrical arrangement shown below have a low degree of magnetic interaction and it is therefore not surprising that they can give rise to normal magnetic moments.



However since the empirical formula of this complex is $C_{11}H_{16}NO\ CuCl$ for copper to complete its coordination number to 4, then dimerisation must take place. The above representation for the complex is not possible and structures a or b section 4.2.2. would be a better representaton. If the dimer has halogen bridges such as in a then the high magnetic moment found suggests that the intramolecular distances are fairly large. There are many compounds with normal magentic moments [92] in which halogen bridging is present. Structure (a) section 4.2.2. would therefore be supported by the high magnetic moment.

DIFFUSE REFLECTANCE SPECTRUM. The spectrum shows a charge transfer band at 25 000 cm^{-1} and bands at 14 800 cm^{-1} and 12 500 cm^{-1}, which are consistent with a $d_{x^2 - y^2}$ ground state.

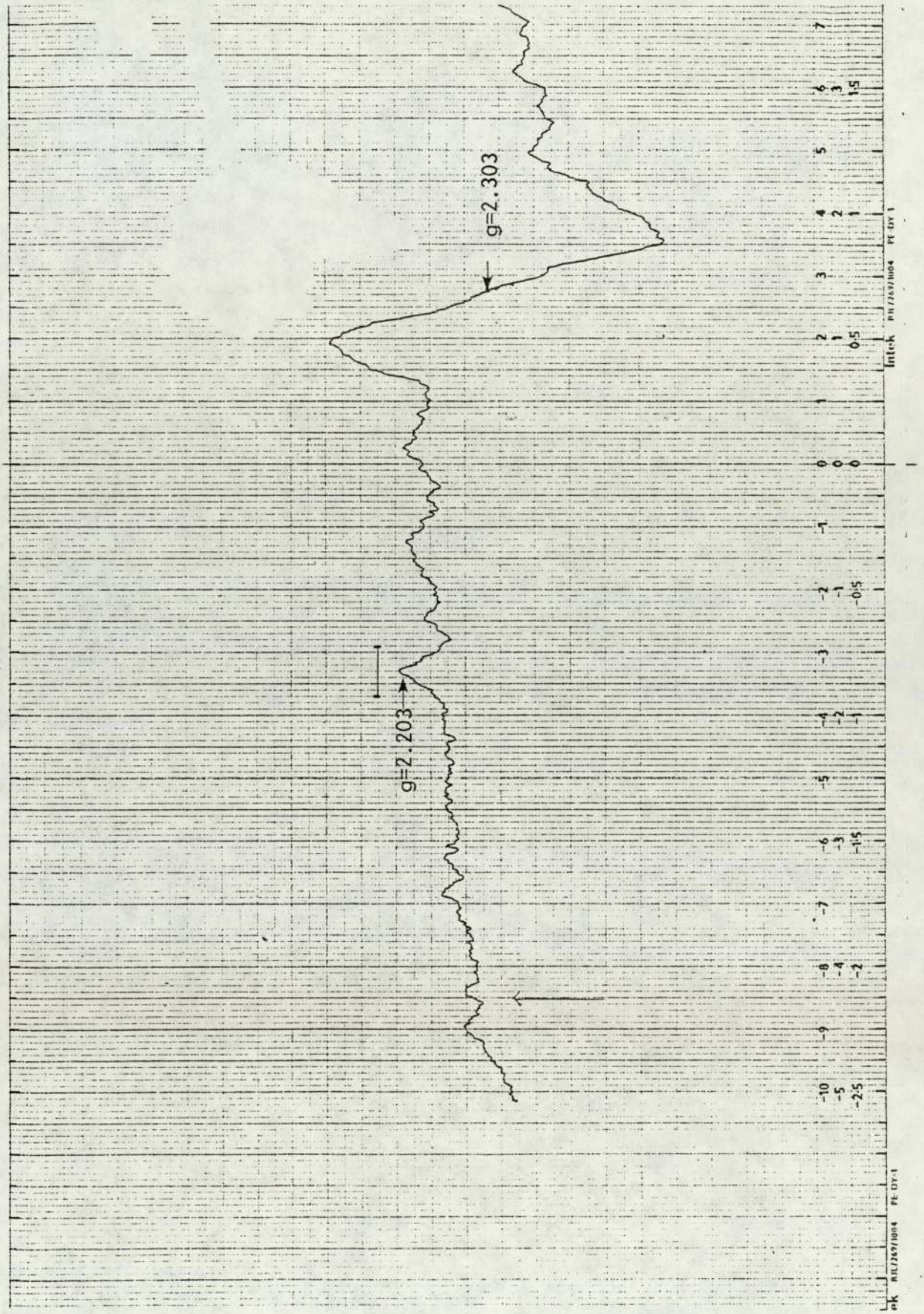


Figure 4.2.10

Table 4.2.9(i) IR spectra of dl-N-methylephedrine and its complexes

$C_{11}H_{17}NO$	$C_{11}H_{17}NO$ HCl	Tentative assignments
	cm^{-1}	
3200-2700br		Associated
	3280v.s	OH
	2640v.s	νNH^+

$[(C_{11}H_{16}NO)Cu(C_{11}H_{17}NO)OH]_2 8H_2O$	$[C_{11}H_{17}NO\ CuCl]_2$	Tentative Assignments
3500 - 3200		ν O-H
1660		H_2O
395	435	νCu-O
280		νCu-O
310		
245	260	
	220	νCu-N
	245	νCu-Cl

Table 4.2.10 Electronic and Magnetic Data for complexes of dl-N-methylephedrine

Diffuse Reflectance Spectra cm^{-1}	max $m\mu$	E.S.R. Data	Magnetic Moment BM
$\left[(C_{11}H_{16}NO)\,Cu(C_{11}H_{17}NO)\,OH\right]_2 \cdot 8H_2O$			
21 300	469	2.059	1.37
18 000	556		
$Cu(C_{11}H_{16}NO)Cl_2$			
25 500	392	4.14	1.85
14 800	676	2.203	
12 500	800		

Complexes of l -phenylephrine

INFRARED SPECTRA. A sharp peak observed at 3625 cm^{-1} in the spectrum of the free base and is assigned to the meta OH group of l-phenylephrine. A band at approximately 3600 cm^{-1} is observed in the spectra of alcohols or phenols in which intermolecular hydrogen bonding is minimized[79].

4.2.11 Bis(l-phenylephrinato)copper (II) dihydrate $C_9H_{12}NO_2\ Cu.2H_2O$

A double peak is observed at 3330 and 3000 cm^{-1}. Both of these are sharp. The split peak is assigned to the NH group on the basis that many of the peaks in the spectrum of the free base and the complex are split. A broad band between 3500 and 3200 cm^{-1} is assigned to water. In the far infrared spectrum of l-phenylephrine are strong absorptions which make it difficult to assign metal ligand bands with certainty. Assignments made are therefore tentative. A band at 355 cm^{-1} is assigned to copper-oxygen stretching. A split band at 246 and 228 cm^{-1} is assigned to copper-nitrogen stretching vibrations.

The far infrared region does not give any positive evidence for the coordination of water.

It is possible that the hydroxyl proton of the OH group is lost on chelation of copper to the ligand.

DIFFUSE REFLECTANCE SPECTRUM. The spectrum was very similar to the spectra observed for the violet chelates of the sympathemimetic amines already described. Bands were observed at 21 000 and 12 500 (shoulder) cm^{-1}. These bands are consistent with copper in a trans square planar environment[90].

E.S.R. SPECTRUM. The observed spectrum was isotropic giving an average g - value of g = 2.087. It was similar to the spectrum observed for similar complexes of the group.

THERMOGRAVIMETRIC ANALYSIS. The results showed that the complex was decomposed gradually by pyrolysis, initially losing water and then decomposing within a narrow range of temperature under the conditions employed.

The X-ray crystal structure of the monohydrate form of this complex has recently been investigated[67].

The findings of this work are in agreement with the structural assignment here reported by Nakai and Noden[67]. They reported that the copper environment is trans square planar, the two phenylephrino ligands acting as bidentate ligands through the N and O atoms, and that the crystal was composed of neutral complexes and uncoordinated water molecules.

Data from elemental analysis indicated that the dihydrate form at the complex had been prepared in this work, section 3.2.11.

The authors in preparing the complex used aqueous copper (II) nitrate instead of aqueous copper (II) sulphate. They were unable to recrystallise this complex.

4.2.12 di-μ- dichlorobis(1-phenylephrinato)copper(II) $[(C_9H_{13}NO_2)CuCl_2]_2$

green

In the region above 3000 cm^{-1} a broad band indicating hydrogen bonding in the complex is observed. No single band could be identified which could be assigned to any functional groups.

In the far infrared region a band observed at 248 cm^{-1} is assigned to copper chlorine stretching and bands at 230 and 210 cm^{-1} are assigned to copper-nitrogen stretching vibrations.

DIFFUSE REFLECTANCE SPECTRUM. Bands were observed at 27 200 and 13 200 cm^{-1} and in this respect the complex was similar to the complex of methylamphetamine, $[(C_{10}H_{15}N)CuCl_2]_2$.

E.S.R. SPECTRUM. The E.S.R. spectrum showed low and high field signals, indicating the presence of a dimeric species. The low field signal observed at 1630G was 4.46 g and the signal observed at high field gave $g_{av.} = 2.050$.

No other physical data were obtained for this complex, but in view of the similarities of the physical data with the complex of methylamphetamine is $C_{10}H_{15}N)\ CuCl_2\ _2$ together with data from elemental analysis a similar structure is proposed in which the amino nitrogen is involved in coordination and the oxygen from the hydroxyl group is not coordinated

Table 4.2.11 IR spectra of l-phenylephrine, l-phenylephrine hydrochloride and its complexes.

$C_9H_{13}NO_2$	$C_9H_{13}NO_2.HCl$	Tentative assignments cm^{-1}
	3450	ν O-H
	3200	ν O-H
	2800br	ν NH_2^+

$(C_9H_{12}NO)_2Cu\ 2H_2O)$	$[(C_9H_{13}NO_2)CuCl_2]_2$	Tentative assignments cm^{-1}
3635	3600-3100	ν OH
3335		ν OH
3300		νN-H
530		Cu⟨O⟩Cu
470		Cu-N
355v.s		Cu-O+ Ligand
	248	Cu-Cl
287		
276s	230	Cu-N
	210	
246		
228vs		

Table 4.2.11(ii) Electronic and Magnetic Data for complexes of l-phenylephrine.

$Cu(C_9H_{12}NO_2)_2\ 2H_2O$

Diffuse Reflectance spectra cm^{-1}	max $m\mu$	E.S.R. Data	Magnetic Moment BM
21 000	476	2.086	
12 500	800		

$[Cu(C_9H_{13}NO_2)Cl_2]_2$

27 200	368		
13 200	758		

Complexes of d-amphetamine

INFRARED SPECTRA. The infrared spectrum of the free base d-amphetamine Fig 4.2.14 (i) shows absorptions that are typical of a primary amine. Bands at 3470 and 3300 cm^{-1} are assigned to N-H stretching vibrations. A shoulder is also observed at 3140 cm^{-1} and is assigned to NH_2

4.2.14. Dichlorobis (d-amphetamine) copper (II) Dichloro-bis (d - N, α- methylphenylethylamine) copper (II) $(C_9 H_{13}N)_2CuCl_2$ blue

INFRARED SPECTRUM. In the infrared spectrum of the complex Figure 4.2.14 (ii) the NH_2 stretching vibrations are shifted to lower frequency. 3310 and 3240 cm^{-1} indicating that the NH_2 group is coordinated to the copper. A sharp band is also observed at 3140 cm^{-1} which is probably the shoulder that was observed in the infrared spectrum of the free base.

The far infrared spectrum was traced using the complexes synthesized using the stable isotopes ^{63}Cu and ^{65}Cu.

The very strong symmetrical band at 295 cm^{-1} and the band at 207 cm^{-1} are assigned to the copper-chlorine stretching vibration. The band at 230 cm^{-1} is assigned to the copper-nitrogen stretching vibration.

DIFFUSE REFLECTANCE SPECTRUM. A broad band with a maximum at 16 300 cm^{-1} was observed which is consistent with a $d_{x^2-y^2}$ ground state.

E.S.R. SPECTRUM. A broad isotopic spectrum showing a point of inflection between the two maxima was observed [86] Figure 4.2.14 (iii) The observed g-values were $g_{\parallel} = 2.204$ and $g_{\perp} = 2.024$. This does not give any conclusive information on the electronic ground state present[85,86]

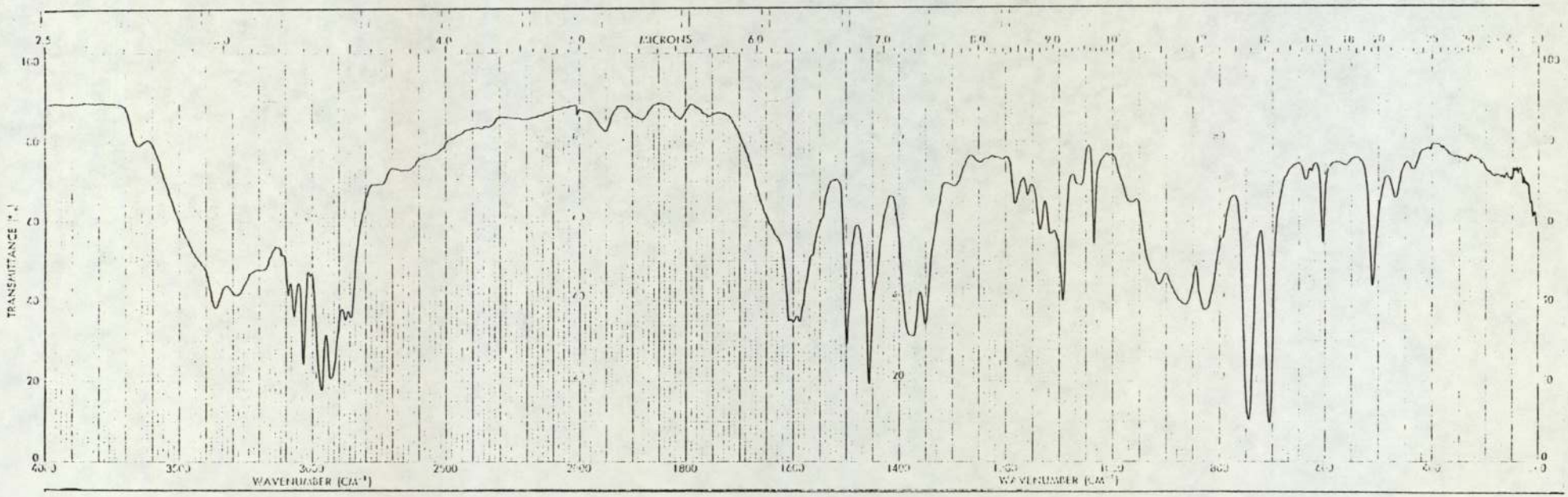


Figure 4.2.14 (i)

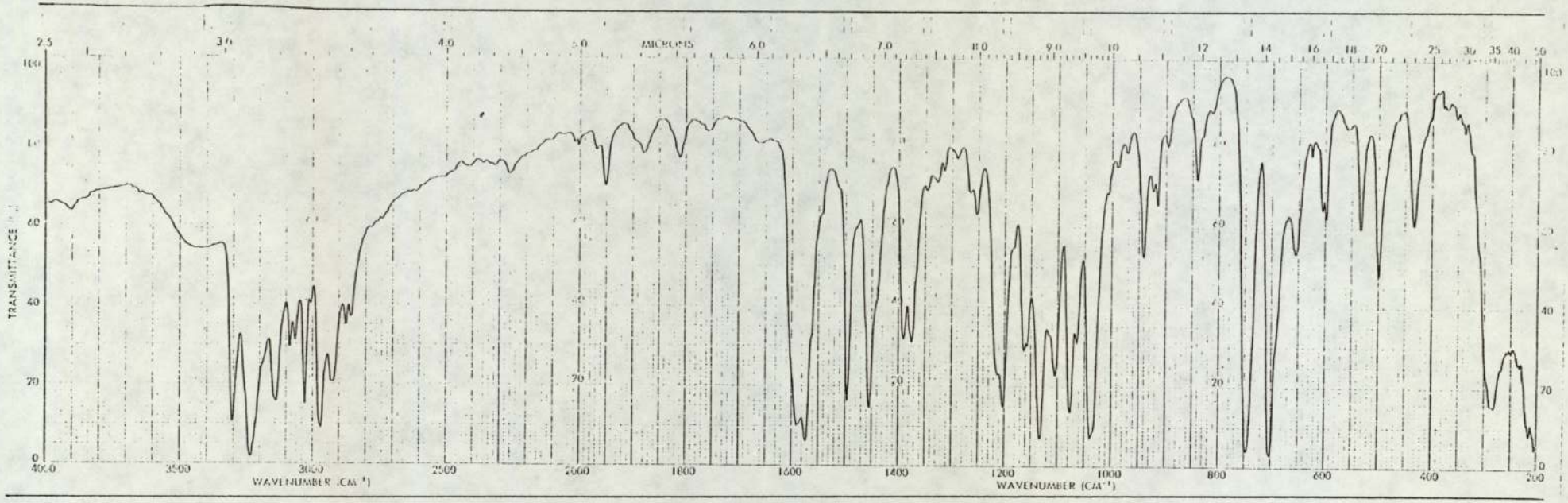
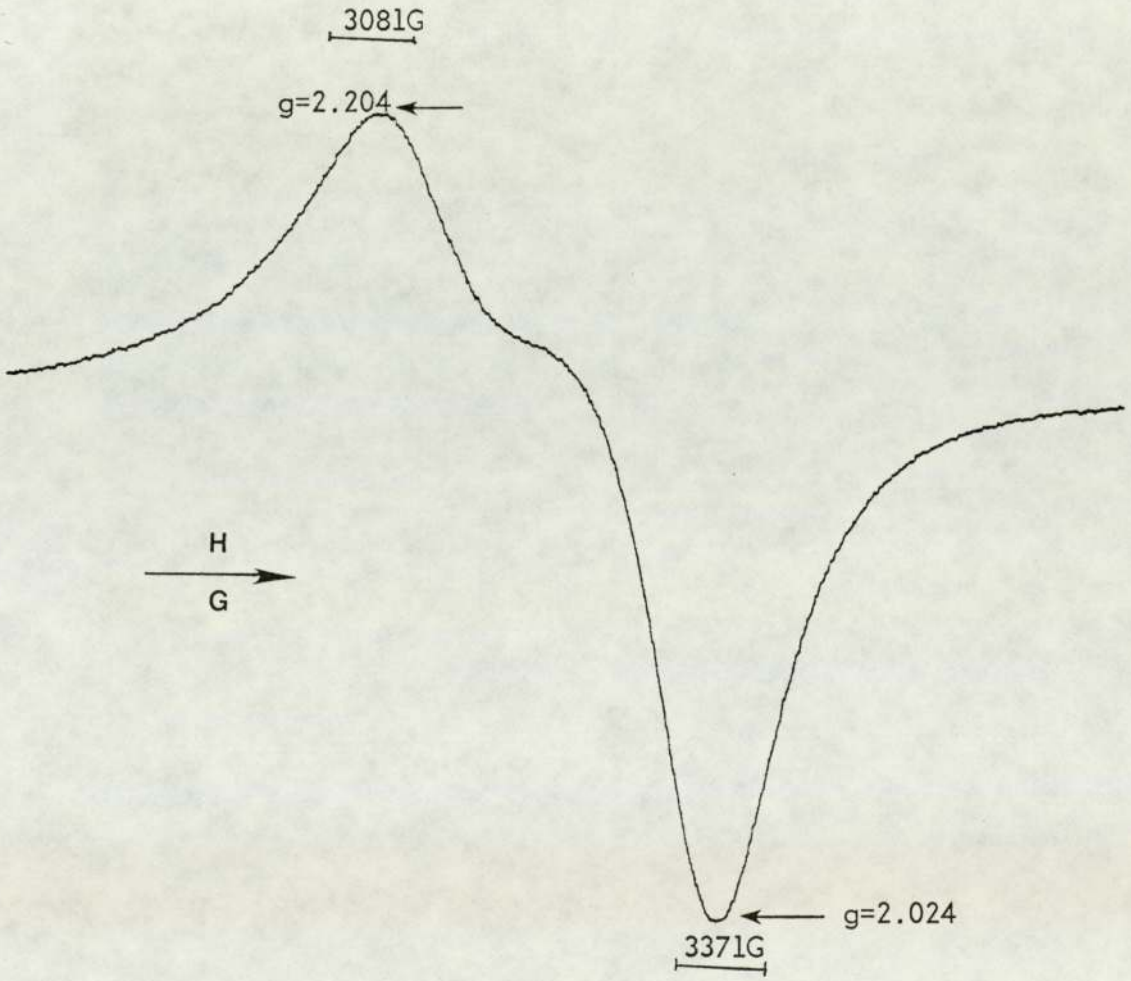


Figure 4.2.14 (ii)

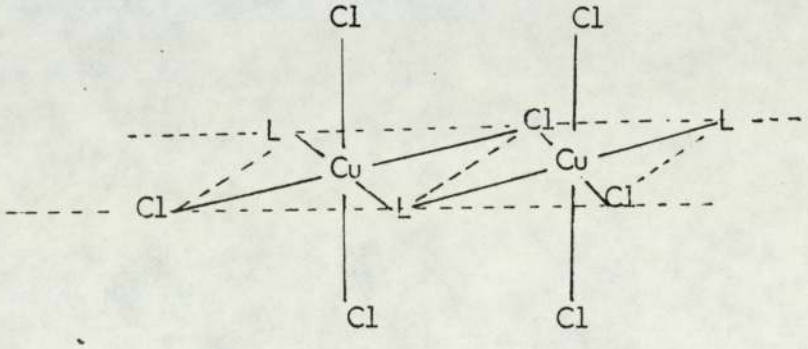
Figure 4.2.14 (iii)



It is possible that extensive exchange coupling takes place between copper atoms .

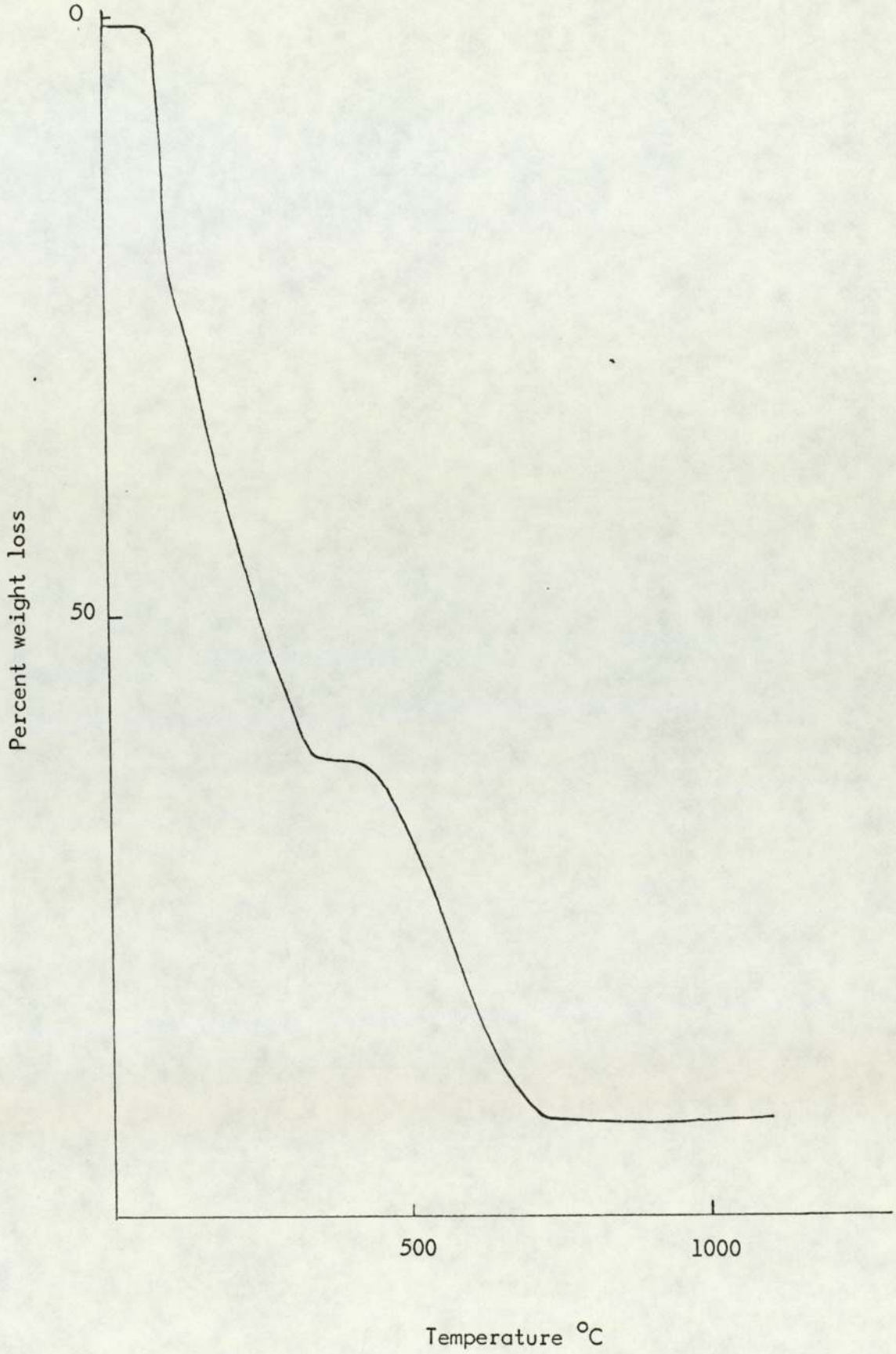
MAGNETIC SUSCEPTIBILITY. Bulk susceptibility measurements giving the room temperature magnetic moment as 1.67 B.M. which is less than the expected experimental value in the absence of interaction between copper centres, supported the results of the E.S.R. data i.e. extensive exchange coupling was occuring.

If this complex has a similar structure to $Cu(Py)_2Cl_2$ then the structure would consist of trans square planar Cu $(C_9H_{13}N)_2$ Cl_2 groups which are linked together to form chains by weak copper-chlorine interactions as shown in Figure 4.2.14 (iv)



THERMOGRAVIMETRIC ANALYSIS. The results indicated that the complex started to decompose at approximately 120° , losing two moles of d-amphetamine Figure 4.2.14 (v). At 361° both ligands had been completely removed leaving $CuCl_2$ indicating that the d-amphetamine had been lost cleanly

Figure 4.2.14 (v)



4.2.15 $Cu_4C_{20}H_{34}N_2O_2Cl_4$ green

INFRARED SPECTRUM. In the region above 3000 cm^{-1} a broad band with a maximum at 3320 cm^{-1} is observed. This is assigned to associated OH stretching. A shoulder is observed at 3500cm^{-1} which is quite broad. It is possible that this band is due to N-H stretching vibrations.

A strong broad band centred at 1600 cm^{-1} in the spectrum of the free base is assigned to deformation of the NH_2 group. In the spectrum of this complex a strong sharp band at 1580 cm^{-1} is assigned to a secondary amine[79] suggesting that the amphetamine has become alkylated and that the NH group is involved in coordination. The C.H.N. data, Table 3.2.14 confirmed this. There are bands in this complex that are not very well resolved.

A band at 325 cm^{-1} is assigned to copper-chlorine stretching and a broad band at 470 cm^{-1} is assinged to bridging Cu-O-Cu. It is possible that the OH group forms a bridge between two copper atoms

A band at 280 cm^{-1} is assigned to bridging copper-chlorine and a band at 230 cm^{-1} is assigned to copper-nitrogen stretching vibrations.

DIFFUSE REFLECTANCE SPECTRUM. The spectrum shows aband at 12 500 cm^{-1} which is characteristic of dimeric complexes prepared in this work with Copper (II) and β-phenylethylamine; and also bands at 27 200 and 14 500 cm^{-1}

E.S.R. SPECTRUM. Both low and high field signals are observed for this complex indicating the presence of a dimeric structure. The low field signal was observed at 4.2 g and the high field signal at 2.024 g. The signal at high field was very broad indicating that exchange coupling was present between copper (II) ions in the complex.

MAGNETIC SUSCEPTIBILITY. The magnetic moment was 1.66 B.M. indicating that the copper (II) ions were not well separated, and that interaction was taking place between the copper centres. If the structure of the complex can be represented as shown below then it is possible that direct interaction could take place between the individual copper (II) ions, such as is found in binuclear copper (II) acetate or superexchange interaction through the OH or Cl bridges or both bridges. There is also a possibility of mixed bridges in the complexes

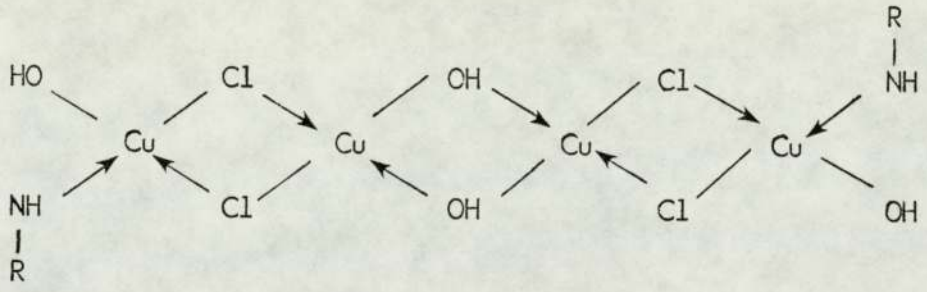


Figure 4.2.15(a)

The formation of such a complex is suggested by data from elemental analysis. The complex was formed in methanol after the evolution of heat. Section 3.2.15 it is possible that copper(II)chloride could catalyse the alkylation of amphetamine in methanol.

This reaction seems only to occur when there is a free primary amine group. The alkylation of substituted amines did not seem to take place under similar conditions.

THERMOGRAVIMETRIC ANALYSIS. The results showed that the complex began at decompose at 133°. The initial weight loss occured within a narrow interval of temperature. After this decomposition was gradual. Decomposition was complete at 747°

Figure 4.2 . 14 a

ΔH_{diss} = 47·78 kJ/mol

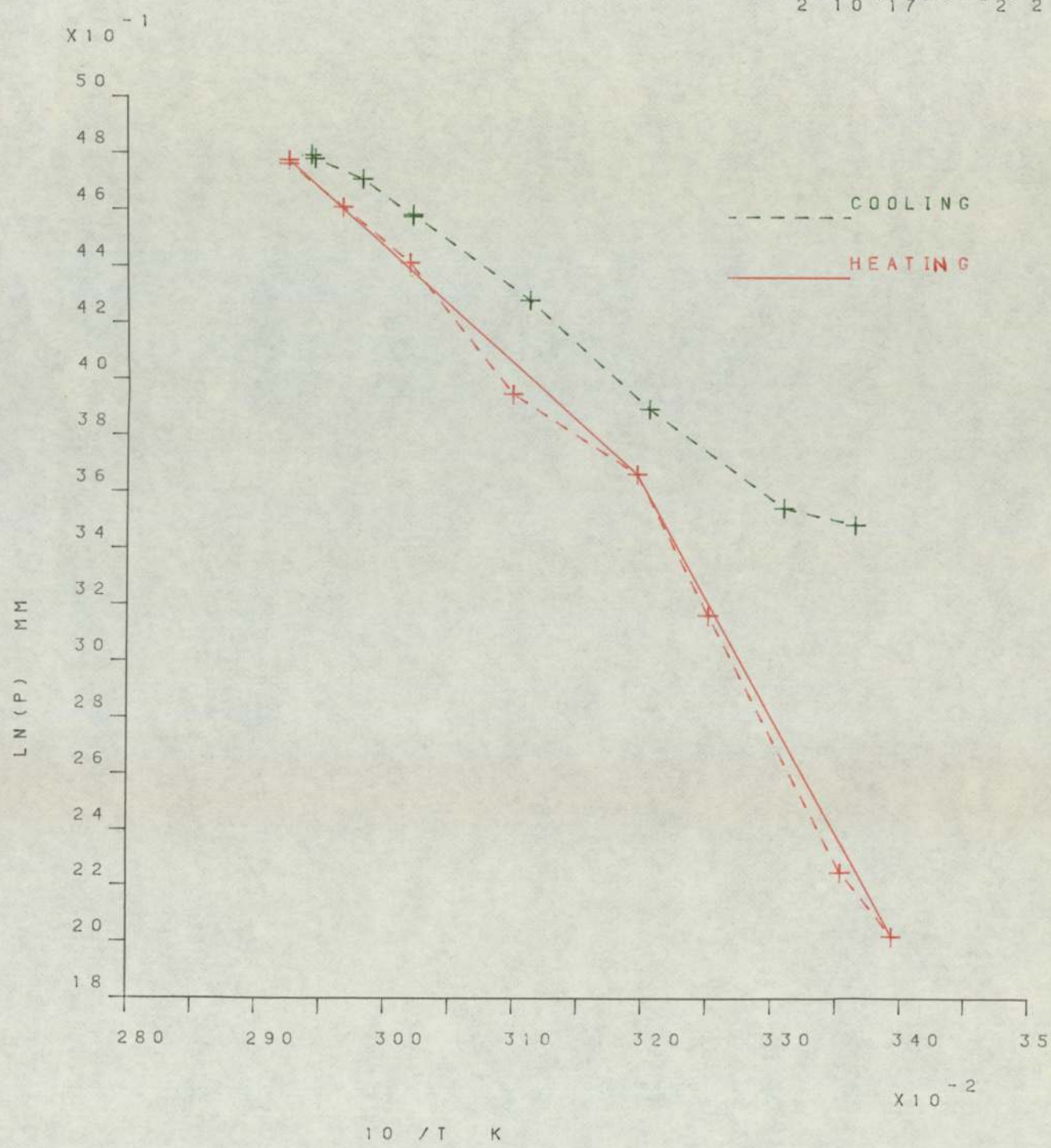


Figure 4.2.14(b)

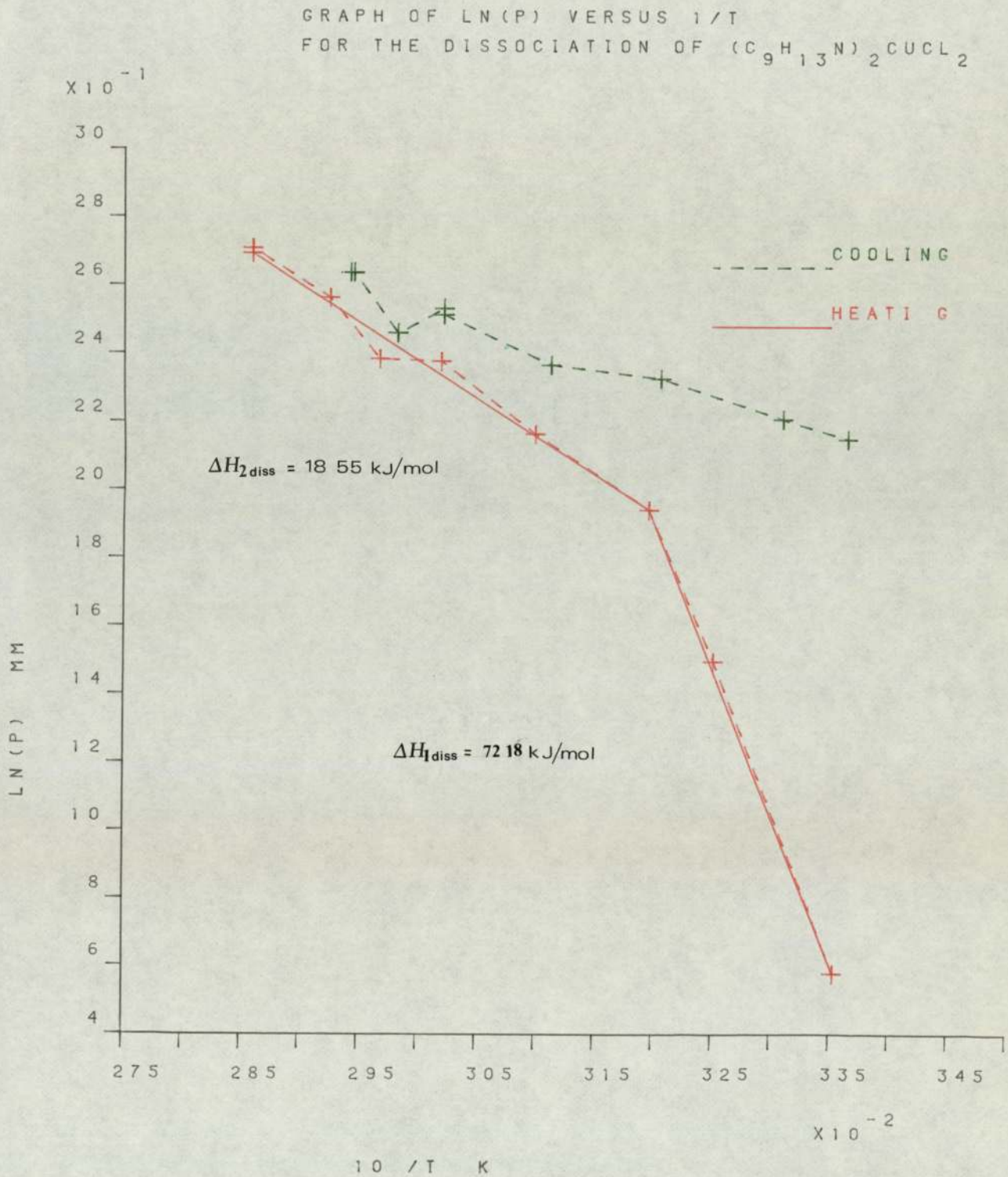


Figure 4.2.14(c)

ΔH_{vap} = 46.51 kJ/mol

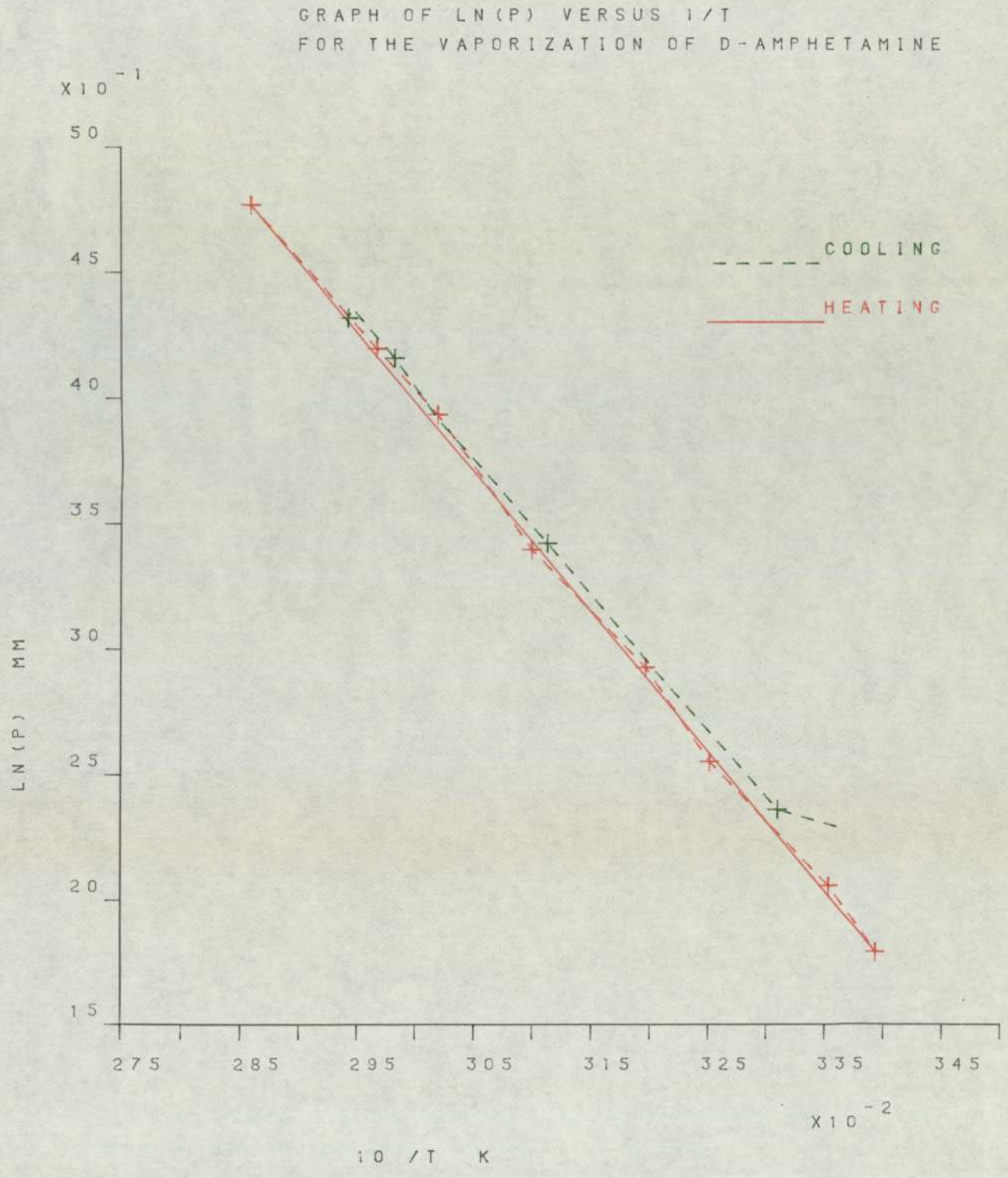


Table 4.2.14(i) IR Spectra of d-amphetamine and its complexes.

$C_9H_{13}N$	$Cu(C_9H_{13}N)_2Cl_2$	Tentative assignemnts cm^{-1}
3470	3310vs	νNH_2
3300	3240vs	
	3140	
1600		νN-H
	295s,br	Cu-Cl
	207	
	230	Cu-N

$[Cu_2C_{10}H_{17}NO_2Cl_2]_2$	assignments cm^{-1}
3500	νO-H
3320	νN-H
1580	νNH
470	Cu O Cu
325	Cu-Cl
280	
230	Cu-N

Table 4.2.14 ii Electronic and Magnetic Data for complexes of d-amphetamine

$Cu(C_9H_{13}N)_2Cl_2$

Diffuse Reflectance Spectra ν_{max} cm^{-1}	$m\mu$	E.S.R. Data	Magnetic Moment BM
16 300	615	g_1 2.204	1.67
		g_2 2.024	
		$\left[Cu_2C_{10}H_{17}NOCl_2\right]_2$	
27 200	368	g 2.024	1.66
14 500	690		
12 500	800		

Complexes of d - methylamphetamine

INFRARED SPECTRA. A broad band in the spectrum of d - methylamphetamine at 3400 cm^{-1} with a shoulder at 3300 cm^{-1} is assigned to the N-H stretching vibration

4.2.16 Dichloro-bis(d - N, α - dimethylphenylethylamine Copper (II) $(C_{10}H_{15}N)\ CuCl_2$ Violet

INFRARED SPECTRUM. In the spectrum of the complex a sharp band at 3240 cm^{-1} is assigned to the N-H stretching vibration. This band is lowered relative to the band observed for d-methylamphetamine. This shift to lower wavenumber indicates that the nitrogen atom is coordinated to copper.

In the far infrared region a very strong band at 315 cm^{-1} and a weak absorption band at 270 cm^{-1} are assigned to copper - chlorine stretching vibrations. A band at 230 cm^{-1} is assigned to copper - nitrogen stretching.

The strong Cu - Cl band at 315 cm^{-1} is indicative of a terminal copper - chlorine band The simple far infrared spectrum with very few bands indicates a symmetrical structure.

DIFFUSE REFLECTANCE SPECTRUM. A band is observed at 28 800 which is probably a charge transfer band. Bands are observed at 19 000 and 15 000 (shoulder) cm^{-1} which are consistent with copper is a trans square coplanar environment [90].

E.S.R. SPECTRUM. The observed spectrum, Figure 4.2.16 is anisotropic showing two g-values, g_{11} = 2.183 and $g_{\perp}$ = 2.041. The lowest g-value

is greater than 2.03 which suggests a $d_{x^2-y^2}$ ground state is present rather than d_{z^2}. Relating the two g-values by the expression $G = g_{11} - 2 / g_1 - 2 = 4.45$ shows that exchange coupling if present is negligible and the local tetragonal axes are aligned parallel or only slightly misaligned and the observed g-values reflect the local environments of the copper (II)

MAGNETIC SUSCEPTIBILITY. The magnetic moment calculated from the experimental measurement of the magnetic susceptibility was 1.75 B.M. and was withinthe experimental range expected for compounds with strong covalent bonds. The magnetic moment does not indicate any interaction between the copper atoms and it is possible that the complex does not exist in a polymeric form such as in $Cu(Py)_2Cl_2$ where there are chlorine bridges forming chains throughout the complex structure.

The balance of data suggests that the copper (II) is in a trans square planar environment, where the two chlorine and two d-methylamphetamine ligands are coordinated trans, such that the chlorines are equivalent and the d-methylamphetmine ligands are equivalent. This complex has been reported in the literature [69] the authors said that the complex isolated was not pure due to its unstable nature.

As earlier explained in section 3.2.16 this complex was found to be unstable in the presence of air. Analysis of the decomposition product indicated that one mole of the ligand was lost. The complex changed from violet to green, $[(C_{10}H_{15}N)CuCl_2]_2$

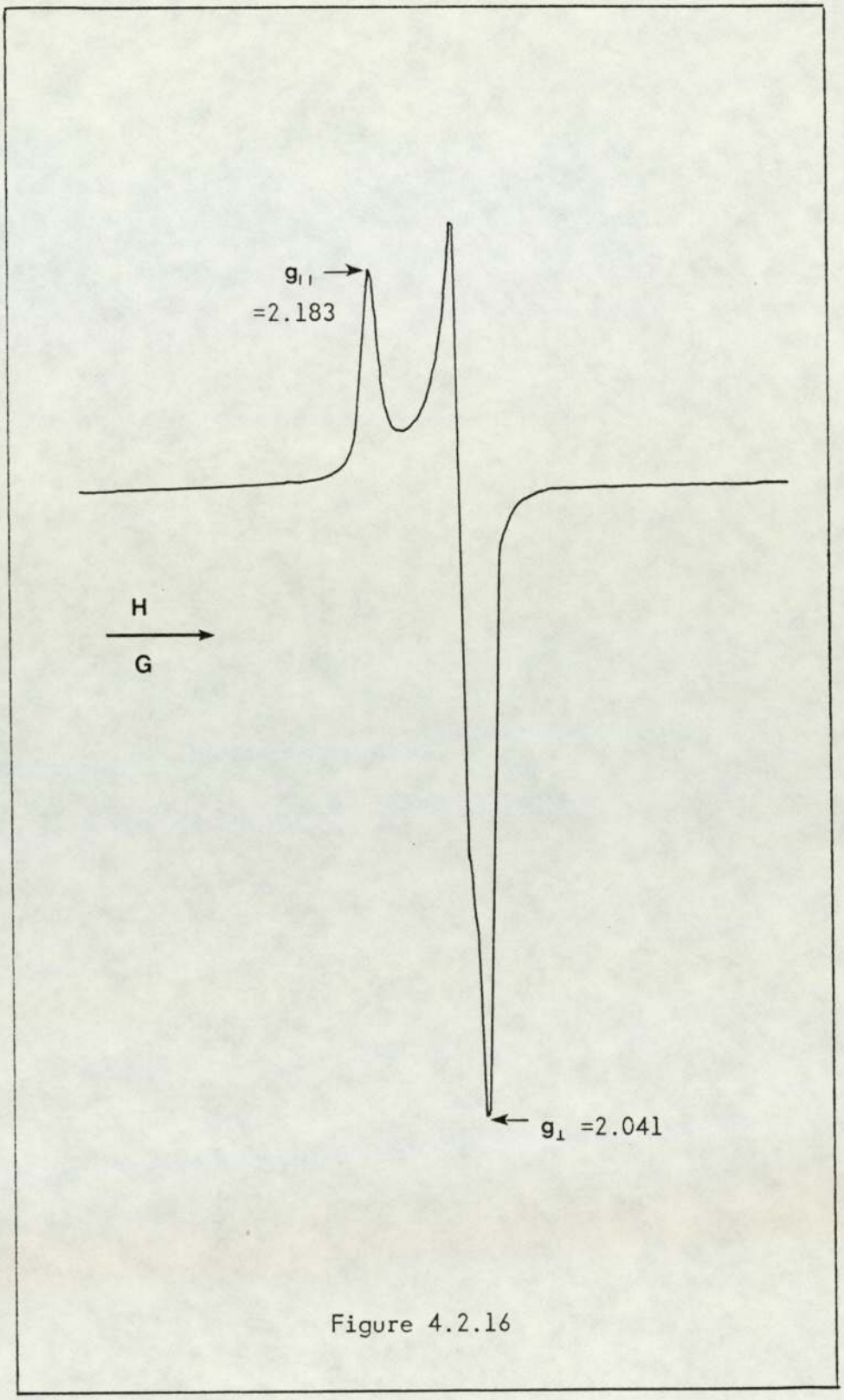


Figure 4.2.16

4.2.17 Di-μ-dichlorobis (d-N,α- dimethylphenylethylamine) Copper II $[(C_{10}H_{15}N)CuCl_2]_2$ green

INFRARED SPECTRUM. A band at 3180 cm^{-1} with a shoulderat 3280 was assigned to the N-H stretching vibration.

In the far infrared region a band at 276 cm^{-1} was assigned to bridging copper chlorine and a band at 228 cm^{-1} was assigned to copper nitrogen. These bands were not very well resolved and assignments are tentative.

DIFFUSE REFLECTANCE SPECTRUM. Bands at 27 200 and 13 200 were observed. The former band is probably a charge transfer band. The latter band observed is consistent with a $d_{x^2-y^2}$ ground state.

E.S.R. SPECTRUM. Both low and high field signals were observed indicating that a dimeric species was present. The low field signal at 1520 G was 4.46 g, $g_{av.}$ at high field was observed to be 2.050 g. The most significant piece of information from this E.S.R. spectrum is the presence of the low field signal which has been observed in complexes which are dimeric. The data is supportive of a $d_{x^2-y^2}$ ground state[100].

The experimental data suggests that a correct representation of the complex is as indicated below. Dimerisation is thought to take place to increase the coordination number of copper from 3 to 4. The E.S.R. data supports this proposal

The present data does not distinguish between structures a and b structure a would be more favourable because the electrostatic replusion between the chlorines would be less than in b.

Thermogravimetric analysis of this complex showed that it began at decompose at 80°. Decomposition was complete at 341° D-methylamphetamine was lost cleanly leaving $CuCl_2$.

Figure 4.2.16a

$\Delta H_{diss.}$ was determined and found to be -75.68 kJ/mol

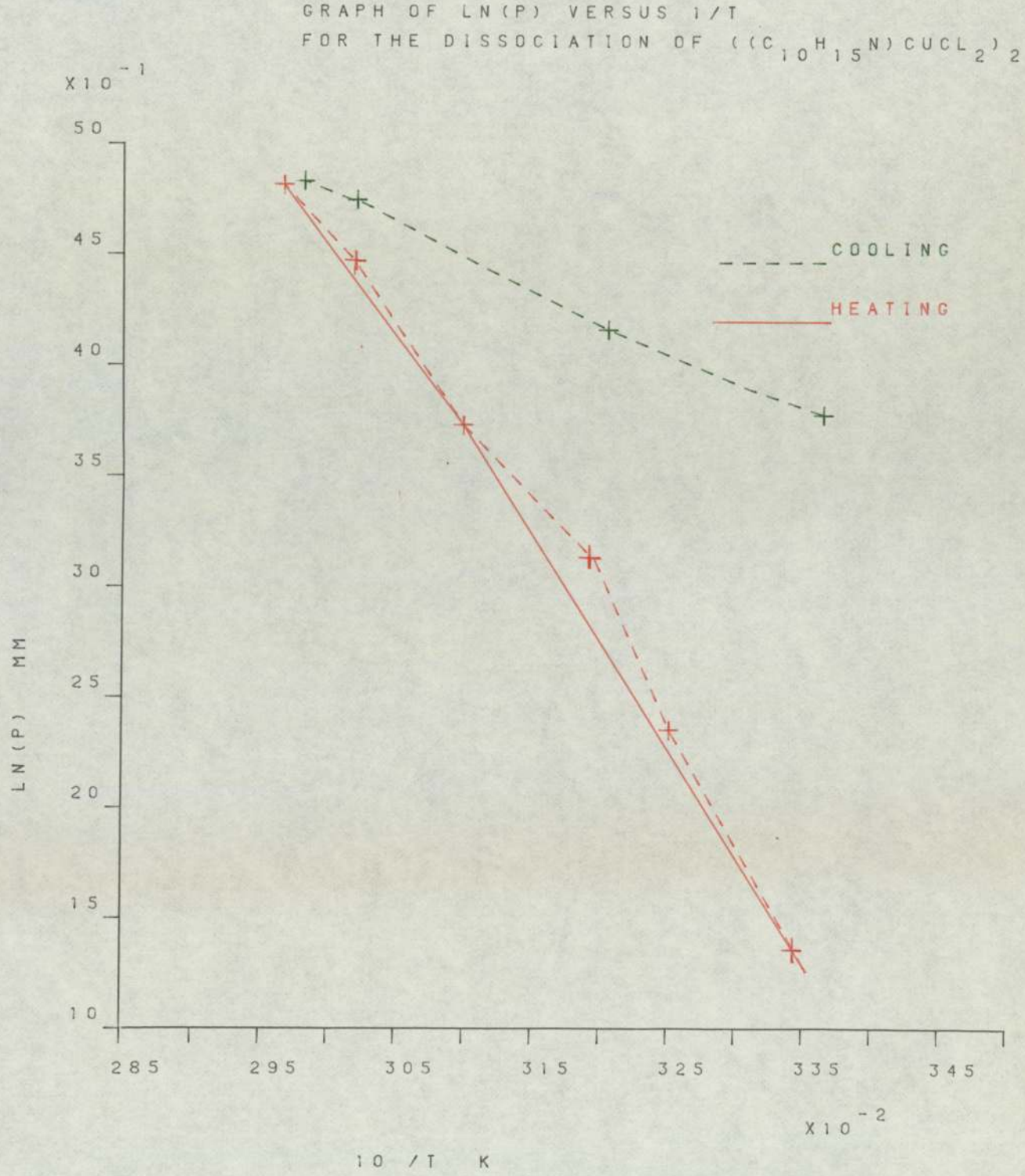


Figure 4.2.16 b

$\Delta H_{diss} = 38{\cdot}2$ kJ/mol

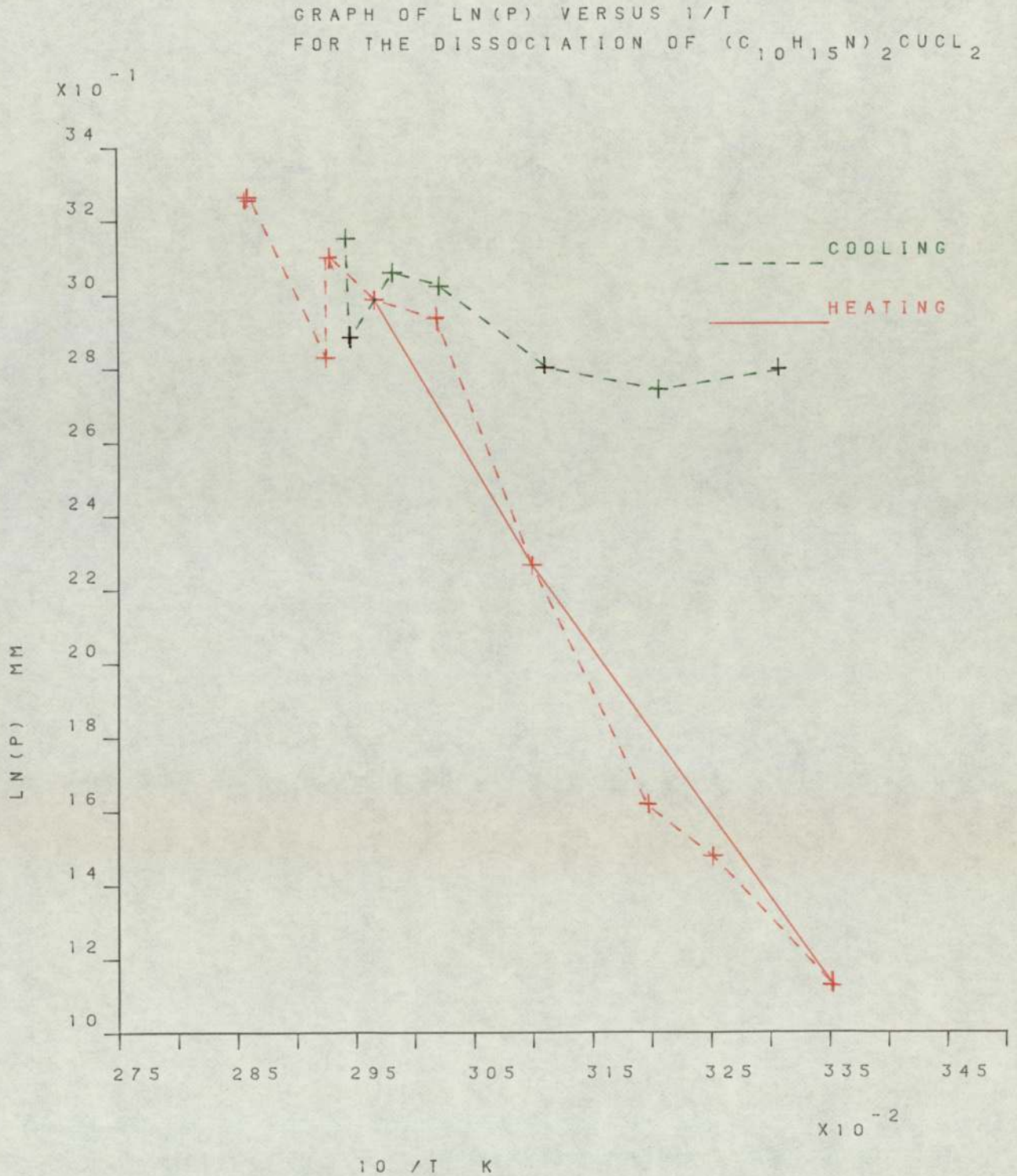


Figure 4.2.16(c)

ΔH_{vap} = 42.98 KJ/mol

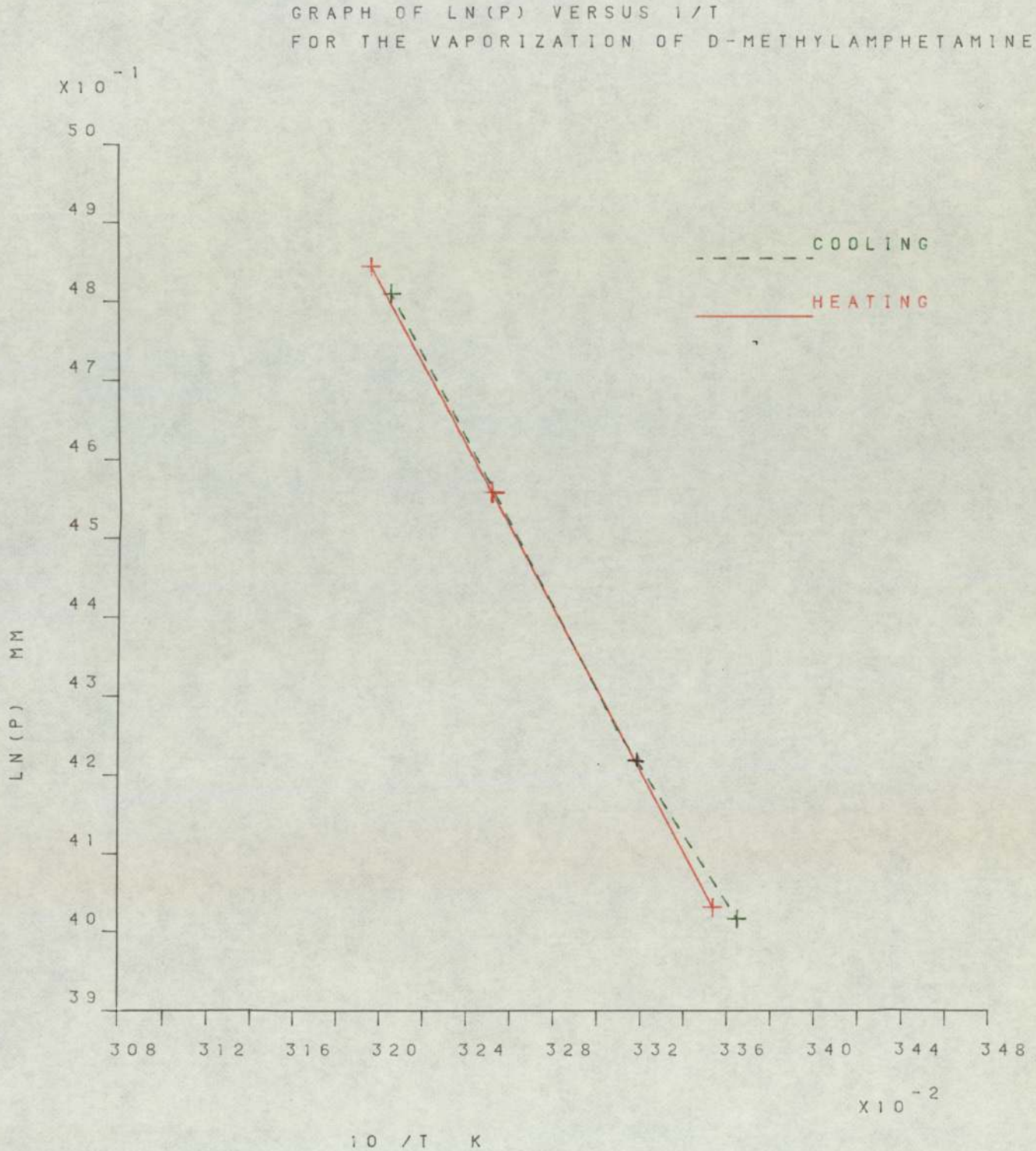


Table 4.2.16(i) IR spectra of d-methylampetamine, its hydrochloride and complexes.

$C_{10}H_{15}N$	$C_{10}H_{15}N.HCl$	Tentative assignments cm^{-1}
3400		ν_{N-H}
3300sh	2475	$\nu_{NH_3^+}$

$[(C_{10}H_{15}N)_2CuCl_2]_2$	$(C_{10}H_{15}N)CuCl_2$	Tentative assignments cm^{-1}
3240	3280 3180sh	ν N-H
315		ν_{Cu-Cl}
270	276	
230	228	ν_{Cu-N}

Table 4.2.16 (ii) Electronic and Magnetic Data for complexes of d = methylamphetamine

$Cu(C_{10}H_{15}N)Cl_2$

Diffuse Reflectance spectra cm^{-1}	$max_{m\mu}$	E.S.R. Data	Magnetic Moment B.M.
28 800	347	g = 2.183	
19 000	526	g 2.1041	1.75
15 000 sh	667	G 4.46	

$Cu(C_{10}H_{15}N)Cl_2\ 2$

27 200	368	low field = 4.161	
14 000	714	g = 2.392	
13 2 00	758	g = 2.059	

Complexes of β- phenylethylamine

INFRARED SPECTRA. The infrared spectrum showed a doublet typical of primary amines at 3380 and 3300 cm^{-1}.

4.2.18 Dichlorotetrakis (β- phenylethylamine) copper (II) $Cu(C_8H_{11}N)_4Cl_2$

Royal blue

INFRARED SPECTRUM. The infrared spectrum of this complex is charactersied by two pairs of doublets at (i) 3340 and 3280 cm^{-1} (ii) 3200 and 3120 cm^{-1}. These bands are assigned to NH_2 stretching vibrations. On coordination of nitrogen to the metal the bands are shifted to lower wavenumber relative to the free base β- phenylethylamine. The presence of two pairs of doublets indicate that the nitrogen atoms are in different environments. If the complex has a rhombic octahedral stereochemistry in which elongated tetragonal distortion occurs this would be consistent with the infrared data in the region above 3000 cm^{-1}

A strong band at 290 cm^{-1} is assigned to the Cu-Cl stretching vibration; bands at 240 (shoulder) 223 and 209 cm^{-1} are assigned to copper nitrogen stretching vibrations.

DIFFUSE REFLECTANCE SPECTRUM. A broad band was observed with a maximum at 17 500 cm^{-1} with a shoulder at 13 500 cm^{-1}. This is consistent with copper bonded to four ligands, the two chlorine atoms in a square plane in a trans position, two β - phenylethylamines occupying the other two positions and two β- phenylethylamines occupying the axial positions.

MAGNETIC SUSECPTIBILITY. The magnetic susceptibility measurement gave a room temperature magnetic moment of 1.84BM which lies in the range normally found for copper (II) complexes in the absence of antiferromagnetic coupling.

E.S.R. SPECTRUM. An axial spectrum was observed for this complex. Figure 4.2.18 (a). The g values obtained were g_{11} = 2.173 and $g_{\perp}$ = 2.041. The lowest g value was greater than 2.03 which indicated that a $d_{x^2-y^2}$ ground state was present. For the spectrum G equal to $(g_{11}-2)/(g_{\perp}-2)$ = 4.22 suggested that the observed g values accurately reflected the local copper (II) environment, the tetragonal axes aligned parallel and exchange coupling if present very small.

The E.S.R.data is consistent with elongated tetragonal-octahedral stereochemistry.

The data is consistent with the formulation shown in Figure 4.2.18 (ii)

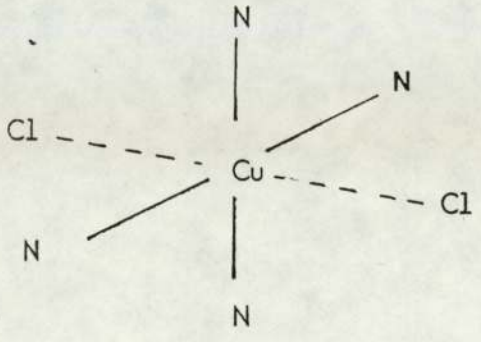


Figure 4.2.18(ii)

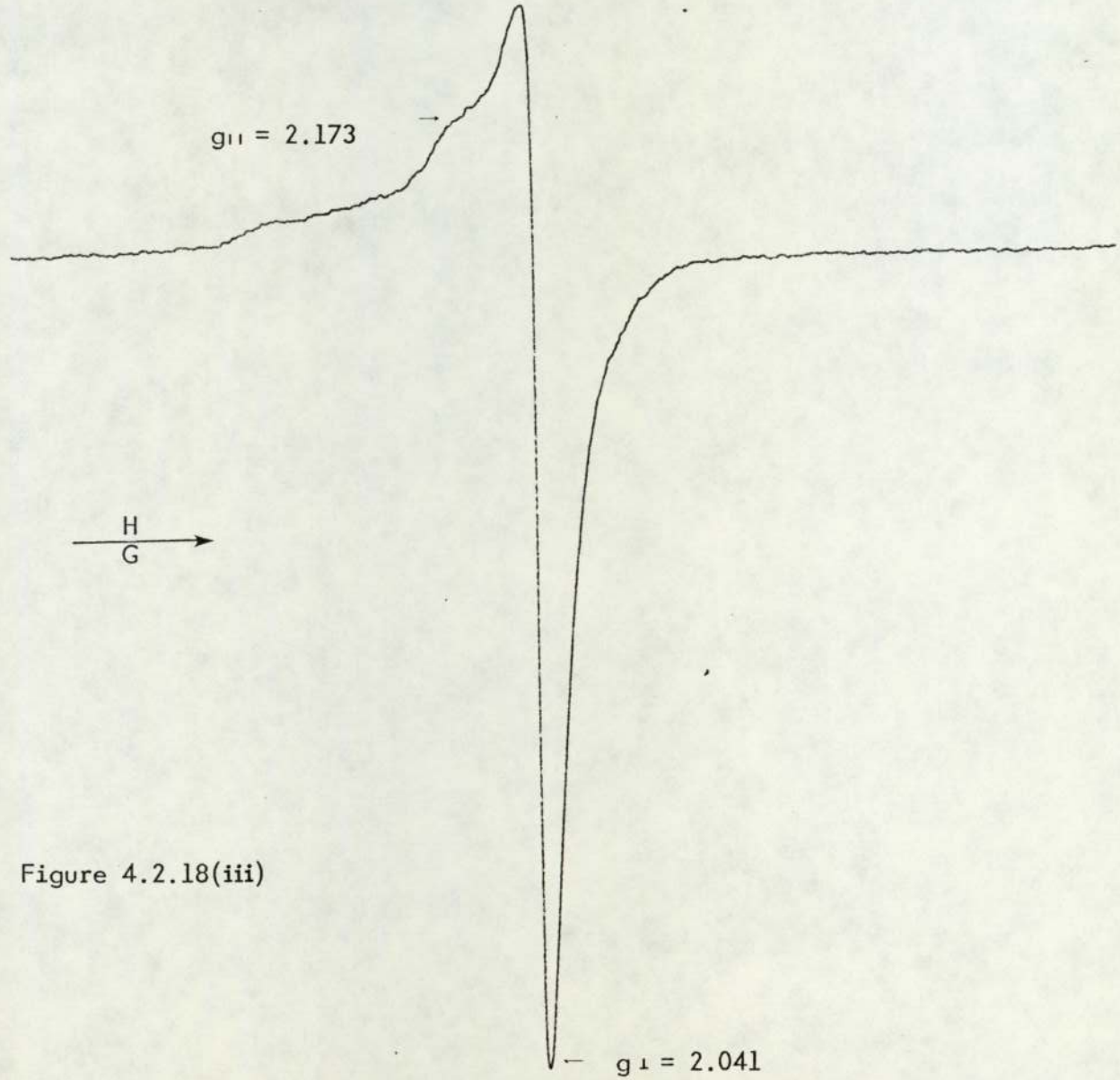


Figure 4.2.18(iii)

This complex was unstable if left in a vessel in which air was present. Aftertime one mole of phenylethylamine was lost as indicated by elemental analysis, giving dichlorotris (β- phenylethylamine) copper (II) $(C_8 H_{11} N)_3 CuCl_2$.

Thermogravimetric analysis of this complex showed that the phenylethylamine ligands were lost cleanly.

4.2.18i Dichlorobis (β-phenylethylamine) copper (II) $Cu(C_8H_{11}N)_2Cl_2$

turquoise

INFRARED SPECTRUM. The infrared spectrum showed that the bands assigned to NH stretching vibrations at 3280 and 3260 cm^{-1} had been shifted to lower wavenumber relative to β-phenylethylamine. The lowering of these bands indicated coordination through the amino nitrogen atoms.

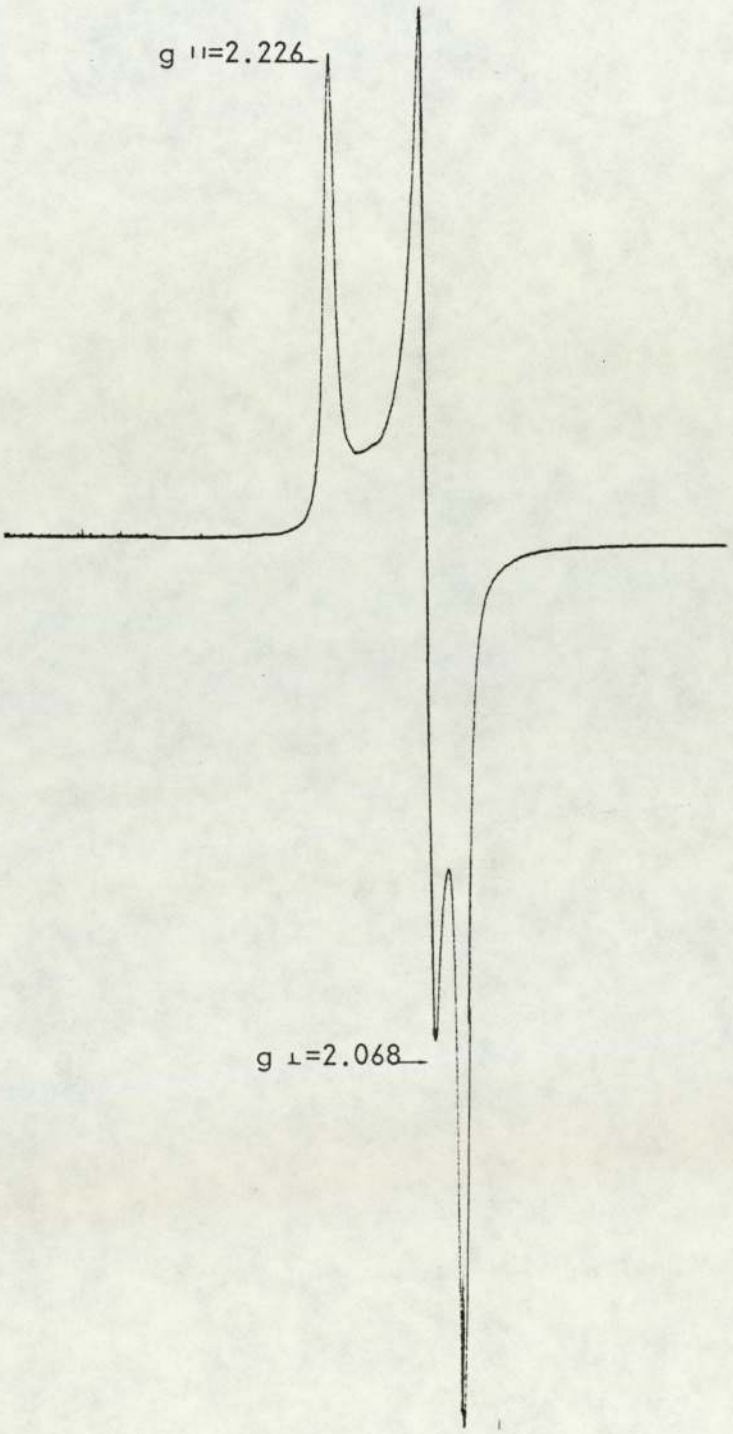
In the far infrared region a strong band at 280 cm^{-1} and a medium band at 250 cm^{-1} were assigned to copper-chlorine stretching vibrations. A band at 220 cm^{-1} was assigned to the Cu-N stretching vibration.

E.S.R. SPECTRUM. The E.S.R. Spectrum is shown in Figure 4.2.18 (iii) An axial spectrum is observed giving two g-values, $g_{11} = 2.226$ and $g_{\perp} = 2.068$. The lowest g-value is greater than 2.03 and indicates a $d_{x^2-y^2}$ rather than d_{z^2} However the observed G value equal to $(g_{11} - 2)/g_{\perp} - 2)$ 3.32 being less than 4 suggested the presence of exchange coupling and misalignment of the tetragonal axes. The E.S.R. data is consistent with an elongated tetragonal sterechemistry for copper (II)

MAGNETIC SUSCEPTIBILITY. The room temperature magnetic moment calculated from the magnetic susceptibility was 1.68 B.M. which was consistent with exchange coupling between copper (II) ions and supportive of the E.S.R. data. This type of elongated tetragonal stereochemistry is found for the copper (II) complex of pyridine, dichlorobispyridinecopper (II) $Cu(Py)_2Cl_2$ [107] which is represented in Figure 4.2.14(iv)

DIFFUSE REFLECTANCE SPECTRUM. A broad band with a maximum was observed at 15 750 cm^{-1} and a shoulder at 14 000 cm^{-1} which is not inconsistent with the proposed trans square planar stereochemistry.

Figure 4.2.18(iv)



THERMOGRAVIMETRIC ANALYSIS. Decomposition began at approximately 146°. The two modes of ligand were lost cleanly leaving $CuCl_2$. Decomposition was complete at 381°.

4.2.19 (a) $Cu_2C_{18}H_{26}N_2Cl_3$ and $Cu_2C_{17}H_{24}Cl_3$ green

INFRARED SPECTRUM. The infrared spectra of these complexes were identical. In the region above 3000 cm^{-1} two sets of absorptions are observed. (i)A doublet at 3270 and 3210 cm^{-1} with a shoulder at 3320 cm^{-1} typical of a primary NH_2 group, and a sharp band at 3140 cm^{-1} typical of a secondary NH group, indicating that there were two types of nitrogen groups coordinated to the copper atom. These bands are lowered relative to the bands in the spectrum of β- phenylethylamine assigned to NH stretching vibrations.

In the far infrared region of the spectrum, bands observed at 230 and 220 cm^{-1} are assigned to copper-nitrogen stretching vibrations.

A band at 250 cm^{-1} is assigned to the copper-chlorine stretching vibration.

DIFFUSE REFLECTANCE SPECTRUM. Bands were observed at 24 000 and 12 600 cm^{-1} for both complexes. These spectra were similar to the spectrum observed for $Cu_2C_{16}H_{22}N_2Cl_3$ indicating a similar sterochemistry. The solution spectrum in chloroform gave ϵ_{max} = 3 x 10^2 l mol^{-1} cm^{-1}

E.S.R. SPECTRUM. High and low field signals were observed. The low field signal suggested the presence of a dimeric species with g = 4.22 at 1617G. Hyperfine structure was observed indicating the interaction of the atoms of the ligand with copper. The high field signal gave a value = 2.198g

MAGNETIC SUSCEPTIBILITY. The observed room temperature magnetic moment of 1.31 B.M. indicated the presence of exchange coupling between copper centres in the complex. This supports the E.S.R. data.

The results of the data from elemental analysis for these complexes indicated the presence of an alkyl group. The incorporation of an alkyl group could have taken place when the mixture of complexes resulting from the addition of 2 moles of the ligand to anhydrous or aqueous $CuCl_2$ were vigorously boiled in ethanol or methanol.

It is possible that Cu (II) chloride in the presence of the amine and ethanol (or methanol) could have catalysed the alkylation of the amine. A proposed structure for the complex is shown in Figure 4.2.19 (a). As in the case of $Cu_2C_{16}H_{22}Cl_3$ a dimeric or coupled dimeric species is thought to exist.

It is possible that a mixed-valence complex with rapid electron exchange exists. For this exchange to happen a binding site for copper which does not change ligand geometry drastically during the uptake or loss of an electron is needed.

A square planar or distorted tetrahedral configuration would fit this criterion.

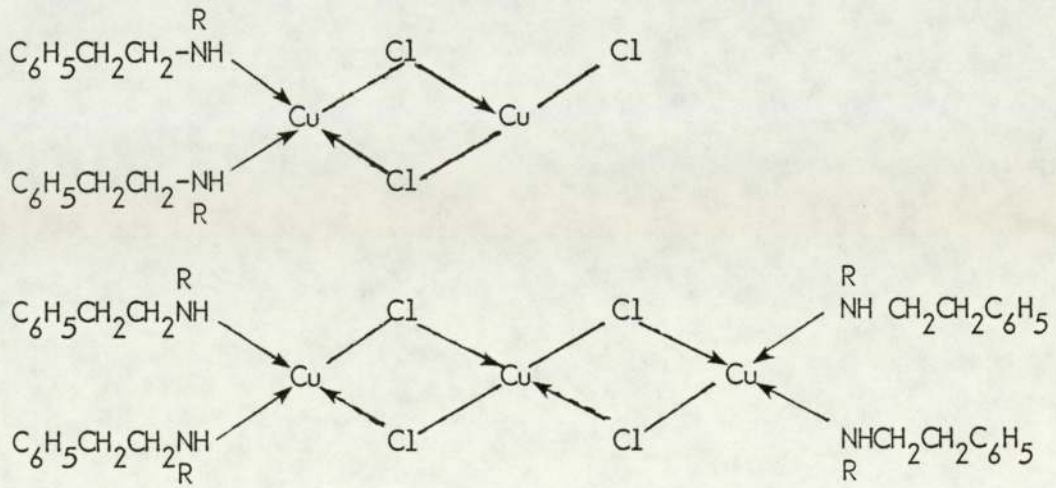


Figure 4.2.19(a)

THERMOGRAVIMETRIC ANALYSIS. This complex was thermally stable until 181°. The complex decomposed gradually and decomposition was complete at 844°.

4.2.19 $Cu_2C_{16}H_{22}N_2Cl_3$ yellow/brown

INFRARED SPECTRUM. Bands observed at 3280 and 3240 cm^{-1} are assigned to NH stretching vibrations and are lowered relative to β- phenylethylamine indicating coordination of the amino nitrogen to copper.

The far infrared region showed a broad band which was split. A band at 250 cm^{-1} is assigned to bridging copper-chlorine stretching. Bands at 230 and 220 cm^{-1} are assigned to copper nitrogen stretching vibrations.

DIFFUSE REFLECTANCE SPECTRUM. A band with a maximum at 12 600 cm^{-1} was observed. The intensity of the band suggested that it was a charge transfer band. The solution spectrum in chloroform gave ϵ_{max} = 3 x 10^2 l mol^{-1} cm^{-1} A band at ~ 24 000 cm^{-1} was also observed.

E.S.R. SPECTRUM. The observed spectrum showed low and high field signals. The signal at low field, g = 4.18 was indicative of a dimeric structure. The main signal at high field gave an observed g - value of 2.134 for a very broad spectrum. No information on the ground state of the complex could be obtained from the spectrum.

MAGNETIC SUSCEPTIBILITY. The room temperature magnetic moment, 1.37 B.M. calculated is consistent with exchange interaction between the copper ions in the complex and supports the E.S.R. data.

Superexchange interaction would be possible through the chlorine bridges in the complex.

The data from elemental analysis suggested that the empirical formula of the complex was $Cu_2C_{16}H_{21}N_2Cl_3$. For this formulation a possible tentative structure that is consistent with the data is represented in Figure 4.2.19(a)

In this representation it is proposed that copper is in a mixed valence state of copper (I) and copper (II). Sigwart et al have isolated a Cu(I) - Cu(II) mixed-valence acetate complex from methanol. They reported that the Cu(I):Cu(II) and the copper:acetate ratios were 1:1 and said that it could beused as a model for copper - copper interactions in enzymes. They reported that the absorption spectrum of the complex synthesized showed a sharp peak at 508 mμ (19685 cm^{-1}) and a broad peak at 900mμ (11111 cm^{-1}) which they said was indicative of interaction between the two valence states of copper, since neither of the peaks existed in either of the component species.

The diffuse reflectance spectrum observed for this complex showed a sharp intense band at 12 600 cm^{-1} and an intense band at 24 000 cm^{-1}, which is not in agreement with the spectrum reported by Sigwart et al, but is characteristic of dimeric complexes prepared in this work with a similar empirical formula. Section 4.2.19 (a). These complexes also gave very similar E.S.R. spectra and room temperature magnetic moments that were lower than the spin only value $\mu_{s.o}$ = 1.73 found in magnetically dilute complexes where there are no interactions between the individual copper centres.

It is therefore possible that mixed valence copper complexes have been prepared in methanol or ethanol.

THERMOGRAVIMETRIC ANALYSIS. This complex began to decompose at approximately 170° and decomposition which was a gradual process was complete at 836°.

Table 4.2.18i IR Spectra of β-phenylethylamine and its complexes

$C_8H_{11}N$	$Cu(C_8H_{11}N)_4Cl_2$	Tentative assignments cm^{-1}
3380 3300 3200sh	3340 3280 3200	NH_2
	360 345	Cu-N
	280s	Cu-Cl

$Cu(C_8H_{11}N)_2Cl_2$	$Cu_2C_{16}H_{22}N_2Cl_3$	Tentative assignments cm^{-1}
3280 3260 3150w	3280 3240 3150	NH_2
280v.s.	250v.w.	Cu-Cl
250 220	230 220s.w. 207	Cu-N.

$Cu_2C_{18}H_{26}N_2Cl_3$ and	$Cu_2C_{17}H_{24}N_2Cl_3$	Tentative assignments cm^{-1}
3320 3270 330		
230 220		Cu-N
250		Cu-Cl

Table 4.2.18ii Electronic and Magnetic Data for complexes of β - Phenylethylamine

$Cu(C_8H_{11}N)_4Cl_2$

Diffuse Reflectance spectra cm^{-1}	max $m\mu$	E.S.R. Data	Magnetic Moment B.M.
17 500	571	g = 2.173	1.84
12 500	800	g = 2.041	
		G = 4.22	

$Cu(C_8H_{11}N)_2Cl_2$

27 000	370	g = 2.228	2.08
15 750	635	g = 2.068	
14 000	714	G = 3.23	

$Cu_2C_{18}H_{26}N_2Cl_3$ or $Cu_2C_{17}H_{24}N_2Cl_3$

24 000	417	low field g = 4.18	1.31
12 600	794	g = 2.134	

$Cu_2C_{16}H_{22}N_2Cl_3$

24 000	417	low field g = 4.22	1.37
12 6 00	794	g = 2.198	

Complex of Dl-α-phenylethylamine

INFRARED SPECTRA. The spectrum of the free base showed absorptions in the region greater than 3000 cm^{-1} typical of primary amine. A doublet was observed at 3480 and 3300 cm^{-1} with a shoulder at 3200 cm^{-1}.

3.2.19(c) Dichlorobis(dl-α-phenylethylamine)copper(II)$Cu(C_8H_{11}N)_2Cl_2$

The infrared spectrum of the complex showed a doublet at 3230 and 3240 cm^{-1} and a sharp band at 3160 cm^{-1}. These bands were assigned to N-H stretching vibrations. On coordination to copper they are shifted to lower wavennumber.

The far infrared region shows a very strong absorption at 330cm^{-1} which is assigned to terminal copper chlorine. A band at 275 is also assigned to terminal Cu-Cl and bands at 230 and 206 cm^{-1} are assigned to copper-nitrogen stretching vibrations.

The infrared spectrum suggests that the complex is not symmetrical.

DIFFUSE REFLECTANCE SPECTRUM. A band is observed at 15 400 cm^{-1}. This spectrum is similar to the spectrum observed for α-$Cu(N\text{-}H)_3{}_2Br_2$[85]. It is possible that $d_{x^2-y^2}$ ground state exists.

E.S.R. SPECTRUM. An isotropic spectrum was observed, similar to that for the d-amphetamine complex with a similar formula. A spectrum with a point of inflection between two maxima was observed. The g-values were, g = 2.351 and g_2 = 2.133. The isotropy of the

spectrum suggests that there is exchange coupling occurring between grossly misaligned tetragonal axis.

MAGNETIC SUSCEPTIBILITY. The measurement of magnetic susceptibility at room temperature gave a magnetic moment of 1.81 B.M., the value of which lies in the range expected for a magnetically dilute complex. This is indicative of the complex existing as a monomer as opposed to a dimer or polymer.

The data suggested that the α-phenylethylamine groups were coordinated in the cis positions of a square coplanar structure.

Table 4.2.19(c)i IR spectra of dl-α-phenylethylamine and dichlorobis(dl-α-phenylethylamine) copper (II)

$C_8H_{11}N$	$Cu(C_8H_{11}N)_2\ Cl_2$	Tentative assignements (cm^{-1})
3480 3300 3200sh	3330sh 3240 3160	NH_2
	330 275	Cu-Cl
	230 206	Cu-N

Table 4.2.19(c)ii Electronic and Magnetic Data for dichlorobis-(dl-α-phenylethylamine) copper (II)

Diffuse Reflectance spectrum max cm^{-1}	 mμ	E.S.R. Data	Magnetic Moment BM
15 400	649	$g_1 = 2.351$ $g_2 = 2.133$	1.81

4.2.20b $CuZnC_{20}H_{30}N_2O_4Cl_2$

The analytical data for the mixed complex of l-ephedrine with Zn(II) and Cu(II) indicates the formation of zinc hydroxide. The complex although synthesized as a possible copper(II) doped zinc(II) complex of l-ephedrine was not isomorphous with the copper(II) complex of l-ephedrine and will not be discussed further.

Infrared, electronic and magnetic data are presented in Tables 4.2.20 for this complex.

Table 4.2.20b IR spectrum of copper(II)-doped zinc(II) complex of l-ephedrine

$CuZn\ C_{20}H_{30}N_2\ O_4\ Cl_2$	Tentative Assignements (cm^{-1})
3100	N-H
570	M-O-M
480sh 460	M-N
280	M-Cl

Table 4.2.20 ii Electronic and Magnetic Data for copper(II) doped zinc(II) complex of l-ephedrine

Diffuse Reflectance spectrum cm^{-1}	max $m\mu$	E.S.R Data low field
17 100	585	g = 4.45
13 500	741	g = 2.426

Table 4. Molar Conductances.

Complex	Λ Ohm^{-1} cm^{2} mole^{-1}
l-ephedrine	
$Cu(C_{10}H_{14}NO)Cl_2$	13
dl-N-methylephedrine	30
$Cu(C_{11}H_{16}NO)Cl_2$ d-amphetamine	7
$Cu(C_9H_{13}N)Cl_2$ β-phenylethylamine	
$Cu(C_8H_{11}N)_2Cl_2$	7
$Cu_2C_{18}H_{26}N_2Cl_3$	4
$Cu_2C_{17}H_{24}N_2Cl_3$	4

The molar conductances of 10^{-3}M solutions of certain complexes were measured in acetonitrile. The low values obtained were consistent with neutral complexes showing weak dissociation in solution.

CHAPTER FOUR

DISCUSSION

PART II

COMPLEXES OF SELECTED PHENOTHIAZINES

Complexes of chlorpromazine

INFRARED SPECTRA. The infrared spectrum of the free base showed sharp bands between 3000 and 2700 cm^{-1}. These bands are assigned to aromatic and aliphatic C-H stretching vibrations. Bands typical of the aromatic nucleus[79] are assigned at 1595, 1580 and 1450 cm^{-1}. Aromatic tertiary amines are extremely difficult to identify spectroscopically. In general they are found to occur between 1360 and 1310 cm^{-1} [79]. Tertiary alkyl amines are also difficult to identify but occur in the range 1070-1050 cm^{-1}.

In the spectrum of chlopromazine there are many bands occuring in these regions so the task of assignment with any degree of certainty is difficult. Further complications arise because of the presence of C-S in chlorpromazine. The assignment of the C-S band in aromatics is difficult because of coupling within the aromatic ring. C-S bands are also very weak.

Therefore in general the I.R. spectrum is unhelpful in determining whether the sulphur atom or nitrogen atom are coordinated to copper.

4.2.21 $Cu_2C_{34}H_{38}N_2Cl_5$ orange

Copper-sulphur stretching vibrations are variable and it is therefore difficult in general to assign bands in the infrared spectrum.

Copper-nitrogen and copper chlorine stretching vibrations are more reliable.

The far infrared region shows bands at 248, 228 and 204 cm^{-1}. The band at 248cm^{-1} is assigned to copper-chlorine and the split band

at 228 and 204 cm^{-1} is assigned to copper-nitrogen. These bands in general are weak. Although the sulphur atom seems to be the most probable choice for coordination to copper(II), the affinity of nitrogen for copper being greater could possibly override the steric factor of the attached methyl groups and coordinate with copper.

On the other hand sulphur has a greater affinity for copper (I) than nitrogen and it is possible that if a species is present in which dynamic electron exchange is occuring between the copper centres then the sulphur atom could be involved in coordination to the copper.

E.S.R. SPECTRUM. The E.S.R. spectrum of this complex is shown in Figure 4.2.21. Low and high field signals were observed. The low field g-value was observed to be 4.22 g and the high field value g was observed to be 2.163.

The low field value suggests that this complex is a dimer.

MAGNETIC SUSCEPTIBILITY. The room temperature magnetic moment calculated from the magnetic susceptibility is 0.42 B.M. This low value indicates that the copper centres are in close proximity and there is interaction between them. The low value of μ_{eff} could also be an indication that Cu(I) is present in the complex.

DIFFUSE REFLECTANCE SPECTRUM. Bands were observed at 28 000 and 12 700 cm^{-1}. The appearance of this spectrum is very similar to that of the complexes of β- phenylethylamine, with a similar empirical formula ie.e $Cu_2L_2Cl_3$ where L= ligand i.e. chlorpromazine

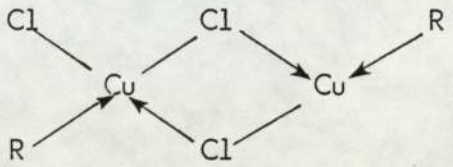
or β- phenylethylamine. The intensity of both bands suggest that they are charge transfer bands. The best investigated mixed valence copper complex is the Cu(I) - Cu(II) chloride system McConnell and Davidson[109] found this complex in chloride solutions to have the stoichiometric formula Cu_2Cl_3. They compared this to the solid hexammine cobalt (III) chlorocuprates which showed similar spectra in the visible region. They said that the absorption was due to the presence of both valence states (580 mμ) for the solid compound and 555 mμ for the system in solution. Day and Smith[110] assigned the absorption in the solid, to an intermolecular charge transfer from a chlorocuprate (I) anion to a chlorocuprate (II) anion.

The chlorpromazine nucleus consists of a system of conjugated C = C having an extensive pool of delocalized electrons and lone pairs of electrons on the sulphur and amino nitrogen atoms. Chlorpromazine is thus a strong monovalent electron donor and could readily be involved in oxidation/reduction processes in copper complexes.

The empirical formula for the complex supports the possibility of the presence of Cu(I).

A possible structure for the complex is a tetranuclear copper species such as suggested, for the complexes of the phenylethylamines in section 4.2.19 or the complex could exist as shown in Figures 4.2.21(a)

Figure 4.2.21 (a)



R = S or N from chlorpromazine

4.2.22 $[Cu\ C_{17}H_{19}N_2S\ Cl_3]2$ green

The physical data obtained for this complex were almost identical to the data obtained for the orange complex, $Cu_2C_{34}H_{38}N_4S\ Cl_5$.

The same remarks for the orange complex also apply to this complex and it will not be discussed in detail. The relevant analytical and physical data are shown in tables 3.2.21 and 4.2.21. The analytical data suggest that this complex is a 1:1 dimer in the solid state.

Complex of Trifluoperazine

No simple empinical formula for the complex of trifluopernzine could be found from the analytical data. At this present time insufficient physical data has been collected for this complex and therefore cannot profitably be discussed.

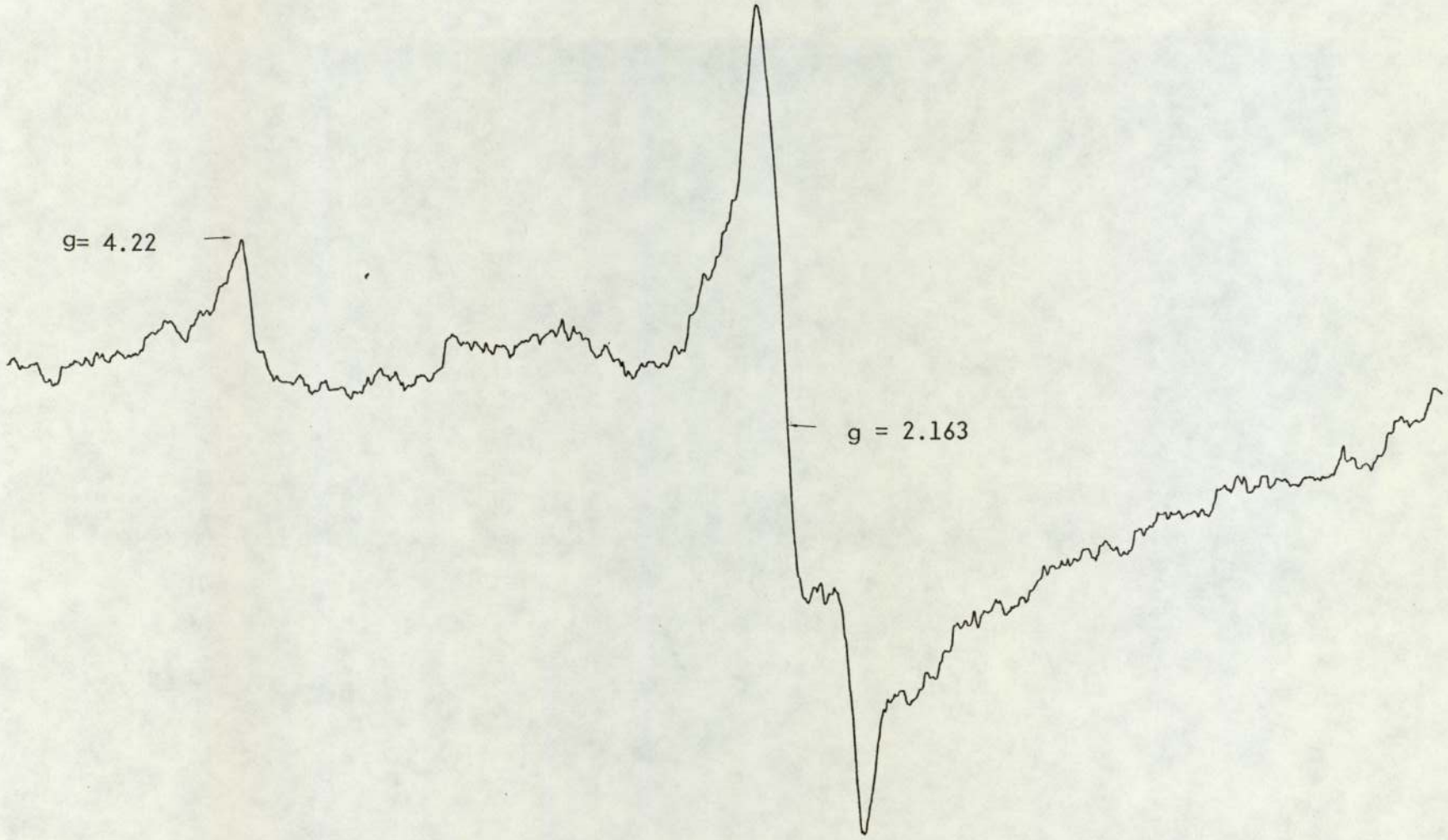


Figure 4.2.21 (a)

Table 4.2.21 Electronic and Magnetic Data for complexes of chlorpromazine

Diffuse Reflectance spectra ν_{max} cm^{-1}	ν_{max} $m\mu$	E.S.R Data	Magnetic Moment B.M.
		$Cu_2C_{34}H_{38}N_2Cl5$	
28 000	357	4.22g	
12 700	787	2.163g	
27 000	368	4.22g	
15 000	667	2.163g	

CONCLUSION AND SUGGESTIONS FOR FURTHER WORK

Conclusion and suggestions for further work.

1. New complexes have been prepared with selected "sympathomimetic amines" and phenothiazines.
2. In general there are two types of "sympathomimetic amines":
   a) Those containing a β-hydroxy group i.e. d-pseudoephedrine, l-ephedrine dl-phenylpropanolamine phenylephrine and dl-N-methylephedrine.
   b) Those containing no β-hydroxy group, phenylethylamine, d-amphetamine, dl-amphetamine and d-methylamphetamine.
3. a) Complexes synthesized with copper (II) chloride and "sympathomimetic amines" from group a) gave two and in some cases three different types of complexes.
   i) The first type of complex prepared as described in alkali medium in section 3.2.1 (method A) were copper (II) chelates of the deprotonated ligand, of the general formula CuL_2xH_2O after recrystallisation where x = 0-3 and L = deprotonated ligand.

The exception to this was the complex synthesized using dl-N- methyl-ephedrine where neutral and deprotonated ligands were present in the complex. These complexes were all crystalline. Similar complexes to these have been reported previously.

   ii) The second type of complex was prepared in neutral solution. General formula: CuLCl . These complexes exist as dimers or possibly polymers.
   iii) The third type of complex was also prepared in neutral solution. General formula $CuLR\ Cl_2 .\ x\ H_2O$ where L = deprotonated ligand. R - neutral ligand, x = 0 or 2.

These complexes were crystalline in nature.

b) Ligands from group (b) also gave two or more complexes

i) General formula $CuLxCl_2$ L = neutral ligand and x = 2 or 4

ii) General formula $CuLCl_2$ x or $Cu_2L_2Cl_3$ x x = 1 or 2

If the ligand contained the $-NH_2$ group in the structure as opposed to NHR group then alkylation of the ligand appeared to take place under certain experimental conditions.

These complexes existed as dimers or tetranudear copper species. Thus these selected "sympathomimetic amines" gave a variety of complexes with copper (II) chloride, in what appears to be complex systems.

It is possible that mixed valence complexes exist.
Mixed valence copper complexes are known for example cytochrome oxidase.

New complexes have been prepared using chlorpromazine and trifluoperazine. It is possible that the complex of chlorpromazine is a mixed valence complexes have been prepared using amphetamine and chlorpromazine that complexes with copper enzymes and either amphetamine or chlorpromazine could exist.

It would be interesting to analyse the crystalline complexes using the single crystal x-ray technique to determine the molecular structures.

Starting from the hypothesis that these compounds interacted with copper containing enzymes, as a first step in the virtual complete lack of information on interaction of these enzymes with these compounds, it was decided for purposes of this work to investigate the interaction of these amines with the simple copper cation. This having been completed in considerable measure. It would now seem profitable to start to investigate the interaction of these amines with relevant copper containing enzymes, a major difficulty here being the accessibility of materials.

During this work additional circumstantial evidence came to light concerning the rather specific interatcion of these compounds with copper. It was noted that when trying to prepare dilute solid solutions of copper (II) complexes in zinc complexes of these amines for e.s.r work that in general zinc failed to yield complexes.

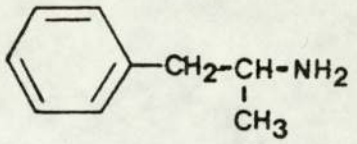
APPENDIX 1

Table 1

Amphetamine

Benzedrine

(+)- α -Methylphenethylamine

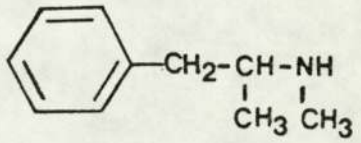


Methylamphetamine

Methamphetamine (U.S.P)

d-Deoxyephedrine

(+)-N α-Dimethylphenethylamine

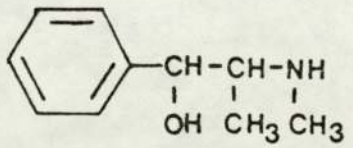


Ephedrine

(-)-2-Methylamino-1-phenylpropan-1-ol

isomer Pseudoephedrine, d-(Ψ)-ephedrine

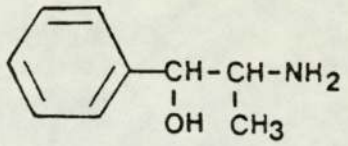
(+)-2-Methylamino-1-phenylpropan-1-ol



Phenylpropanoldmine

Norephedrine

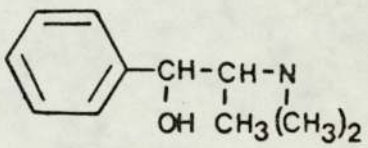
(+)-2-Amino-1-phenylpropan-1-ol



N-Methylephedrine

N-Dimethylnorephedrine

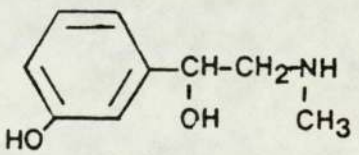
2-Dimethylamino-1-phenylpropan-1-ol



Phenylephrine

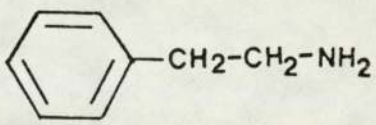
Neosynephrine

(-)-1-(m-Hydroxyphenyl)-2-methylaminoethanol



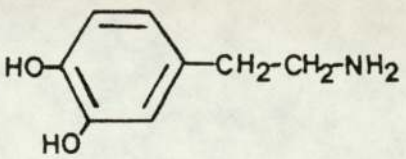
Phenylethylamine

Phenethylamine U.S.P.



Dopamine

4-(-Aminoethyl)-pyrocatechol



Norepinephrine

α-Aminomethyl) 3,4-dihydroxy benzyl-alcohol

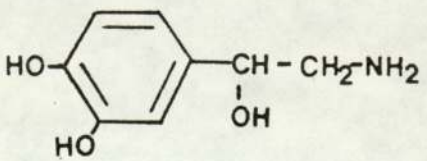
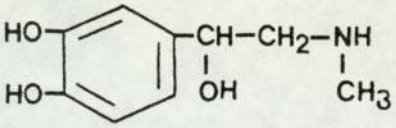


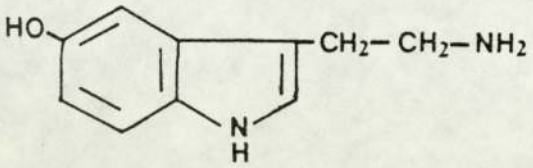
Table 1 continued



Epinephrine

(Adrenaline)

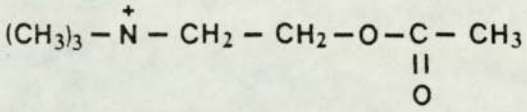
1, 2-Benzenediol, 4- 1-hydroxy-2-(methylamino) ethyl



Serotonin

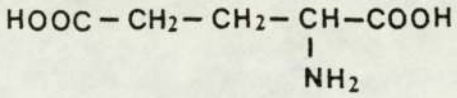
5-Hydroxytryptamine

1 H-Indol-5-ol, 3-(2-aminoethyl)-



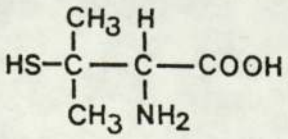
Acetylcholine

Ethanaminium, 2-(acetyloxy)-N, N, N-trimethyl



Glutamic acid

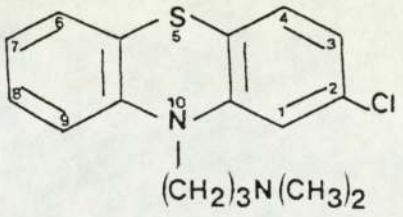
-2-aminopentanedioic acid



D-Penicillamine

D-Valine, 3-mercapto

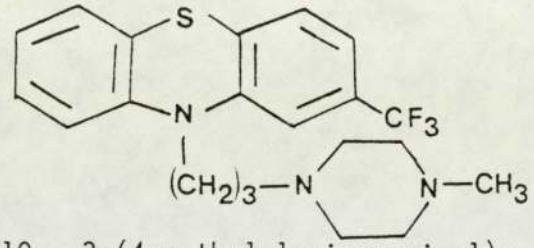
Table 2



Chlorpromazine

Largactil

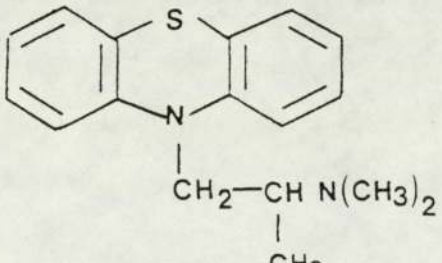
10H-Phenothiazine 10-propanamine, 2-chlor-N, N-dimethyl



Trifluoperazine

Stelazine

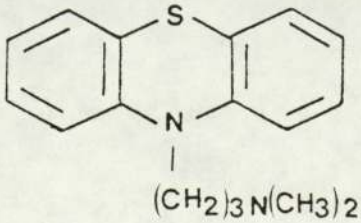
10H Phenothiazine,10- 3-(4-methyl-1-piperazinyl) propyl - 2- (trifluoromethyl)



Promethazine

Phenergan

10H Phenothiazine 10-ethanamine N, N trimethyl

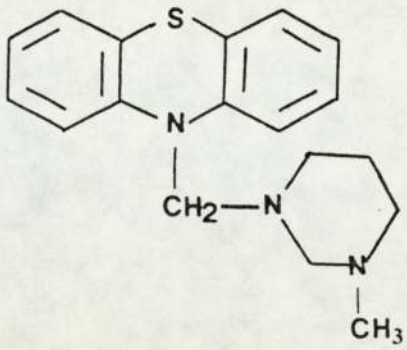


Promazine

Sparine

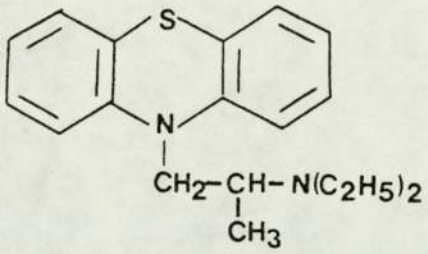
10H-Phenothiazine-10-propanamine, N, N-dimethyl

Table 2 Continued



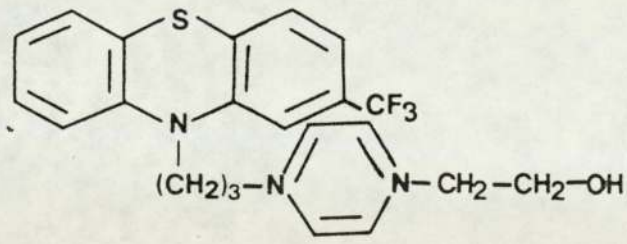
Mepazine

10H-Phenothiazine, 10- (1-methyl-3-piperidinyl) methyl



Diethazine

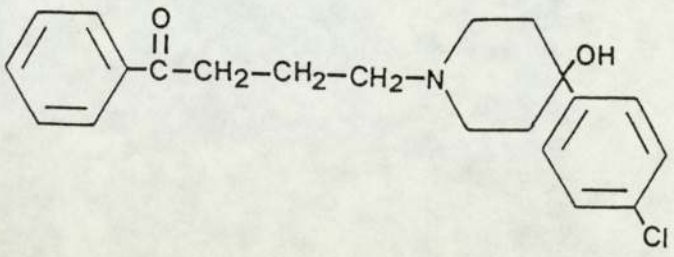
10H-Phenothiazine -10 ethanamine, N, N-diethyl



Fluphenazine

1-Piperazineethanol, 4- 3- 2-(trifluoromethyl)-10H-Phenothiazin -10-YL propyl -

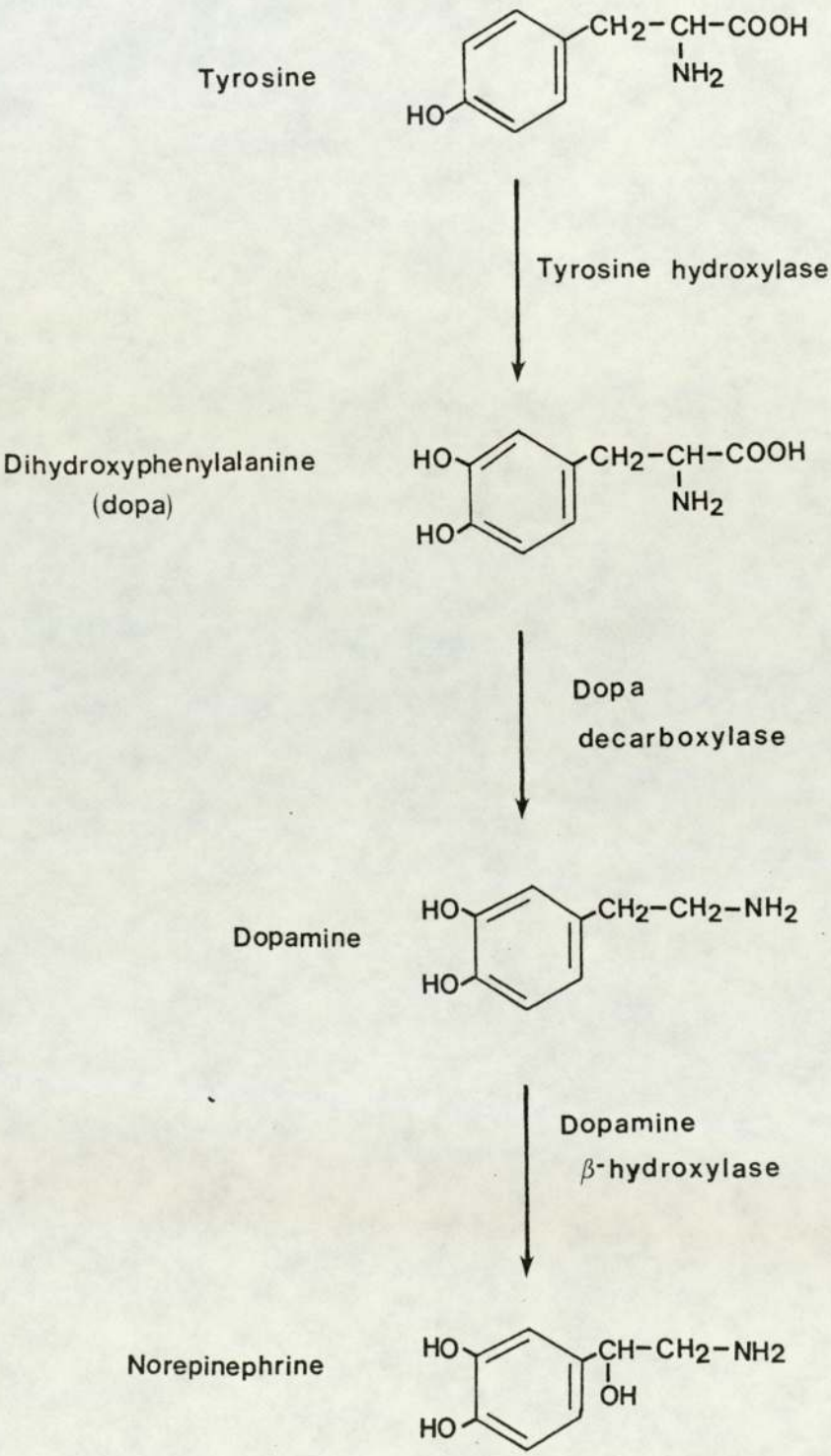
Table 2 continued



Haloperidol

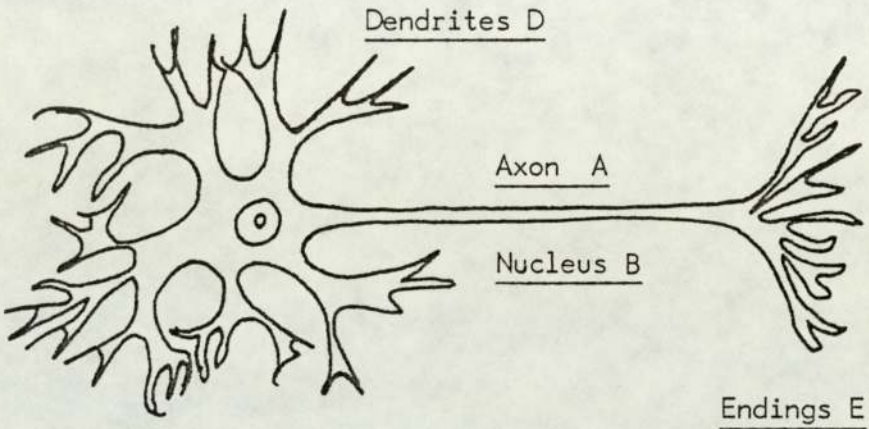
1-Butanone, 4- 4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl -1-(4-fluorophenyl)-

APPENDIX 2



Conversion of Tyrosine to Dopamine and norepinephrine.

NEURONE



Information orginates in D (receiving elements 'antennae' of neurone

C/ Contains nucleus + all machinary for protein manufacture

A/ can travel 1 mm - 30 cm. depending on nature of neurone

E/ Axon terminates

APPENDIX 3

GRAPH OF LN(P) VERSUS 1/T
FOR THE VAPORIZATION OF D-AMPHETAMINE

HOT VALUES		COLD VALUES	
X	Y	X	Y
2.860	4.767	2.943	4.316
2.968	4.195	2.946	4.358
3.020	3.932	2.983	4.156
3.100	3.393	3.022	3.900
3.197	2.923	3.113	3.418
3.252	2.548	3.206	2.903
3.354	2.052	3.310	2.355
3.394	1.788	3.365	2.280

GRADIENT = -5.594
Y-AXIS INTERCEPT = 20.783

GRAPH OF LN(P) VERSUS 1/T
FOR THE DISSOCIATION OF $(C_9H_{13}N)_2CUCL_2$

HOT VALUES		COLD VALUES	
X	Y	X	Y
2.860	2.692	2.943	2.636
2.860	2.707	2.946	2.636
2.926	2.562	2.983	2.458
2.968	2.383	3.022	2.531
3.020	2.376	3.022	2.511
3.100	2.163	3.113	2.364
3.197	1.940	3.206	2.324
3.252	1.495	3.310	2.206
3.354	0.577	3.365	2.147

GRADIENT = -3.664
Y-AXIS INTERCEPT = 13.309

GRAPH OF LN(P) VERSUS 1/T
FOR THE DISSOCIATION OF ($CU_2C_{10}H_{17}NOCL_2$)

HOT VALUES		COLD VALUES	
X	Y	X	Y
2.926	4.772	2.943	4.790
2.926	4.759	2.946	4.776
2.968	4.606	2.983	4.704
3.020	4.409	3.022	4.572
3.100	3.944	3.022	4.580
3.197	3.660	3.113	4.275
3.252	3.160	3.206	3.890
3.354	2.247	3.310	3.540
3.394	2.020	3.365	3.481

GRADIENT = -5.747
Y-AXIS INTERCEPT = 21.697

GRAPH OF LN(P) VERSUS 1/T
FOR THE VAPORIZATION OF D-METHYLAMPHETAMINE

HOT VALUES		COLD VALUES	
X	Y	X	Y
3.197	4.843	3.206	4.809
3.252	4.557	3.310	4.254
3.354	4.031	3.365	4.016

GRADIENT = -5.170
Y-AXIS INTERCEPT = 21.371

GRAPH OF LN(P) VERSUS 1/T
FOR THE DISSOCIATION OF $(C_{10}H_{15}N_2)_2CUCL_2$

HOT VALUES		COLD VALUES	
X	Y	X	Y
2.860	3.264	2.943	3.153
2.860	3.279	2.946	2.883
2.926	2.830	2.983	3.059
2.926	3.114	3.022	3.026
2.968	2.987	3.022	3.022
3.020	2.934	3.113	2.799
3.100	2.266	3.206	2.741
3.197	1.613	3.310	2.795
3.252	1.477		
3.354	1.125		

GRADIENT = -4.595
Y-AXIS INTERCEPT = 16.486

GRAPH OF LN(P) VERSUS 1/T
FOR THE DISSOCIATION OF $((C_{10}H_{15}N)_2CUCL_2)$

HOT VALUES		COLD VALUES	
X	Y	X	Y
2.968	4.813	2.983	4.829
3.020	4.474	3.022	4.734
3.100	3.729	3.022	4.744
3.197	3.114	3.113	4.445
3.252	2.352	3.206	4.159
3.354	1.258	3.310	3.891
		3.365	3.776

GRADIENT = -9.102
Y-AXIS INTERCEPT = 31.947

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