STRUCTURES AND SPECTRA OF SOME PLATINUM ANTI-CANCER COMPLEXES

By

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PLATINUM ANTI-CANCER COMPLEXES

To My Parents

Between the conception

And the creation

Between the emotion

And the response

Falls the Shadow

T.S. Eliot
(The Hollow Men)

Yet the timelessness in you is aware of life's timelessness,

And knows that yesterday is but today's memory

and tomorrow is today's dream.

Kahlil Gibran
(The Prophet)

A man who has never gone to school may steal from a freight car; but if he has a university education, he may steal the whole railroad.

Theodore Roosevelt

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ABSTRACT

The structures of some of the products obtained from the aquation of cis-$PtCl_2(NH_3)_2$ were determined. They help clarify the complex nature of what was considered to be a simple chemical reaction.

The products of the reactions between K_2PtCl_4 and various alicyclic amines were also studied by X-ray crystallography and vibrational spectroscopy. The variety of products obtained was considerably greater than was expected and indicates the need for better control of the purity of compounds used in animal tests. The structures of some of these compounds also suggest a possible reason for their low toxicity.

NOMENCLATURE

Abbreviation	Name
A (am)	amine
Å	Angstrom (10^{-8} cm)
°C	degrees celsius
cm	centimeter
deg	degree
dien	diethylenetriamine
DNA	deoxyribonucleic acid
en	ethylenediamine
E. coli	*Escherichia coli*
EXAFS	Extended X-ray Absorption Fine Structure
g	gram
GpG	guanylyl[3',5']guanosine
h	hour
kg	kilogram
min	minute
mg	milligram
mL	milliliter
nmr	nuclear magnetic resonance
py	pyridine
RNA	ribonucleic acid
s	second
X	halogen atom

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CHAPTER 1

GENERAL INTRODUCTION

A number of excellent general reviews on the use of platinum compounds in cancer chemotherapy have been published during the last ten years.[1-11] Condensation of all the material in these reviews would be beyond the scope of this introduction. The general background and the chemistry relevant to the thesis will, however, be discussed.

1.1 Historical Background

While investigating the effects of an electric current on E. coli, Rosenberg and co-workers observed that cell division was inhibited while cell growth continued.[12] A series of control experiments showed that during electrolysis, the supposedly inert platinum electrodes were being attacked by the acidified chloride solution present in the culture medium. The complex, $(NH_4)_2[PtCl_6]$, was thus formed and was thought to be the species responsible for the filamentous growth.[12] Subsequent experiments showed that fresh solutions of this ionic salt were actually bacteriostatic,[13] but when the bacteria were treated with solutions of $(NH_4)_2[PtCl_6]$ which had been aged in the presence of UV light, inhibition of cell division but not of cell growth was again observed.[13,14] The active species was found to be cis-$PtCl_4(NH_3)_2$. Tests

with cis-$PtCl_2(NH_3)_2$ gave similar results, but the trans analogues of the two compounds had little effect on bacteria.[14]

Filamentous growth occurs in response to a variety of agents, among them X-irradiation and alkylating agents[15] which have been used in the treatment of cancer. A number of diamine complexes of platinum were therefore tested against cancerous tumors in mice[16] (Table 1). Unfortunately, while there was effective inhibition of tumor growth,[a] some toxicity that could be ascribed to the platinum complexes themselves was observed.[16] Later animal tests showed that these cis compounds caused severe kidney toxicity as well as anorexia, abdominal pain and some bone marrow toxicity,[17] while trans

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[a] The effectiveness, or selectivity, of the drug can be measured using a number of different parameters such as % cures, % I.L.S., T/C and T.I. Percent I.L.S. refers to the percent increase in life span when compared to a control group, and T/C to the ratio between the weight of the treated tumor and that of the untreated or control tumor. The latter ratio, expressed as a percentage, is considered significant if the value is less than fifty. The therapeutic index, T.I., is the ratio of $L.D._{50}$, the dose lethal to fifty percent of the test sample, to $I.D._{90}$, the dose that inhibits tumor growth in ninety percent of the test sample. Clearly, a large value of T.I. is beneficial.

Table 1. Inhibition by platinum compounds of Sarcoma 180 and Leukaemia L1210 in mice

Compound	Dose Schedule[a] mg/kg body weight	Sarcoma 180 T/C(%)[b]	Sarcoma 180 % cures[c]	Leukaemia L1210 % I.L.S.[b]
cis-$Pt(NH_3)_2Cl_4$	2.5 daily	83		49
	10.0 daily	29		
	8.0 day 8		50	
	8.0 day 8,16,23		83	
cis-$Pt(NH_3)_2Cl_2$	0.5 daily	75		
	1.0 daily	44		
	1.25 daily			87
	5.0 day 1			59
	10.0 day 1			> 83
	2.0 daily	1.8	0[d]	
	4.0 day 8,17		83	
	6.0 day 8		67	
	8.0 day 8		100	
$Pt(en)Cl_4$	0.62 daily	54		
	2.5 daily	23		
$Pt(en)Cl_2$	1.25 daily	17		
	5.0 daily	3.6		

Continued.....

Table 1 (Continued)

[a] The tumor was implanted at day 0.

[b] Data from reference 16a. Treatment for 9-10 days.

[c] Data from reference 16b. Treatment for 25-30 days.

[d] Death attributed to platinum.

compounds were neither beneficial nor very toxic.[17b] Despite these drawbacks, the cure rates were sufficiently high that the most effective compound, cis-dichlorodiammineplatinum(II), which has been assigned the generic name cisplatin, was deemed acceptable for testing on terminally ill patients. Here, initial tests showed that patients suffered from side effects such as renal function impairment, nausea and vomiting, with some anorexia, high-frequency hearing loss and depression of the white blood cell count.[18] Nephrotoxicity was considered to be the major injury and severely limited the usefulness of the new drug. Proceedings from a number of conferences on the use of platinum complexes in cancer research have been published[19-23] and include the results of clinical tests and toxicity studies on these drugs. Both topics have been recently reviewed[24,25] and will not be discussed in detail in this thesis.

1.2 Structure-Activity Relationships

In the hope that cisplatin would be the precursor to a large family of anti-cancer drugs, some of which might show enhanced activity, or at least similar activity coupled with reduced toxicity, many complexes of the form PtA_2X_2 were tested against various tumors.[4,26-28] In these complexes A_2 can represent either one bidentate diamine ligand or two monodentate amine ligands. Similarly, X_2 can represent either one bidentate leaving group or two monodentate leaving

groups. A small sampling of these initial results, shown in Tables 2 and 3, compares the effectiveness of the compounds chosen. Even this limited amount of data shows that a number of trends need to be considered.

1.2.1 Variation in X:

In substitution reactions on $Pt(NH_3)Cl_2$, the chloride ions are replaced.[29-31] Because of this, variation in X was expected to have a primary effect on the activity of the complexes. The order of leaving ability for the reaction

$$[Pt(dien)X]^+ + py \rightarrow [Pt(dien)py]^{2+} + X^-$$

has been established[30] and the following order of decreasing rate constants was observed:

$$X = NO_3^- > H_2O > Cl^- > Br^- > I^- > \underline{S}CN^- > \underline{N}O_2^-$$

The test results seemed to reflect this order (Table 2). Ligands such as SCN^- and NO_2^- which are strongly bonded to platinum and thus not easily displaced, give compounds which showed no anti-tumor effect. Those complexes with ligands of intermediate leaving ability (Cl^-, Br^-) showed high activity. Finally, compounds with readily replaceable ligands, such as H_2O and NO_3^-, showed a high and immediate toxicity which led to convulsions and death.

Studies have been carried out in our laboratory and others on the reaction of cisplatin with silver nitrate and

Table 2. Change in activity on varying X in cis-$Pt(NH_3)_2X_2$

X	Solvent	T/C (%)[a]
NO_3^-	Water	54[b]
NO_3^-	Saline Solution	8
H_2O	Water	--[b]
Cl^-	Saline Solution	1
Br^-	Sodium Bromide/H_2O	30
I^-	Water Slurry	110
SCN^-	Saline Solution	70
NO_2^-	Saline Slurry	99

[a] Data from reference 4. Sarcoma 180 tumor.

[b] Highly toxic.

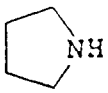
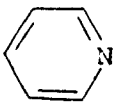
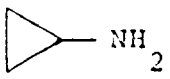
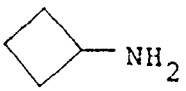
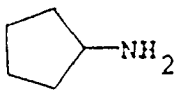
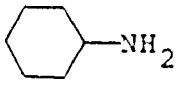
the subsequent aquation of the products obtained from the nitration.[32-38] Results from these studies cast doubts on the accuracy of the screening tests which used NO_3^- and H_2O as leaving groups. Some of the data will be presented as part of this thesis and consideration of the aqueous system is left until the Discussion.

1.2.2 Variation in A:

The relative inertness of the ammine in $Pt(NH_3)_2Cl_2$ to substitution[39] led to the prediction that variation of the ligand A in PtA_2Cl_2 should modify the activity of the complexes in a secondary manner.[4,6] From Table 3, it can be seen that variation in A actually has a very large effect on the anti-tumor properties of the compounds tested. Complexes with primary amines (RNH_2, R = alkyl) showed activity similar to, or slightly reduced from, that of cisplatin. With secondary amines (R_2NH, R = alkyl) reduction in activity was significant. Complexes with the heterocyclic amines ethyleneimine, (C_2H_4NH), and pyrrolidine, (C_4H_8NH), did, however, show enhanced selectivity. When tertiary amines were coordinated to platinum, no activity was observed, a fact which suggests the importance of hydrogen bonding.[4,5]

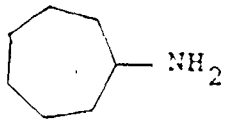
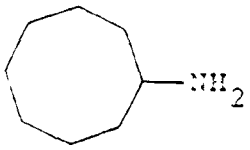
The most interesting series in this group seemed to be complexes with alicyclic amines (cyclopropylamine to cyclohexylamine) attached to platinum. The increase in ring size brought about a corresponding increase in therapeutic index,

Table 3. Change in activity on varying A in *cis*-PtA_2Cl_2

A	L.D.$_{50}$ (mg/kg)	I.D.$_{90}$ (mg/kg)	T.I.[a]	T/C (%)[b]
NH_3	13.0	1.6	8.1	1.0
CH_3NH_2	18.5	18.5	1.0	14
$(CH_3)_2NH$				25
	18.0	> 18.0	< 1.0	
	56.5	2.6	21.7	
	240	17.5	13.7	
CH_3CN	27.0	> 27.0	< 1.0	
				94
	56.6	2.3	24.6	
	90	2.9	31.0	
	565.6 (480)[c]	2.4	235.7 (200)[c]	
	> 3200	12.0	> 267	

Continued.....

Table 3 (Continued)

A	L.D.$_{50}$ (mg/kg)	I.D.$_{90}$ (mg/kg)	T.I.[a]	T/C (%)[b]
	1000	7.7	130	
	660	230	2.9	

[a] Data from reference 26. ADJ/PC6 tumor.

[b] Data from reference 4. Sarcoma 180 tumor.

[c] Data from reference 27. ADJ/PC6 tumor.

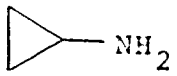
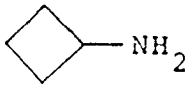
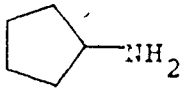
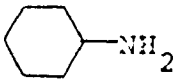
mainly through a significant decrease in toxicity rather than any drastic improvement in activity. Unfortunately, similar results were not obtained[10] when a different tumor system was studied (Table 4). Nevertheless, the dramatic decrease in toxicity makes this series interesting to the chemist and a number of reasons for the observed trend have been suggested;[11] they include the labilizing effect of the amine, lability of the amine, solubility of the complex and structural variations.

1.2.2a Kinetic Studies:

Since Cl^- was assumed to be the leaving group, the rate of replacement of chloride in cis-$Pt(am)_2Cl_2$ by dimethyl sulfoxide, (DMSO), where (am) is an alicyclic amine, was studied.[41] The rate constants were shown to be not very sensitive to the nature of the amine ligand.

Alternatively, replacement of the chloride ion in vivo by a strong trans labilizing ligand could in turn cause the replacement of the amine trans to the new ligand. Complexes of the form cis-$[Pt(am)_2(DMSO)Cl]^+$ were studied[41,42] and did show sensitivity of the rate of amine replacement to the basicity of (am). The sulphur donors expected in biological systems, however, were much less effective as trans labilising ligands,[43] a fact which leads to the view that straightforward displacement of the amine is not involved in the anti-tumor activity of these systems.

Table 4. Effect of cis-PtA_2Cl_2 on PC6 tumor and L1210 Leukaemia

A	Tumor System	
	PC6 (T.I.)[a]	L1210 (% I.L.S.)[b]
NH_3	8.1	95
	24.6	70
	31.0	52
	235.7	41
	> 267	3

[a] Data from reference 26.

[b] Data from reference 40.

1.2.2b Solubility:

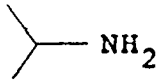
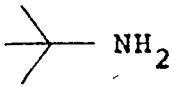
The relatively low aqueous solubility of many of the complexes studied has complicated the analysis of the screening tests. Many of the compounds must be administered interperitonally as an oil suspension, a practice which introduces a new variable - the rate of absorption of the material from the peritonal cavity. In an effort to study this rate, which crucially controls the concentration of platinum in the blood stream, chloroform was chosen as a model for the lipid phase and the ratio of chloroform solubility to aqueous solubility was determined[41] for a number of complexes, cis-PtA_2Cl_2.

As can be seen in Table 5, the distribution coefficients of these complexes vary dramatically with minor changes in the amine substituents, but these variations do not parallel the change in therapeutic index. While solubility is bound to play an important role in activity of a species, solubility-activity relationships cannot explain the activity trends.

1.2.2c Structural Changes:

The series of alicyclic amines is characterized by the steady increase in size of a bulky substituent close to platinum. Since kinetic and solubility effects were of limited importance, Tobe et al.[41] suggested that activity might be related to some structural effect. Thus, the need for structural studies becomes evident. The major part of this thesis comprises structural studies of complexes in

Table 5. Aqueous and chloroform solubilities, distribution coefficients[a] and effect on PC6 tumor of cis-PtA_2Cl_2

A	S_{H_2O} (mM)	S_{CHCl_3} (mM)	$D=S_{CHCl_3}/S_{H_2O}$	T.I.
NH_3	8.9	0.071	0.008	8.1[b]
CH_3NH_2	30.8	0.0037	0.00012	1.0[b]
	0.22	0.0038	0.0173	37[c]
	0.21	0.294	1.4	---[a]
cyclo-$C_3H_5NH_2$	1.6	0.0112	0.007	24.6[b]
cyclo-$C_4H_7NH_2$	0.21	0.0105	0.050	31.0[b]
cyclo-$C_5H_9NH_2$	0.013	0.0112	0.86	200[c]
cyclo-$C_6H_{11}NH_2$	0.0041	0.0176	4.3	> 267[b]
cyclo-$C_7H_{13}NH_2$	0.0014	0.0115	8.2	130[c]
cyclo-$C_8H_{15}NH_2$	0.00056	0.00935	16.7	37[c]

[a] Data from reference 41.

[b] Data from reference 26.

[c] Data from reference 27.

this series. These structures will be considered in Chapter 4, and compared in the Discussion.

1.3 Interaction with DNA

Shortly after confirmation of the anti-tumor activity of cisplatin, attempts were made to discover the attack site of the drug. Hydroxyurea, another anti-cancer drug which also causes filamentous growth in *E. coli*[44] causes inhibition of DNA synthesis.[44,45] Studies on the distribution of *cis*-$Pt(NH_3)_2Cl_4$ using ^{191}Pt showed that platinum was associated with protein and nucleic acids in bacteria.[46] These data led to many attempts to clarify the binding of cisplatin to biological molecules.

Simultaneous studies *in vivo*[47] and *in vitro*[47,48] observed the action of cisplatin on DNA, RNA and protein. DNA synthesis can be monitored by measuring the uptake and incorporation of one of its component molecules which has been labelled with a radioactive isotope such as ^{3}H or ^{14}C. Similarly, protein and RNA syntheses can be followed by measuring the uptake of radioactive components unique to them. Thymidine-^{3}H, uridine-^{3}H,[47,48] and L-leucine-^{3}H [48] (L-leucine-^{14}C)[47] were the precursors used to measure syntheses of DNA, RNA and protein, respectively.

Harder and Rosenberg,[48] using tissue cells in a culture medium, found selective inhibition of DNA synthesis at low cisplatin concentration. At high concentration of

cisplatin, DNA synthesis was more rapidly inhibited than that of RNA or protein, although in time, all three were virtually totally inhibited. The analogous trans complex had no effect.

Howle and Gale[47] observed the same effect on tumor cell suspensions in vitro. They then studied tumor cells which had been removed from rats a short time after a cisplatin injection. Initially, incorporation of all three precursors was inhibited; subsequently, RNA and protein synthesis rates returned to the control level, while suppression of the rate of thymidine incorporation persisted. More recent studies have confirmed reaction with DNA as the basis for interaction of cisplatin and other platinum chemotherapy agents with biological systems.[49-57]

Molecules which react with DNA can do so at the phosphate groups, the sugar residues or the purine and pyrimidine bases. In an effort to specify which of these areas is involved in interaction with cisplatin, the ultraviolet and circular dichroism spectra of DNA treated with cisplatin were studied.[58] The results, which indicated that platinum was bonded to the purine and pyrimidine bases rather than sugar or phosphate, have since been supported by other researchers.[52,59]

Subsequent studies using DNA of varying guanine-cytosine (G-C) content showed that the amount of platinum uptake increased with increasing G-C content,[59-68] a fact which led to the hypothesis that platinum bonds preferentially

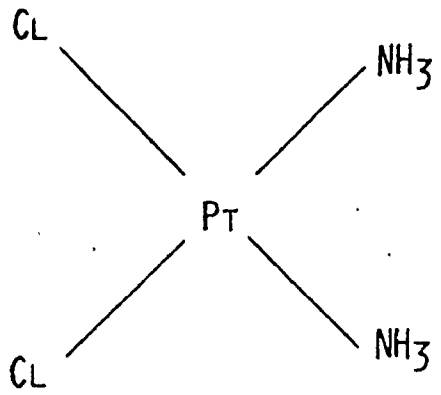
to guanosine or cytidine. This has since been narrowed down to preferential bonding to guanosine.[52,69-74]

1.4 Models for Platinum-DNA Binding

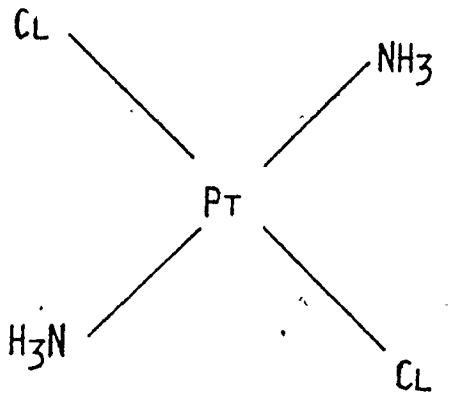
The studies on PtA_2X_2 complexes which were compared in Section 1.2 all showed a lack of activity of the trans isomers similar to that observed in the initial tests. This fact led to a great deal of theorizing about the mode of action of cisplatin.

Although trans-dichlorodiammineplatinum(II) does not inhibit DNA synthesis at low platinum concentration,[48] Pascoe and Roberts[55] showed that at the concentration where only the cis isomer killed cells, more trans isomer than cis was actually bound to DNA. This implies that the type of binding to DNA is different for cis and trans complexes, a suggestion which leads to consideration of the structures of the two isomers (Figure 1).

The X-ray structures of cis and trans-dichlorodiammine-platinum(II) showed[75] that the labile ligands in cisplatin are 3.35 Å apart while the chlorine atoms in the trans isomer are 4.64 Å apart. This led to the suggestion that the major factor in the difference between the reactions of the cis and trans isomers with DNA is likely to be their different stereochemical requirements and the ability of the cis compounds to form chelates.[4,5,51,76] The difference of approximately 3.4 Å between the cis chlorines has led to a



cis-dichlorodiammineplatinum(II)



trans-dichlorodiammineplatinum(II)

Figure 1

Structures of cis- and trans-$PtCl_2(NH_3)_2$

number of chelate models (Figure 2) which make use of the possible bifunctional binding of cisplatin to DNA. Monofunctional bonding to the bases has, however, also been proposed, and some discussion of both types of model will be presented here.

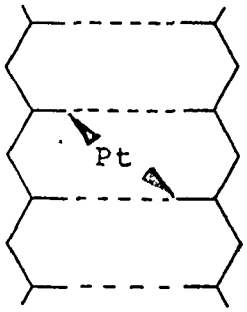
1.4.1 Bifunctional Bonding:

Various authors have suggested the importance of chelates between cisplatin and DNA simply on the basis of stereochemistry.[1-5,58,77-79] Some proof that crosslinks occur was obtained, however, during studies of intercalators. It was suggested[2] that because of the difference in dipole moment between cis and trans isomers, their binding to DNA may differ by the ability of the cis complexes to intercalate into DNA. It was subsequently discovered that not only do the drugs not intercalate,[59,80,81] but they also inhibit the action of known intercalators.[64,81-83] Intercalation changes the interplanar base separation from 3.4 Å to 6-7 Å at the intercalation site.[84] Interbase chelates (crosslinks) as shown in Figure 2 could hold the interplanar separation constant; or possibly decrease it.

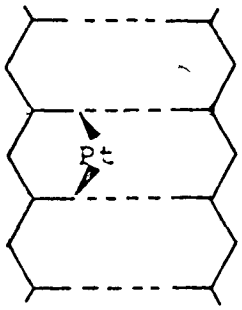
1.4.1a Interstrand Crosslinks:

Roberts and Pascoe[85] showed that cisplatin can crosslink DNA strands in vitro. This type of binding was initially considered to be significant; although the ability of cis and trans isomers to form interstrand crosslinks in vitro

Interbase Chelates



Interstrand crosslink



Intrastrand crosslink

Intrabase chelate with guanosine

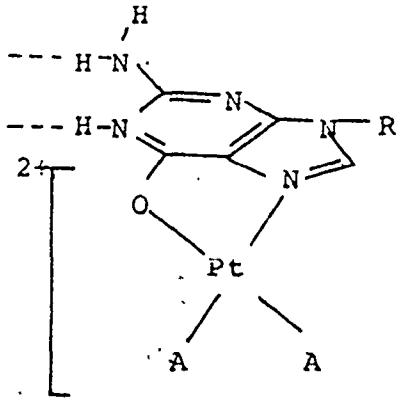


Figure 2

Postulated bifunctional binding of platinum complexes to DNA

is similar,[51,55] cis complexes were ten times as efficient at crosslinking as trans, in vivo.[55] The frequency of interstrand crosslink formation was, however, found to be extremely rare at pharmacologically realistic platinum concentration,[51,55,60,63,86] thus other types of binding have received more recent studies. Work by Zwelling et al.[87] using DNA alkaline elution techniques has shown crosslinking at low platinum concentration, but it is not clear whether it is interstrand or intrastrand.

1.4.1b Intrastrand Crosslinks:

With the previously mentioned rarity of interstrand crosslinks established, a number of researchers have favoured a model incorporating intrastrand crosslinks.[51,55,56,63,68,71,81,82,88] This was initially postulated because the interplanar base separation of 3.4 Å is similar to the cis chlorine distance[88,89] of 3.35 Å in cisplatin. Should, however, the platinum bond to nitrogen or oxygen atoms on the DNA bases, the shorter Pt-N/Pt-O distances would reduce the ligand separation to less than 3 Å. This would cause the planes of the bases to tilt from their former parallel arrangement. Such an effect has been observed in X-ray structures of compounds containing the PtA_2B_2 unit where A is the amine ligand and B, the DNA base.[90-94] The strain on the DNA helix caused by such a distortion would be quite large. Because of the importance of platinum-guanosine bonding (Section 1.3), the X-ray

structure of the product formed by the reaction of cisplatin with GpG would be significant, especially since the presence of the GpG sequence has been shown[71] to increase the binding of platinum to polynucleotides.

1.4.1c Intrabase Chelation:

The model which has stirred up the greatest amount of controversy during the last few years is the intrabase chelate shown in Figure 2. The N(7) position of guanosine is accepted to be the site most favoured for primary attack.[95] Because the strain that intrastrand crosslinking would cause is expected to be quite large, the replacement of the second labile ligand by O(6) of the same guanosine rather than by an atom on an adjacent base has been suggested.[96]

Early nmr experiments[97] and more recently, Raman difference spectroscopy,[88,98] have failed to show evidence for any N(7)-O(6) chelate. Despite this, X-ray photoelectron spectroscopy[99] and infrared spectroscopy[100,101] have been interpreted to show the existence of N(7)-O(6) chelation. These interpretations have been disputed by other workers in this field.[98,102]

One main problem with the model is that it explains neither the importance of GpG sequences[71] nor the inhibition of intercalation.[63,80-82] To overcome this, there have been attempts to combine the two theories of N(7)-O(6) chelation and intrastrand crosslinking. Goodgame et al.,[90] who saw

no evidence of an N(7)-O(6) chelate in their X-ray studies, suggested that the chelate is formed, but that the Pt-O bond is weak and is easily broken when the strands separate. This strand separation would cause the helix to become more flexible and an intrastrand crosslink could be formed. This suggestion has been repeated by a number of other researchers.[62,101,103]

Although the postulate of N(7)-O(6) chelation is attractive because it shows a clear difference between possible modes of cis and trans binding to DNA, sufficient hard chemical evidence for such a chelate does not yet exist.

1.4.2 Monofunctional Bonding:

The ability of both cis and trans platinum complexes to bond monofunctionally to DNA bases has caused most of the theories to concentrate on bifunctional coordination. Two cases of monofunctional coordination will be discussed here.

1.4.2a Co-stacking:

The 3.4 Å distance between the stacked bases has been suggested to be of importance for bonding other than chelation.[65] Some cis-PtA_2Cl_2 complexes have been shown to stack in the solid state so that metal-metal interactions exist between platinum atoms at a distance of about 3.4 Å;[75,104,105] there is no short platinum-platinum distance in trans-$Pt(NH_3)_2Cl_2$.[75] Eichhorn and co-workers[65] suggested that when cis complexes of platinum are bound to DNA, they could co-stack with the bases, preserving this 3.4 Å metal-metal

distance. Further consideration of this theory will be left to the Discussion, since a number of X-ray structure determinations of cis-PtA_2Cl_2 complexes were carried out as part of this thesis.

1.4.2b Base Mispairing:

The recently published structure[106] of the complex of the cis-$[Pt(NH_3)_2]^{2+}$ unit attached to 9-ethyl-guanine (9-EtG) and 1-methylcytosine showed that coordination of platinum at N(7) of 9-EtG shifted the pK of the N(1) position sufficiently to produce significant amounts of both protonated and deprotonated guanine. This allowed G-G base pairing to occur, rather than the Watson-Crick[107] G-C pairing. Investigation of similar structures with trans complexes to see whether the same effect can be induced would be of interest.

1.5 Summary:

The amount of research that is being carried out on platinum complexes has mushroomed since 1970. As new information is discovered, theories about the basic chemistry of platinum compounds as well as their reaction with DNA are either strengthened or discarded.

The structures examined in this thesis help clarify the aquation of cisplatin and lead to some theories about reduction in toxicity for the alicyclic amine complexes. The

variety of products obtained from the reactions used to make these compounds leads one to suggest that more care is necessary to verify that the complexes used in screening tests are pure.

CHAPTER 2

EXPERIMENTS

2.1 Preparation and Analysis:

Details of the preparation of compounds studied in this thesis are given in the appropriate chapters.

Crystals of cis-dinitratodiammineplatinum(II) and di-μ-hydroxy-bis[diammineplatinum(II)]carbonate dihydrate were prepared by

Dr. B. Lippert, Department of Biophysics,
Michigan State University, East Lansing,
Michigan.

B. Lippert was also responsible for obtaining vibrational spectra and elemental analyses of these compounds. Elemental analyses were carried out by

Galbraith Laboratories, Knoxville, Tennessee.

Densities of these complexes were measured in this laboratory by displacement in light paraffin.

Crystals of cis-dichlorodi(cyclohexylamine-N)-platinum(II) bis(hexamethylphosphoramide) were prepared by

R.A. Speranzini, this laboratory.

The density of this compound was not measured because it powdered when placed in solvent other than hexamethylphosphoramide. Densities of the other compounds, all of

which were synthesized in this laboratory, were measured by flotation in aqueous zinc bromide solution with the exception of cyclohexylammonium trichloro(cyclohexylamine-N)platinate(II). Density of this compound was measured by flotation in a bromoform/chloroform mixture.

Analyses of the compounds synthesized in this laboratory were carried out by

Microanalyses Laboratory, Toronto, Ontario,

Guelph Chemical Laboratories Ltd., Guelph, Ontario,

and Canadian Microanalytical Service Ltd., Vancouver, B.C.

2.2 X-ray Crystallography:

2.2.1 Single Crystals:

Small crystals with well developed faces were examined under a polarizing microscope for homogeneity, and the best of these chosen for data collection. Where possible, the crystal which was chosen was ground into a sphere ($[(NH_3)_2Pt(OH)_2Pt(NH_3)_2](CO_3)\cdot 2H_2O$) or cylinder (trans-$PtBr_2(C_6H_{11}NH_2)_2$ and $[C_6H_{11}NH_3][PtCl_3(C_6H_{11}NH_2)]$).

The crystals were then mounted on thin glass fibres and precession photographs of zero and first layers were taken using MoK_α radiation. On the basis of the symmetry obtained, space groups were assigned and unit cells calculated. The crystals were then transferred to a Syntex $P2_1$ automatic diffractometer (cis-$Pt(NH_3)_2(NO_3)_2$ and cis-$PtCl_2(C_3H_5NH_2)_2$

to a Syntex $P\bar{1}$ diffractometer) and an orientation matrix was obtained using Polaroid film. Unit cell parameters were then obtained by least squares refinement from fifteen well-centered medium angle reflections. Intensity data were collected and the crystals were placed on a two circle microscope to find the faces. The relationship between the microscope circles and the Syntex circles is known and the crystal faces could thus be indexed using the ϕ and χ angles from the Syntex output. The distance of each crystal face to the centre of the crystal was measured using the microscope.

Intensity data were measured using graphite monochromatized MoK_α radiation (λ = 0.71069 Å) for the appropriate hemisphere or quadrant to a maximum 2θ = 55°. Data were collected[108] using a coupled θ(crystal) - 2θ(counter) scan from 1° in 2θ below K_{α_1} to 1° in 2θ above K_{α_2}. Scan rates ranged from 2.0 deg min^{-1} for weak reflections (1.0 deg min^{-1} for very small crystals) to 29.3 deg min^{-1} for strong reflections (4.0 to 24.0 deg min^{-1} when the $P\bar{1}$ was used) and were selected by the program supplied with the instrument.[b] The stability

[b] For this program a reflection is counted for 2s, and the point at which the count falls between the chosen maximum and minimum count limits determines the scan rate for that reflection. The high intensity limit is set at 1500 counts/2s and higher values are collected at the fastest scan rate; the low intensity limit is set at 150 counts/2s and lower values are collected at the slowest scan rate. Intermediate values cause collection at intermediate rates. Below 500 counts/s no coincidence correction is made. Between 500 and 50000 counts/s a coincidence correction is made. Above 50000 counts/s the coincidence correction is considered invalid and such reflections are rejected.

of each system was monitored by measuring one, two or three standard reflections after every forty-nine, forty-eight or forty-seven reflections. In the case of di-μ-hydroxo-bis-[diammineplatinum(II)]carbonate dihydrate three standard reflections after every thirteen reflections were measured. Only for cis-dichlorodi(cyclohexylamine-N)platinum(II) bis-(hexamethylphosphoramide) was a decrease in intensity of the standard reflections observed, even at -30°C (all other data sets were collected at room temperature). Corrections were applied to the intensity of each reflection to allow for this decomposition. Stationary counts at the limits of each scan were made for half the scan time to establish the background. The intensity of a reflection was taken as $I = N_T - N_{BG_1} - N_{BG_2}$, where N_T is the total peak count and N_{BG_1} and N_{BG_2} are the background counts. $\sigma(I)$'s were taken as $(N_T + N_{BG_1} + N_{BG_2})^{\frac{1}{2}}$.

2.2.1a Data Processing:[109]

Of the total symmetry-independent reflections measured, reflections with $I > 3.0\sigma(I)$ were labelled observed and those with $3.0\sigma(I) > I > 0$ were labelled unobserved. The latter were given no weight in the refinement unless $F_c > F_o$. Absorption corrections were applied to the intensity using the measured dimensions of each crystal. Unscaled structure amplitudes, F_o, and their standard deviations, $\sigma(F)$, were calculated from the expressions

$$F_o = \left(\frac{I}{Lp}\right)^{\frac{1}{2}}$$

$$\sigma(F) = \frac{1}{2} \frac{1}{(Lp)^{\frac{1}{2}}} \left(\frac{\sigma(I)^2}{I}\right)^{\frac{1}{2}}$$

Lp, the Lorentz-polarization factor was $(1 + \cos^2 2\theta)/(2 \sin 2\theta)$. Corrections were made for secondary extinction using the method of Larson.[110]

Unscaled structure amplitudes, F_c, were calculated using the equation

$$F_c(hk\ell) = \sum_{j=1}^{n} T_j f_j \exp[2\pi i(hx_j + ky_j + \ell z_j)]$$

where f_j is the scattering factor of the jth atom in the unit cell and x_j, y_j and z_j are the fractional coordinates of the jth atom along the three crystallographic axis $\underset{\sim}{a}$, $\underset{\sim}{b}$ and $\underset{\sim}{c}$, respectively. The temperature factor, T_j, describes the magnitude of vibration of the atoms about their mean positions as

$$T_j = \exp[-2\pi^2 U_j \left(\frac{1}{d_{hk\ell}}\right)^2]$$

where U_j is the isotropic thermal parameter expressed in terms of mean square amplitudes in $\mathring{A}^2$ for the jth atom in the unit cell and $\frac{1}{d_{hk\ell}}$ is the reciprocal of the interplanar spacing for the set of planes defined by the Miller indices h,k,ℓ. The general temperature factor expression is

$$T = \exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}\ell^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}h\ell a^*c^* + 2U_{23}k\ell b^*c^*)]$$

where U_{ij} are the anisotropic thermal parameters expressed in terms of mean square amplitudes of vibration in $\mathring{A}^2$ and a*, b* and c* are the reciprocal cell axes. U_{ij} are obtained from $\beta_{ij} = 2\pi^2 b_i b_j U_{ij}$ where b_i are the reciprocal lattice vectors.

The programs used for initial data treatment (DATCO3/DATCO5, ABSORB, DATRN, FOURR) were from the X-RAY 71/X-RAY 76 package.[113a,112b] Structure solution and most least squares refinement used SHELX.[111c] Final refinements and differences used the full matrix least squares program CUDLS and the Fourier program SYMFOU, written internally by J.S. Stephens and J.S. Rutherford, respectively. Least squares planes and torsional angles were calculated by either the local program PALS (P.G. Ashmore) or the program NRC-22.[111d] Diagrams were prepared using the program ORTEP II.[111e] All calculations were carried out on CDC-6400 and CYBER 170/730 computers. Scattering curves[112a] and anomalous dispersion corrections[112b] were taken from the "International Tables for X-ray Crystallography". Anomalous dispersion corrections were applied to the curves for Pt, Cl, Br and P atoms only.

2.2.1b Structure Solution

All structures were solved by the heavy atom method, i.e., the coordinates of the platinum atoms were found from three-dimensional Patterson syntheses. Least squares refinement of the platinum positions followed by three-dimensional electron difference maps revealed the non-hydrogen atoms.

The hydrogen atoms attached to nitrogen in trans-dichlorobis-(cyclobutylamine-N)platinum(II) were found from a further difference map. In the initial stages, isotropic temperature factors were used for all atoms. As the refinement progressed, the temperature factors for Pt, Cl, Br and P were made anisotropic. When warranted by significance tests,[113] the temperature factors of the light atoms (O,N,C) were made sequentially anisotropic. Further refinement using full matrix least-squares minimizing $\Sigma w(|F_o| - |F_c|)^2$, where w is the weighting term, was terminated when the maximum shift/error was 0.2 for non-hydrogen atoms. The residuals used in CUDLS are

$$R_1 = \frac{\Sigma||F_o| - |F_c||}{\Sigma|F_o|}$$

and

$$R_2 = \left(\frac{\Sigma w(|F_o| - |F_c|)^2}{\Sigma w F_o^2}\right)^{\frac{1}{2}}$$

The moduli of F_o and F_c for the structures reported in the results section are listed in reference 180.

2.3 Infrared Spectra:

Infrared spectra were recorded on a Perkin-Elmer model 283 spectrometer. Solid samples were ground into a mull with nujol or hexachlorobutadiene and mounted between potassium bromide plates. Nujol mulls between polythene discs were used to obtain spectra between 500 cm^{-1} and 200 cm^{-1}. The spectra were calibrated with polyethylene. Liquid samples were dissolved in carbon tetrachloride and run against a CCl_4

reference between KBr plates.

2.4 Raman Spectra:

Raman spectra were recorded on a SPEX 14018 double spectrometer. Radiation was obtained from a Spectra-Physics model 164 Argon ion laser. Spectra were recorded using the 5145 Å (green) exciting line. Powder samples were contained in glass melting point tubes and liquid samples in nmr tubes.

2.5 Powder Diffraction:

Samples were ground to a fine powder and sealed in quartz capillary tubes. X-ray diffraction pattern photographs were then recorded on a Debye-Scherrer camera using CuK_α radiation. Line intensities were measured from the films with a Joyce-Loebl microdensitometer.

CHAPTER 3

STRUCTURES OF COMPOUNDS OBTAINED FROM THE REACTION OF CISPLATIN WITH SILVER NITRATE

In their initial studies on the reaction of cisplatin with biological macromolecules, both Howle and Gale[47] and Harder and Rosenberg[48] concluded that there must be an intermediate involved in the action of cisplatin on DNA. Because the chloride ion concentration in the cell is much lower than in human blood plasma, it seemed logical to suggest that hydrolysis of cisplatin gave the active species.[3,52,58,78] Other workers found that cisplatin had more effect on DNA if the solution was aged and that presence of X^- in the solution retarded reaction,[60,114-116] facts that also suggest the importance of aquation.

Unfortunately, this led to the paradoxical situation that the complex which was supposedly directly involved in bonding to DNA was, when tested against tumors, highly toxic.[4] This sparked an interest in the hydrolysis of cisplatin, the results of which will be summarized in the Discussion. The structures presented in this chapter are two of the many involved in these studies.

3.1 The Crystal and Molecular Structure of cis-dinitrato-diammineplatinum(II)[34]

3.1.1 Preparation (by B. Lippert)

cis-Dichlorodiammineplatinum(II) (3 g) (Engelhard Industries) was stirred with silver nitrate (3.38 g) in water (25 mL) in a stoppered, foil wrapped flask at room temperature for 20 h. The silver chloride which had formed was filtered and washed with water (5 mL). The pale yellow filtrate (pH 2) was kept in a stoppered flask in the refrigerator (5°C) for 3 days. The colourless needles which formed were filtered off and are being investigated elsewhere. The filtrate was concentrated (rotary evaporator, 30°C water bath) to a volume of 10 mL and allowed to evaporate slowly to half of its volume (5°C, 20 days). Pale yellow rhombic crystals were filtered, washed with 10 mL of water and ether and dried on a rotary pump vacuum.

The deuterated analogue was prepared by reacting cisplatin with 2 mol of $AgNO_3$ in D_2O solution (slightly warmed) and allowing the filtrate (c = 0.5 M) to stand in a stoppered flask (0°C, 8 weeks). Crystals of the deuterated compound were used for the X-ray studies.

3.1.2 X-ray Studies:

Crystal data and other numbers related to data collection and structure refinement are summarized in Table 6. The atom parameters from the final refinement are listed in Table 7, and selected bond lengths and angles are listed in

Table 6

Compound	cis-$Pt(ND_3)_2(NO_3)_2$
Formula Weight	359.21
crystal size	polyhedron with faces: {001} 0.194 mm apart {111} 0.240 mm apart
systematic absences	$Ok\ell$ $k \neq 2n$ $hO\ell$ $\ell \neq 2n$ hkO $h \neq 2n$
space group	Pbca (No. 61)
unit cell parameters (Å)	a = 9.760(4) b = 10.087(7) c = 13.495(5)
volume ($Å^3$)	1328.6(9)
Z	8
$\rho_{calc.}$ (gcm^{-3})	3.53
ρ_{obs} (gcm^{-3})	3.7(2)
linear absorption coefficient (cm^{-1})	220.7
absorption coefficient limits	16.11-41.47
Max 2θ; quadrant	55°; h,k,ℓ
standard reflection	1 0 $\bar{2}$
overall e.s.d.	1.9%

Continued.....

Table 6 (Continued)

no. of independent reflections	1399
$I > 3\sigma(I)$	975
$3\sigma(I) > I > \sigma(I)$ $F_c > F_o$	138
$F_c > F_o$	206
$\sigma(I) > I$, rejected	80
final R_1, obs. (all)	0.0465 (0.0537)
final R_2, obs. (all)	0.0428 (0.0493)
final shift in e.s.d. Max.	8.73×10^{-2}
Ave.	1.63×10^{-1}
g (secondary extinction)	3.230×10^{-8}
Final difference map:	
Highest peaks; location	2.0e/Å^3; 0.07, 0.08, 0.10
	1.7e/Å^3; 0.10, 0.04, 0.08
Lowest valley; location	-3.5e/Å^3; 0.14, 0.12, 0.10
Weighting scheme	$\frac{1}{\omega} = (83.411 - 1.1751\|F_o\| + 0.05\ F_o^2)$
Error in an observation of unit weight	1.008
Analysis* calc., obs. (%)	H 1.70, 1.73 N 15.86, 15.66 O 27.20, 27.33 Pt 55.24, 55.09

* Analysis is for the non-deuterated compound.

Table 7. Atom parameters for cis-$Pt(NH_3)_2(NO_3)_2$ ($\times 10^3$)*

Atom	x	y	z
Pt	141.74(5)	114.58(5)	88.19(4)
N(1)	30(1)	199(1)	- 19(1)
N(2)	- 4(1)	141(1)	189.4(9)
O(1)	264(1)	39(1)	191.5(9)
O(2)	152(2)	-148(1)	186(1)
O(3)	330(2)	-128(1)	280(1)
N(3)	247(2)	- 84(2)	218(1)
O(4)	303(1)	112(1)	- 7.6(9)
O(5)	430(1)	10(2)	-106(1)
O(6)	256(1)	- 91(1)	- 54(1)
N(4)	329(2)	7(2)	- 57(1)

Anisotropic temperature factors U_{ij} ($\mathring{A}^2$) ($\times 10^3$)*

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	21.3(3)	28.7(3)	30.8(3)	- 1.9(3)	0.1(3)	- 2.6(3)
N(1)	40(7)	35(8)	32(7)	- 2(6)	- 1(6)	3(6)
N(2)	33(6)	51(10)	21(6)	- 1(6)	8(5)	- 8(6)
O(1)	46(7)	30(6)	40(7)	- 8(6)	-11(6)	2(5)
O(2)	62(9)	42(7)	55(8)	0(7)	-21(8)	8(6)
O(3)	70(10)	65(9)	43(7)	14(8)	-20(7)	- 9(7)
N(3)	34(7)	54(9)	35(8)	7(7)	- 7(6)	1(7)
O(4)	24(5)	48(7)	48(7)	4(6)	8(5)	-11(7)

Continued.....

Table 7 (Continued)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(5)	30(7)	109(13)	54(10)	19(8)	14(6)	-21(9)
O(6)	48(8)	29(6)	64(8)	- 3(6)	0(7)	- 8(6)
N(4)	43(9)	46(8)	35(7)	9(7)	- 1(6)	- 5(7)

* Estimated standard deviations (e.s.d.'s) in terms of the last significant figure are given in parentheses in all tables of positional and thermal parameters, interatomic distances and angles.

Table 8. The molecule, cis-$Pt(NH_3)_2(NO_3)_2$ is shown in Figure 3.

The ammonia nitrogen atoms and an oxygen atom from each nitrate group form a rough square-planar arrangement about the platinum atom. The distortion of the plane can be seen clearly in Figure 3A; the platinum lies 0.1 Å out of the best square plane formed by the four ligand atoms. The molecule is also twisted so that the dihedral angle between N(1)PtN(2) and O(1)PtO(4) is 8.6°. The dihedral angles between the nitrate planes and the ligand plane are 73.3° (N(3) nitrate) and 87.2° (N(4) nitrate) and the angle between the two nitrate planes themselves is 80.6°. In other words, the nitrate groups are nearly perpendicular to the ligand plane and to each other as shown in Figure 3B. The nitrate groups lie on the same side of the ligand plane, and there is no evidence of any bonding interaction between the platinum atom and either O(2) or O(6); thus, the nitrate group is monodentate.

The Pt-N distances (2.00(1), 1.99(1) Å) do not differ significantly from values seen in other cis-$Pt(NH_3)_2X_2$ complexes.[32,33,35-38,75] The Pt-O bond lengths (1.99(1), 2.03(1) Å) imply reasonably strong bonds and are comparable to those found for stable bridging hydroxo compounds of platinum.[32,33,35-38]

Coordination seems to cause some distortion of the nitrate group. The N-O (coordinated) bond distances (N(3)-O(1), 1.30(2) Å; N(4)-O(4), 1.28(2) Å) appear to be larger than the other N-O distances (range 1.19(2)-1.24(2) Å)

Table 8. Interatomic distances (Å) and angles (deg) for cis-$Pt(NH_3)_2(NO_3)_2$

Bonded distances

Atoms	Distance	Atoms	Distance	Atoms	Distance
Pt-N(1)	2.00(1)	N(3)-O(1)	1.30(2)	N(4)-O(4)	1.28(2)
Pt-N(2)	1.99(1)	N(3)-O(2)	1.22(2)	N(4)-O(5)	1.19(2)
Pt-O(1)	1.99(1)	N(3)-O(3)	1.24(2)	N(4)-O(6)	1.22(2)
Pt-O(4)	2.03(1)				

Possible hydrogen bond distances

Atoms	Distance	Atoms	Distance
O(1)...N(2)[a]	2.96(2)	O(4)...N(1)[f]	2.95(2)
O(2)...N(1)[b]	2.91(2)	O(5)...N(2)[g]	3.23(2)
O(2)...N(2)[c]	3.08(2)	O(5)...N(1)[e]	3.37(2)
O(3)...N(1)[d]	3.12(2)	O(6)...N(1)[e]	3.01(2)
O(3)...N(2)[e]	3.13(2)	O(6)...N(2)[b]	3.11(2)
O(3)...N(2)[a]	3.19(2)	O(6)...N(1)[b]	3.16(2)

Angles

Atoms	Angle	Atoms	Angle	Atoms	Angle
N(1)-Pt-N(2)	93.0(6)	Pt-O(1)-N(3)	119(1)	Pt-O(4)-N(4)	120(1)
N(1)-Pt-O(1)	175.8(5)	O(1)-N(3)-O(2)	120(1)	O(4)-N(4)-O(5)	116(2)
N(1)-Pt-O(4)	88.0(5)	O(1)-N(3)-O(3)	117(1)	O(4)-N(4)-O(6)	123(2)
N(2)-Pt-O(1)	89.9(5)	O(2)-N(3)-O(3)	123(2)	O(5)-N(4)-O(6)	121(2)
N(2)-Pt-O(4)	171.8(6)				
O(1)-Pt-O(4)	88.8(5)				

Continued.....

Table 8 (Continued)

a-g Atoms are related to those in Table 7 by:

a	½+x,y,½-z	e	½-x,y-½,z
b	-x,-y,-z	f	½+x,½-y,-z
c	-x,y-½,½-z	g	½-x,-y,z-½
d	½-x,-y,½+z		

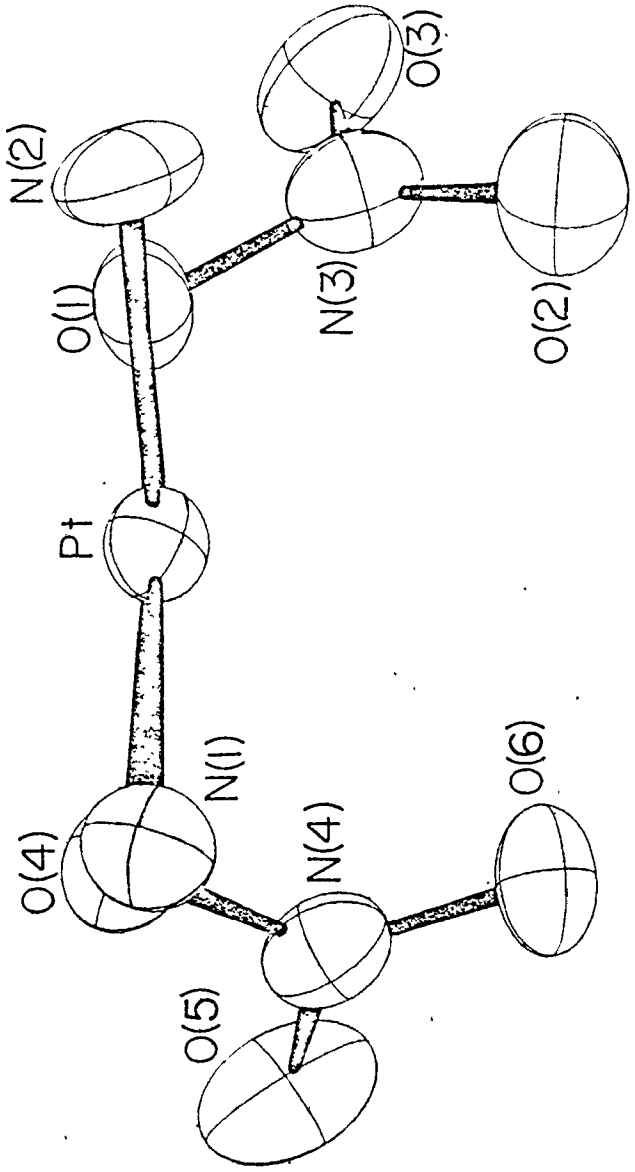


Figure 3A

The molecule cis-$Pt(NH_3)_2(NO_3)_2$ viewed along the vector Pt-O(1)-O(4) bisector)

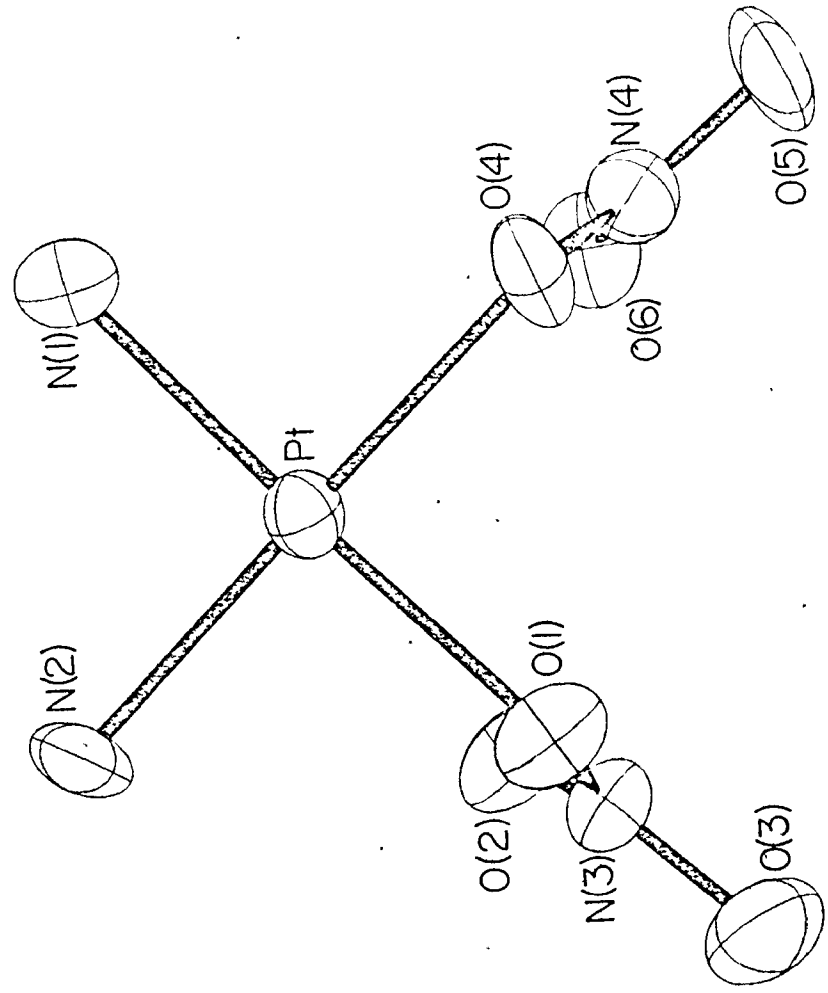


Figure 3B

The molecule cis-$Pt(NH_3)_2(NO_3)_2$ viewed along a vector perpendicular to the N(1)N(2)O(1)O(4) plane

and the equivalent angles O(4)N(4)O(5) (117(1)°) and O(1)N(3)O(3) (116(1)°) appear to be less than the other ONO angles (range 120(1)°-123(1)°). Because of the size of the errors, no definite conclusions can be drawn; however, the fact that the distortions are similar for the two nitrate groups and are similar to those observed previously[117] makes the hypothesis believable. The oxygen atoms also show differences in their probable hydrogen bonding (Table 8). The coordinated oxygen atoms are less than 3.4 Å from one ammonia nitrogen each whereas the other oxygen atoms are each within 3.4 Å of two or three ammonia nitrogen atoms.

The packing within the unit cell is shown in Figure 4. Clearly hydrogen bonding is very important in determining the packing. The plane of the four atoms coordinated to platinum is roughly parallel to the $\underset{\sim}{ac}$ plane with the bisector of N(1)PtN(2) (or O(1)PtO(4)) roughly parallel to $\underset{\sim}{a}$. The ligand plane is twisted relative to the $\underset{\sim}{ac}$ plane such that the ammonia groups on one molecule are brought close to nitrate oxygen atoms in molecules related by the $\underset{\sim}{a}$ glide and by the $\underset{\sim}{a}$ glide followed by the $\underset{\sim}{b}$ glide. In the $\underset{\sim}{c}$ direction, the prime contact is between the nitrate groups, with those on one molecule lying parallel to those on molecules above and below. In the $\underset{\sim}{a}$ direction, the prime contacts are between ammonia groups on one molecule and nitrate groups on the next. In the $\underset{\sim}{b}$ direction, packing is again governed by ammonia-

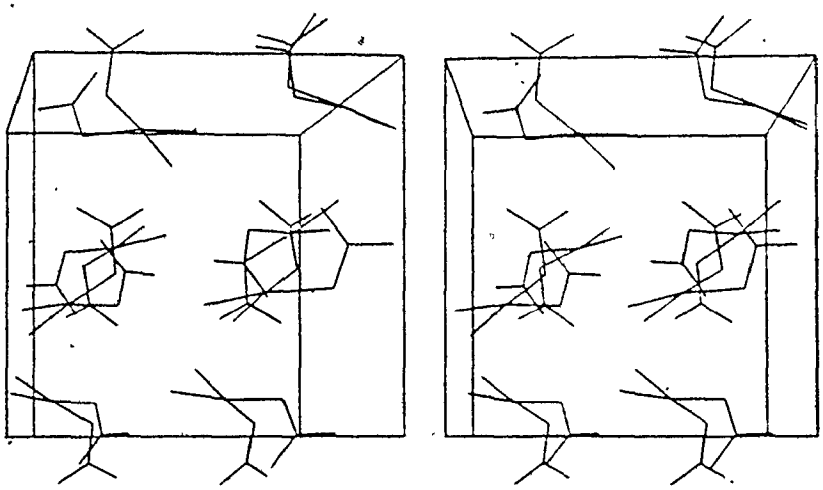


Figure 4

The unit cell contents of cis-$Pt(NH_3)_2(NO_3)_2$.
$\underset{\sim}{a}$ and $\underset{\sim}{b}$ are parallel to the top and side of the page, respectively. The view is down $\underset{\sim}{c}$.

nitrate contacts. The nitrate groups are arranged so that O(2) lies over the vacant axial position on platinum, opposite to the direction in which the nitrate groups are pointing. There is, however, no indication of Pt...O(2) bonding. All contact distances mentioned here are equal to or greater than the van der Waals contact distances.

3.2 The Crystal and Molecular Structure of di-μ-hydroxo-bis[diammineplatinum(II)]carbonate dihydrate[38]

3.2.1 Preparation (by B. Lippert):

Di-μ-hydroxo-bis[diammineplatinum(II)]nitrate[35] (0.308 g) was suspended in freshly prepared 0.05 N NaOH (10 mL) and kept in an open flask at room temperature. After about 2.5 h a few deep yellow crystals had formed. At that time, another equivalent of base (0.5 mL of 1 N NaOH) was added to the open flask (pH 10.65). The solution was kept in an open flask in a refrigerator (0°C) for three days. The yellow solution was then decanted and the residue washed with water (5 times, 20 mL portions) and ethanol. The deep yellow crystals that remained were dried on a rotary pump vacuum for fifteen minutes.

3.2.2 X-ray Studies:

Crystal data and other numbers related to data collection and structure refinement are summarized in Table 9. The atom parameters from the final refinement are listed in Table 10. Selected bond lengths and angles are given in Table 11

Table 9

Compound	$[(NH_3)_2Pt(OH)_2Pt(NH_3)_2](CO_3)\cdot 2H_2O$
crystal size	sphere, radius 0.06 mm
systematic absences	hOℓ ℓ ≠ 2n OkO k ≠ 2n
space group	$P2_1/c$ (No. 14)
unit cell parameters (Å and deg.)	a = 7.127(2) b = 11.416(3) c = 15.379(4) β = 119.15(2)
volume ($Å^3$)	1092.8(5)
Z	4
$\rho_{calc.}$ (gcm^{-3})	3.52
$\rho_{obs.}$ (gcm^{-3})	3.6(2)
linear absorption coefficient (cm^{-1})	265
absorption coefficient limits	7.28-8.80
Max. 2θ; quadrant	55°; h,k,±l
standard reflections, e.s.d. (%)	$\bar{2}11$, 2.4 020, 2.0 220, 2.5
no. of independent reflections	2525
$I > 3\sigma(I)$	1497
$3\sigma(I) > I > 0$ $F_c > F_o$	495
$F_c > F_o$	255
$I < 0$ rejected	278

Continued.....

Table 9 (Continued)

final R_1, obs. (all)	0.0448 (0.0521)
final R_2, obs. (all)	0.0536 (0.0554)
final shift in e.s.d. Max.	3.97×10^{-2}
Ave.	8.09×10^{-3}
g (secondary extinction)	9.771×10^{-8}
Final difference map:	
Highest peak, location	1.20e/$\mathring{A}^3$; 0.0, 0.97, 0.92
Lowest valley, location	-1.55e/$\mathring{A}^3$; 0.29, 0.38, 0.52
Weighting scheme	$\omega = [(\sigma(F))^2 + (0.03\ F_o)^2]^{-1}$
Error in an observation of unit wt.	1.228
Analysis calc., obs. (%)	H 3.06, 3.32 C 2.04, 1.90 N 9.54, 9.53 O 18.90, 16.71 Pt 66.40, 68.01
Formula Weight	588.36

Table 10. Atom parameters for $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2](CO_3)\cdot 2H_2O$

Atom	x	y	z
Pt(1)	292.83(10)	- 38.23(7)	668.73(5)
Pt(2)	259.55(10)	34.83(6)	467.28(5)
O(1)	251(2)	-114(1)	541.7(9)
O(2)	319(2)	109(1)	600.1(8)
N(1)	289(3)	-188(1)	741(1)
N(2)	337(3)	52(1)	790(1)
N(3)	211(2)	- 50(1)	341(1)
N(4)	315(2)	186(1)	415(1)
O(3)	46(2)	257(1)	710(1)
O(4)	58(3)	291(1)	569(1)
O(5)	- 30(2)	433(1)	642(1)
C(1)	26(3)	326(2)	640(1)
OX(1)	193(2)	-108(1)	113(1)
OX(2)	345(3)	95(2)	21(1)

Anisotropic Temperature Factors $U_{ij}(\text{Å})^2$ (x 10^3)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt(1)	24.8(4)	24.2(4)	22.3(4)	0.5(3)	12.5(3)	1.4(3)
Pt(2)	22.3(4)	20.0(3)	20.4(3)	0.2(3)	10.3(3)	0.4(3)
O(1)	35(7)	22(6)	25(6)	-12(6)	16(6)	0(5)
O(2)	36(7)	23(6)	14(5)	9(6)	11(5)	- 1(5)
N(1)	36(9)	24(8)	39(9)	3(7)	22(8)	15(7)

Continued.....

Table 10 (Continued)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(2)	40(9)	37(9)	13(7)	7(8)	9(7)	4(7)
N(3)	27(8)	30(9)	30(9)	- 5(7)	5(7)	- 8(7)
N(4)	30(8)	34(8)	21(7)	- 5(7)	12(7)	4(7)
O(3)	62(10)	25(7)	30(7)	-15(7)	30(7)	- 3(6)
O(4)	60(10)	35(8)	28(7)	10(7)	21(8)	1(6)
O(5)	59(10)	20(6)	33(7)	5(6)	30(7)	2(5)
C(1)	29(9)	26(9)	25(9)	- 5(8)	15(8)	-12(7)
OX(1)	49(9)	32(8)	40(8)	0(7)	9(7)	1(7)
OX(2)	71(13)	57(11)	84(13)	23(10)	48(11)	27(11)

Table 11. Interatomic distances (Å) and angles (deg) for

$[(NH_3)_2Pt(OH)_2Pt(NH_3)_2](CO_3)\cdot 2H_2O$

Atoms	Distance	Atoms	Distance	Atoms	Distance
Pt(1)-N(1)	2.05(2)	Pt(2)-N(3)	2.04(2)	C(1)-O(3)	1.29(3)
Pt(1)-N(2)	2.02(2)	Pt(2)-N(4)	2.02(2)	C(1)-O(4)	1.27(3)
Pt(1)-O(1)	2.02(1)	Pt(2)-O(1)	2.07(1)	C(1)-O(5)	1.29(2)
Pt(1)-O(2)	2.04(1)	Pt(2)-O(2)	2.06(1)		

Metal-metal distances

Atoms	Distance	Atoms	Distance	Atoms	Distance
Pt(1)-Pt(2)	3.104(1)	Pt(2)-Pt(2)[a]	3.167(1)	Pt(1)-Pt(2)[b]	3.443(1)

Possible hydrogen bond distances

Atoms	Distance	Atoms	Distance	Atoms	Distance
O(1)...O(4)[b]	2.86(2)	O(3)...N(3)[b]	2.85(2)	O(5)...OX(1)[e]	2.73(2)
O(1)...N(4)[a]	2.94(2)	O(3)...N(4)[e]	2.85(2)	O(5)...N(3)[e]	3.00(2)
O(2)...O(4)	2.68(2)	O(3)...N(1)[f]	2.90(3)	O(5)...OX(2)[g]	3.05(2)
O(2)...N(3)[a]	3.09(2)	O(3)...N(2)	2.97(2)	O(5)...N(2)[f]	3.16(3)
OX(1)...N(1)[c]	2.90(2)	O(4)...OX(1)[g]	2.73(2)	OX(2)...N(4)[d]	2.94(3)
OX(1)...N(2)[a]	2.99(2)	O(4)...OX(2)[e]	2.82(3)	OX(2)...N(2)[a]	3.16(2)
OX(1)...OX(2)	3.17(3)				

Angles

Atoms	Angle	Atoms	Angle	Atoms	Angle
N(1)-Pt(1)-N(2)	88.0(7)	N(3)-Pt(2)-N(4)	90.0(7)	Pt(2)-Pt(1)-Pt(2)[b]	83.21(2)

Continued.....

Table 11 (Continued)

Atoms	Angle	Atoms	Angle	Atoms	Angle
N(1)-Pt(1)-O(1)	97.5(6)	N(3)-Pt(2)-O(1)	95.6(6)	Pt(1)-Pt(2)-Pt(2)[a]	94.05(2)
N(1)-Pt(1)-O(2)	175.9(7)	N(3)-Pt(2)-O(2)	175.6(5)	Pt(1)-O(1)-Pt(2)	98.8(5)
N(2)-Pt(1)-O(1)	174.5(6)	N(4)-Pt(2)-O(1)	170.5(4)	Pt(1)-O(2)-Pt(2)	98.5(5)
N(2)-Pt(1)-O(2)	92.6(6)	N(4)-Pt(2)-O(2)	93.5(6)	O(3)-C(1)-O(4)	122(2)
O(1)-Pt(1)-O(2)	81.9(5)	O(1)-Pt(2)-O(2)	80.6(5)	O(3)-C(1)-O(5)	117(2)
				O(4)-C(1)-O(5)	120(2)

a-g Atoms are related to those in Table 10 by:

a 1-x,-y,1-z

b -x,-y,1-z

c x,y+½,z-½

d x,½-y,z-½

e x,½-y,½+z

f -x,½+y,1½-z

g -x,½+y,½+z

and a pair of molecular cations is illustrated in Figure 5.

This pair of cations represents one dimeric unit and its centrosymmetrically related unit with a relatively short Pt...Pt distance (3.164 Å) between the two. Platinum-platinum distances in the range 3.1-3.4 Å are well known, not only as the previously mentioned cis-PtA_2Cl_2 stacking distances,[75,104,105] but also in compounds analogous to the platinum "blues",[118-120] Magnus' green salt[121] and μ-pyrophosphato-bis[diammineplatinum(II)].[122] Whereas many of these compounds show evidence of metal-metal interactions,[123] in the title compound, the Pt...Pt distance is not short enough to be considered a covalent bond or a strong metal-metal interaction.

The basic dimer unit containing two hydroxo-bridged platinum atoms (A) is very similar to the cation found in $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2](NO_3)_2$ (B).[35] The relevant distances and angles show this (Pt-N(A) 2.02(2)-2.05(2), (B) 2.01(2), 2.02(2) Å; Pt-O(A) 2.02(1)-2.07(1), (B) 2.03(1) Å; Pt-Pt(A) 3.104(1), (B) 3.085(1) Å; N-Pt-N(A) 88.0(7), 90.0(7), (B) 89.3(6)°; trans-N-Pt-O(A) 170.5(4)-175.9(6), (B) 175.6(6), 176.1(6)°; cis-N-Pt-O (A) 92.6(6)-97.5(6), (B) 94.5(5), 94.9(5)°; O-Pt-O (A) 81.9(5), 80.6(5); (B) 81.3(4)°; Pt-O-Pt (A) 98.8(5), 98.5(5), (B) 98.9(5)°).

There are, however, minor differences. In dimer B, the bonded ligand atoms are very closely coplanar with the platinum atoms. In dimer A, the environment around Pt(1) is

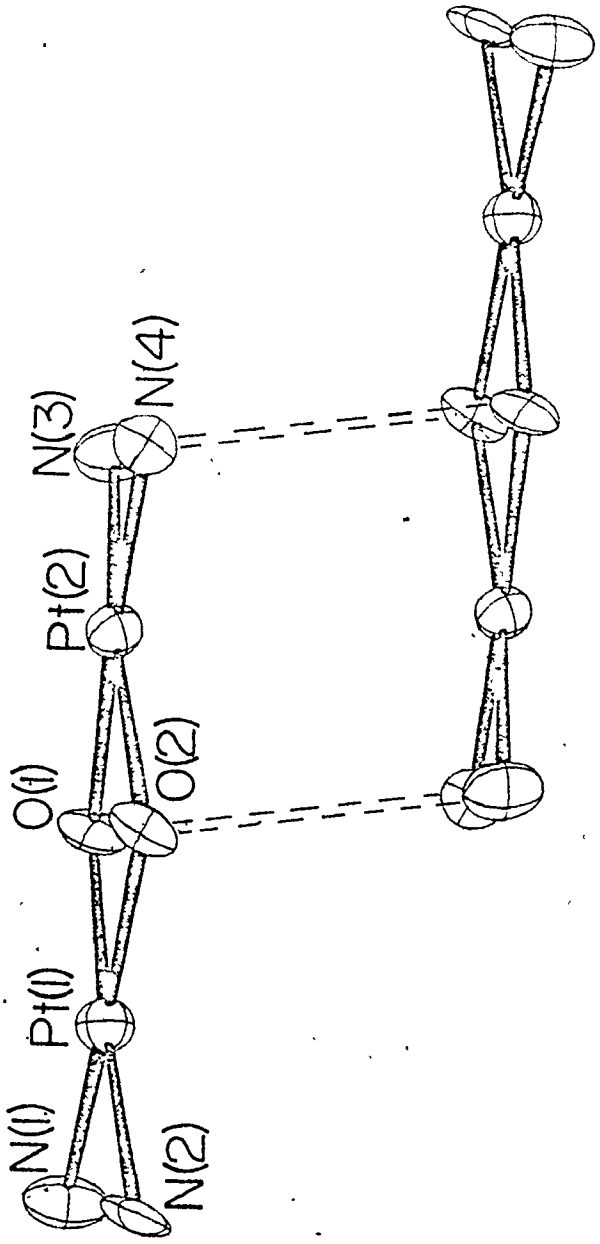


Figure 5

The molecular cation $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ and its centro-symmetrically related neighbour

closely planar (deviations from the best plane (Å): Pt(1), -0.03; O(1), -0.027; O(2), 0.043; N(1), 0.040; N(2), -0.026), but the environment around Pt(2) is much more distorted (deviations from the best plane (Å): Pt(2), -0.088; O(1), 0.047; O(2), -0.048; N(3), -0.043; N(4), 0.044).[c] This distortion appears to be related to the interaction between the two dimer units. The dimer units are arranged so that the Pt(2)...Pt(2)[a] distance is relatively short, but not because of an attractive platinum-platinum interaction, since for the best plane through the atoms around Pt(2), the central metal is displaced from this plane away from Pt(2)[a]. Further, the positive charge on the dimeric units will cause repulsion between the pairs of dimers. The two cations must be held together by some other interaction which could conceivably be hydrogen bonding (O(1)-N(4)[a], O(2)-N(3)[a], O(2)[a]-N(3), O(1)[a]-N(4)) and would be responsible for the distortion of the plane around Pt(2). It can be seen in Figure 5 that the plane formed by the ligand atoms is not at 90° to the plane formed by the four platinum atoms, but is slightly twisted relative to it with a dihedral angle of 86.6°. The reason that this arrangement is observed for the carbonate complex but not the nitrate complex could be related to the

[c] In the planes mentioned all atoms were included in the refinement and given unit weight. The esd in each atom position with respect to the plane is 0.015 Å.

stoichiometry. There are twice as many MO_3^{n-} units available as hydrogen bond acceptors in the nitrate salt as in the carbonate; thus, intercation hydrogen bonding may not be necessary.

The crystal can be considered as an assembly of cations, anions and water molecules with hydrogen bonding a major factor in holding the crystal together. The planes of both the cations and anions lie very roughly parallel to the $\underset{\sim}{bc}$ plane, as is seen in Figure 6. Pairs of dimeric cations form two parallel rows along the $\underset{\sim}{c}$ direction held together by hydrogen bonding. Within the rows along $\underset{\sim}{c}$, each pair of dimers is tilted with respect to the next pair (dihedral angle 13°). This tilt appears to be caused by the requirements of hydrogen bonding. Because of the $\underset{\sim}{a}$ translation, half of a pair of dimers lies almost exactly over the opposite half of the next pair of dimers, but this platinum-platinum distance is relatively long (3.443(1) Å). This is clearly caused by the intercalation of the carbonate anions; hydrogen bonding is now from each dimer to the carbonate ion rather than between the dimers. The water molecules determine the packing in the $\underset{\sim}{b}$ direction. They lie almost in the plane of the dimer and hydrogen bond to the dimer, each other, and the carbonate anions.

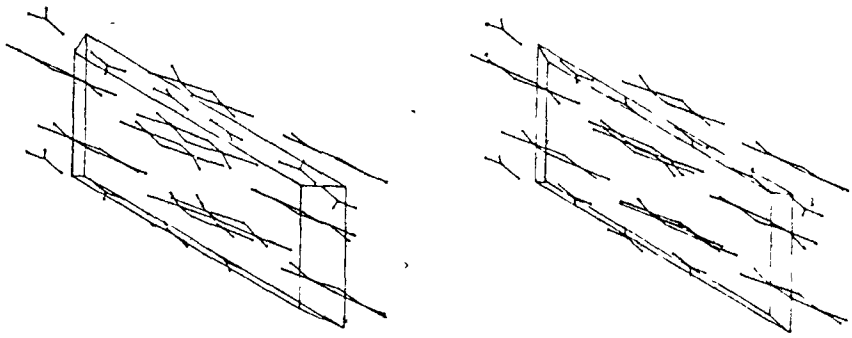


Figure 6

The unit cell contents of $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2]CO_3 \cdot 2H_2O$ with extra ions and water molecules (represented by open circles). The $\underset{\sim}{a}$ and $\underset{\sim}{c}^*$ axes are parallel to the side and top of the page, respectively. The view is approximately along $\underset{\sim}{b}$.

CHAPTER 4

STRUCTURES OF PLATINUM-ALICYCLIC AMINE COMPLEXES

The opposing responses to the PC6 and Leukaemia L1210 cancers obtained using complexes cis-$Pt(am)_2Cl_2$ where am represents an alicyclic amine (Table 4) did not discourage all interest in these compounds. While they may not all be active against the L1210 system, there is still the question of why they show so little toxicity. The results also show that the cyclopropylamine complex, which is more effective than cisplatin against the PC6 tumor, is only marginally less effective against leukaemia L1210. In fact, cis-dichlorobis(cyclopropylamine-N)platinum(II) is one of the compounds selected for testing as a possible second generation drug.[124] It is clear that the structures of these compounds should be of interest not only to the chemist, but also to the medical researchers in the field.

4.1 The Crystal Structure and Vibrational Spectra of cis-dichlorobis(cyclopropylamine-N)platinum(II)[125]

4.1.1 Preparations:

cis-$PtCl_2(C_3H_5NH_2)_2$

The method used is a modification of the method of Dhara.[126] An aqueous solution (10 mL) of K_2PtCl_4 (0.472 g) was mixed with potassium iodide (0.6563 g) and left at room

temperature for a few hours. Cyclopropylamine (0.12 g) was added dropwise and the yellow powder filtered off after a half-hour. The product was stirred in 0.1 M silver nitrate solution (19 mL) for approximately six hours. After removal of silver iodide by filtration, potassium chloride (0.15 g) was added to the filtrate. The yellow product separated over the course of a week and was removed by filtration and washed with a small amount of ice water, followed by ethanol and diethyl ether. Crystals suitable for X-ray diffraction studies were obtained by recrystallization from water at 20°C.

$C_3H_5ND_2$

Cyclopropylamine (2.340 g) was reacted with 1 N HCl (40 mL) overnight. The water was removed under vacuum on a rotary evaporator with slight warming (40°C). The hydrochloride salt was dissolved in D_2O (50 mL) and allowed to stand in a stoppered flask at room temperature for two weeks. The D_2O was removed under vacuum on a rotary evaporator and the white powder redissolved in a minimum of D_2O (~ 3 mL). Sodium bicarbonate (3.431 g) was added and the solution left overnight. The deuterated amine was distilled from the solution at reduced pressure with gentle warming (40°C).

cis-$PtCl_2(C_3H_5ND_2)$

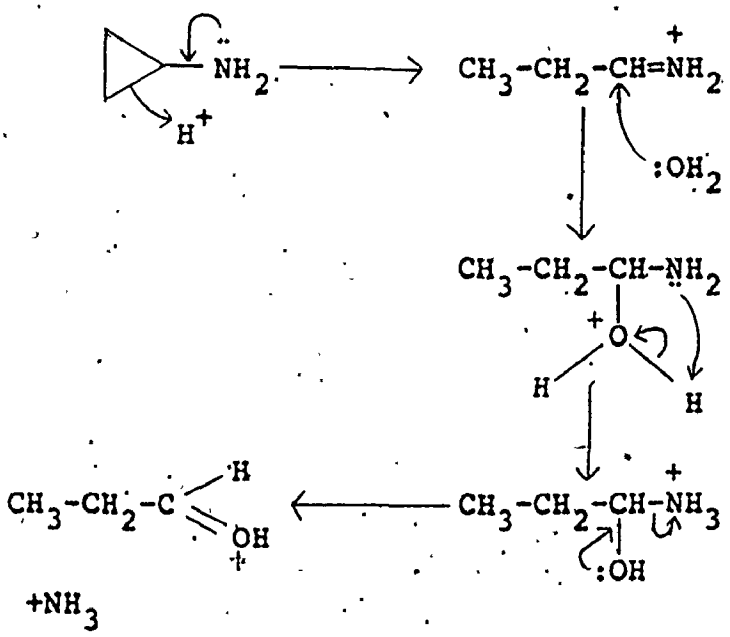
Deuterated cyclopropylamine (0.1464 g) was added dropwise to a solution of K_2PtCl_4 (0.5221 g) in D_2O (10 mL) and left overnight at room temperature. The pale yellow

powder which formed was collected by filtration and washed with a small amount of D_2O and cold acetone.

4.1.1a Discussion:

My first attempts to prepare cis-dichlorobis(cyclopropylamine-N)platinum(II) were based on the method of Connors et al.,[26] which involves the direct reaction of cyclopropylamine hydrochloride with an aqueous solution of K_2PtCl_4 in the presence of sodium bicarbonate and subsequent recrystallization of the black powder and yellow crystals from hot concentrated HCl. The product I obtained from this recrystallization was identified by both powder and single crystal X-ray diffraction as ammonium hexachloroplatinate.

It appears that under the conditions of recrystallization, the following reaction is taking place, together with oxidation by air of platinum(II) to platinum(IV).



Discussions with Professor Tobe have revealed that the procedure in the literature[26] is inaccurate. Instead of recrystallization from hot concentrated hydrochloric acid as reported, the product should be leached with the acid to remove the black, HCl soluble impurities. We have confirmed that the direct reaction of K_2PtCl_4 with cyclopropylamine does give the desired product; in fact, the deuterated analogue of the complex studied here was prepared using a similar procedure.

4.1.2 X-ray Studies:

Crystal data and other numbers related to data collection and structure refinement are summarized in Table 12. The atom parameters from the final refinement are listed in Table 13. Selected bond lengths and angles can be found in Table 14 and the molecule cis-$PtCl_2(C_3H_5NH_2)_2$ is shown in Figure 7.

The bonded ligand atoms are in a rough square around the platinum atom in an essentially planar arrangement. The deviations from the best plane (Pt, 0.006(1); Cl(1), -0.003(4); Cl(2), 0.004(4); N(1), -0.04(1); N(2), 0.03(1) Å) are not significant.

The Pt-N distances (2.05(1), 2.04(1)) are normal, as are the Pt-Cl distances.[75,104,105,127-132] All distances within the cyclopropylamine group are normal.[133] The dihedral angles between the best plane through the ligand atoms and

Table 12

Compound	$PtCl_2(C_3H_5NH_2)_2$
Formula weight	380.19
crystal size	polyhedron with faces: {010} 0.290 mm apart {102} 0.168 mm apart {001} 0.136 mm apart {100} 0.210 mm apart {10$\bar{2}$} 0.162 mm apart
systematic absences	hOℓ ℓ ≠ 2n OkO k ≠ 2n
space group	$P2_1/c$ (No. 14)
unit cell parameters (Å and deg.)	a = 12.770(5) b = 5.358(2) c = 15.113(6) β = 104.46(3)
volume ($Å^3$)	1000.3(7)
Z	4
$\rho_{calc.}$ (gcm^{-3})	2.52
$\rho_{obs.}$ (gcm^{-3})	2.52(1)
linear absorption coefficient (cm^{-1})	152.1
absorption coefficient limits	5.657-15.323
Max. 2θ; quadrant	55°; h,k,±l
standard reflections, e.s.d. (%)	$\bar{2}$13, 2.24

Continued.....

Table 12 (Continued)

no. of independent reflections	2310
$I > 3\sigma(I)$	1577
$3\sigma(I) > I > 0.0$ $F_c > F_o$	286
$F_o > F_c$	240
$I < 0$, rejected	207
Final R_1, obs. (all)	0.0458 (0.0566)
Final R_2, obs. (all)	0.0527 (0.0546)
Final shift in e.s.d. Max.	6.33×10^{-2}
Ave.	1.50×10^{-2}
g (secondary extinction)	8.868×10^{-8}
Final difference map:	
Highest peaks, location	$1.60 e^-/\mathring{A}^3$, 0.34, 0.0, 0.0
	$1.50 e^-/\mathring{A}^3$, 0.19, 0.04, -0.03
Lowest valleys, location	$-1.41 e^-/\mathring{A}^3$, 0.26, 0.24, -0.02
	$-1.3\ e^-/\mathring{A}^3$, 0.28, 0.06, -0.005
Weighting scheme	$\omega = [\sigma^2 + (0.03\ F_o)^2]^{-1}$
Error in an observation of unit weight	1.010
Analysis, calc., obs. (%)	H 3.7, 3.9 C 19.0, 19.2 N 7.4, 7.6

Table 13. Atom parameters for cis-$PtCl_2(C_3H_5NH_2)_2$

Atom	x	y	z
Pt	260.65(4)	55.3(1)	- 5.12(3)
Cl(1)	382.6(3)	-261.5(7)	24.4(3)
Cl(2)	160.2(3)	-114.4(7)	85.6(3)
N(1)	152.6(9)	345(2)	- 28.2(8)
N(2)	346.1(8)	215(2)	- 87.8(7)
C(1)	88.6(9)	373(3)	-120(1)
C(2)	119(1)	563(3)	-175(1)
C(3)	21(1)	602(3)	-142(1)
C(4)	317(1)	122(3)	-180(1)
C(5)	394(1)	170(4)	-240(1)
C(6)	372(1)	- 80(4)	-208(1)

Anisotropic temperature factors, $U_{ij}(\text{Å})^2$ (x 10^3)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	49.3(3)	46.1(3)	40.6(3)	3.5(2)	15.0(2)	- 2.3(3)
Cl(1)	54(2)	57(2)	76(2)	10(1)	16(2)	2(2)
Cl(2)	85(2)	60(3)	64(2)	9(2)	42(2)	10(2)
N(1)	77(7)	60(8)	50(6)	26(6)	36(6)	19(6)
N(2)	56(6)	55(7)	48(6)	- 3(5)	28(5)	- 4(6)
C(1)	42(6)	62(10)	62(9)	- 8(6)	21(6)	2(7)
C(2)	70(8)	88(12)	55(8)	19(8)	25(7)	14(9)
C(3)	58(7)	79(12)	94(12)	27(7)	35(8)	46(10)

Continued.....

Table 13 (Continued)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(4)	56(7)	86(12)	49(8)	4(7)	20(6)	- 2(8)
C(5)	79(10)	116(15)	59(10)	-10(10)	40(8)	- 6(11)
C(6)	78(10)	111(16)	76(11)	-12(10)	42(9)	-20(12)

Table 14. Interatomic distances (Å) and angles (deg) for cis-$PtCl_2(C_3H_5NH_2)_2$

Bonded distances

Atoms	Distance	Atoms	Distance	Atoms	Distance
Pt-Cl(1)	2.272(4)	N(1)-C(1)	1.43(2)	N(2)-C(4)	1.44(2)
Pt-Cl(2)	2.287(4)	C(1)-C(2)	1.43(2)	C(4)-C(5)	1.51(2)
Pt-N(1)	2.05(1)	C(1)-C(3)	1.49(2)	C(4)-C(6)	1.41(3)
Pt-N(2)	2.04(1)	C(2)-C(3)	1.48(2)	C(5)-C(6)	1.48(3)

Possible hydrogen bond distances

Atoms	Distance	Atoms	Distance	Atoms	Distance
Cl(1)...N(2)[a]	3.25(1)	Cl(1)...N(2)[b]	3.37(1)	Cl(2)...N(1)[a]	3.36(1)

Angles

Atoms	Angle	Atoms	Angle	Atoms	Angle
Cl(1)-Pt-Cl(2)	92.6(1)	Pt-N(1)-C(1)	116.1(9)	Pt-N(2)-C(4)	113.6(9)
Cl(1)-Pt-N(1)	178.4(3)	N(1)-C(1)-C(2)	118(1)	N(2)-C(4)-C(5)	118(1)
Cl(1)-Pt-N(2)	89.3(3)	N(1)-C(1)-C(3)	117(1)	N(2)-C(4)-C(6)	122(1)
Cl(2)-Pt-N(1)	87.1(4)	C(1)-C(2)-C(3)	62(1)	C(4)-C(5)-C(6)	56(1)
Cl(2)-Pt-N(2)	178.1(3)	C(2)-C(3)-C(1)	58(1)	C(5)-C(6)-C(4)	63(1)
N(1)-Pt-Cl(2)	91.1(5)	C(3)-C(1)-C(2)	61(1)	C(6)-C(4)-C(5)	61(1)

[a,b] Atoms are related to those in Table 13 by:

[a] x,y-1,z

[b] 1-x,-y,-z.

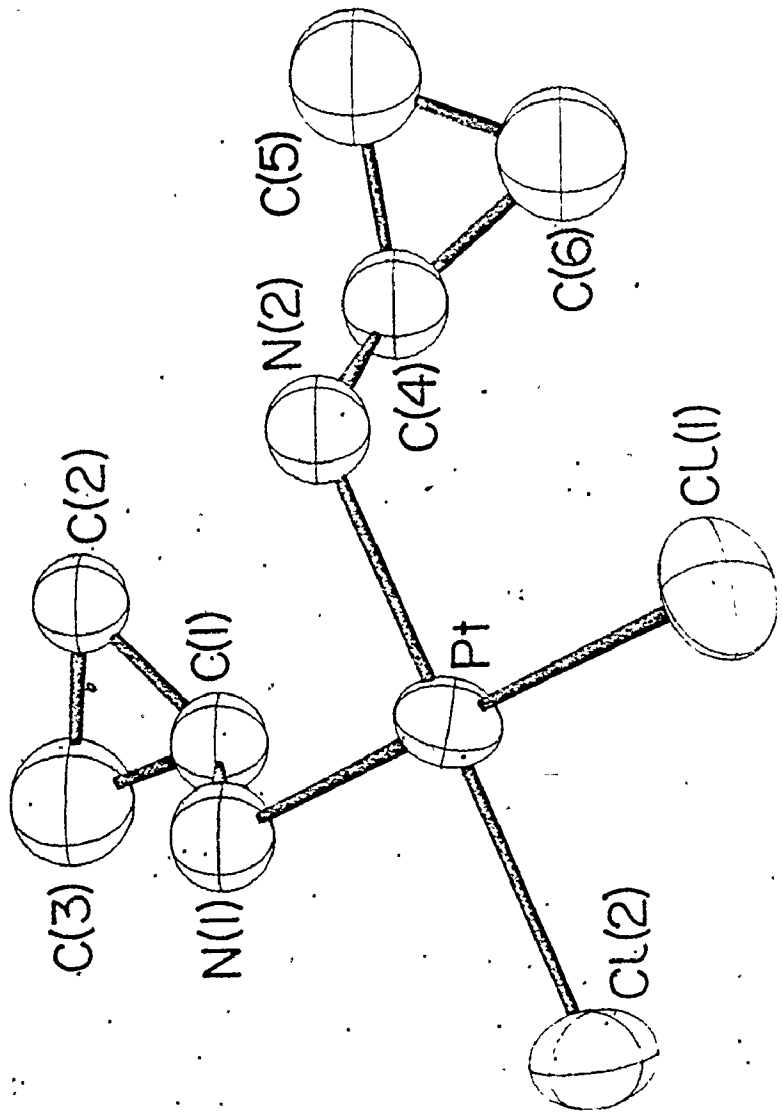


Figure 7

The molecule cis-$PtCl_2(C_3H_5NH_2)_2$

the cyclopropyl rings are relatively small (3.9° for C(1)C(2)C(3) and 26.0° for C(4)C(5)C(6)). This is probably caused by crystal packing since there appear to be no intramolecular steric interactions causing the planes to be parallel. The amine group is in the gauche arrangement with respect to the cyclopropyl ring.

The packing of the molecules within the cell is shown in Figure 8. In the $\underset{\sim}{b}$ direction, molecules related by the y translation are packed head-to-tail, and inclined relative to the $\underset{\sim}{ab}$ plane so that the square ligand planes are stacked roughly like tiles on a roof. The prime contacts are between Cl(2)...N(1)^{a}, 3.35 Å and Cl(1)...N(2)^{a}, 3.25(1) Å, suggesting hydrogen bonding between atom pairs. Hydrogen bonding is also important to the packing in the $\underset{\sim}{a}$ direction. The molecules related by x,y,z and 1-x,-y,-z have Cl(1)...N(2)^{b} contacts of 3.37(1) Å and the other contact in the $\underset{\sim}{a}$ direction is between a chlorine atom on one molecule and the cyclopropyl group on the next. The crystal is thus composed of layers of molecules centred at roughly z = 0 and z = ½. Within the layers, rows of molecules are arranged so that the dipoles are very roughly parallel to the $\underset{\sim}{b}$ direction. The dipoles point in opposite directions in adjacent rows. Contact between rows in different layers is almost entirely between platinum and chlorine atoms of one molecule and the cyclopropyl groups of the adjacent molecule. There is no evidence of hydrogen bonding between layers.

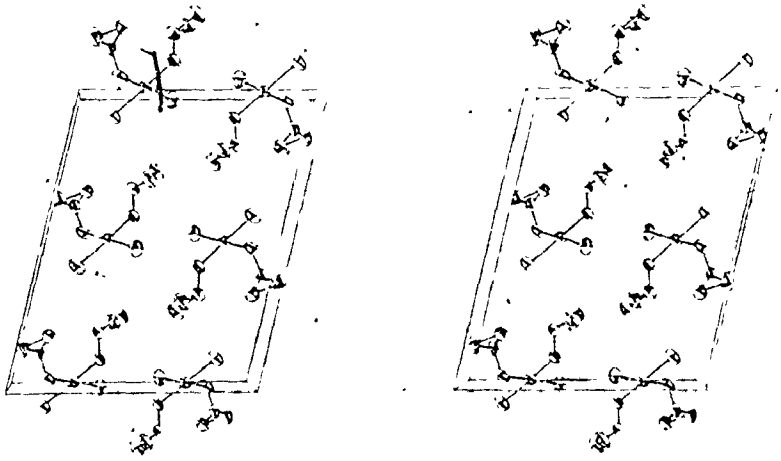


Figure 8

The unit cell contents of cis-$PtCl_2(C_3H_5NH_2)_2$. $\underset{\sim}{a}$ and $\underset{\sim}{c}$ are parallel to the bottom and side of the page, respectively. The view is down $\underset{\sim}{b}$.

4.1.3 Vibrational Spectroscopy:

The infrared and Raman spectra of cyclopropylamine, the d_2-deuterated analogue and the platinum complexes with the two ligands were recorded and examined.

The cyclopropylamine spectrum was essentially the same as that recorded by Kalasinsky et al.[134] with minor variations in wave number for some bands. These variations are not surprising, since the wave numbers used for his assignments were taken from spectra of either the solid or the vapour phase. His assignments can be seen in Table 15 along with the complete spectra and polarization ratios (from this work) of cyclopropylamine and its deuterated analogue. The data from this work support Kalasinsky's assignments with only a few disagreements. He assigns the strong infrared band centred at 830 cm^{-1} to a CH_2 rock. Upon deuteration, the intensity of this extremely broad band decreases and an equally strong, broad band is seen at 630 cm^{-1}. This suggests that the band at 826 cm^{-1} in the infrared contains components of both the CH_2 rock and an NH_2 rock. Kalasinsky assigns a band at 806 cm^{-1} to the NH_2 rock. This band is seen in the Raman spectrum of the liquid, and does not shift upon deuteration. It could be hidden under the very broad band at 833 cm^{-1} in the Raman spectrum of the deuterated ligand. The band at 940 cm^{-1} is seen by Kalasinsky only in the solid spectrum and assigned as an NH_2 wag. There

is a shoulder at ∿ 680 cm^{-1} on the very broad infrared peak centred at 630 cm^{-1} for the deuterated ligand. If this is assigned to the ND_2 wag and the ν_H/ν_D ratios are 1.31 for both the rock and the wag, then the NH_2 wag would have a wave number of 890 cm^{-1} and would be masked by the very broad (∿ 250 cm^{-1}) group centred at 826 cm^{-1}. Either assignment is possible.

The assignments and observed wave numbers for the complex and its deuterated analogue are shown in Table 16. The spectra in the ligand region are much less straightforward than those of the free ligand, firstly because there is now a pair of symmetric and asymmetric modes for each ligand vibration; secondly because some modes shift on complexing and some do not; and finally because there may be interactions between the vibrations of the crystallographically inequivalent cyclopropylamine groups.

The NH_2 stretching vibrations are shifted to lower energies (by about 100 cm^{-1}) in the complex as compared to the ligand as are the NH_2 deformations. Similar assignments have been made previously for $Pt(en)Cl_2$,[135] and various cis-$Pt(RNH_2)Cl_2$ complexes.[136]

The CH_2 stretching vibrations, deformations and bends are close to those observed for the ligand with positions typical for the strained three-membered ring system.[137]

The CH stretch in the free ligand was assigned to

Table 15. Vibrational spectra of $C_3H_5NH_2$ and $C_3H_5ND_2$ (cm^{-1})[a]

		$C_3H_5NH_2$			$C_3H_5ND_2$			
Assignment	Vibration[b]	Infrared	Raman	ρ[c]	Infrared	Raman	ρ	ν_H/ν_D
NH_2 asym. str.	3412 ν_{16}	3392(30)	3374(10)	dp	[2533(36)]	[2520(6)]	dp	1.34
NH_2 sym. str.	3348 ν_1	3320(11)	3327(26)	0.2	[2476(15)]	[2474(17)] [2408(16)]	0.16 0.13	1.34
CH_2 asym. str.	3100 ν_{17} 3100 ν_1	3091(51)	3077(26)	dp	3091(60)	3078(14)	0.17	
CH_2 sym. str.	3032 ν_3 3023 ν_{18}	3010(62)	3005(100)	0.15	3010(71)	3006(100)	dp	
CH str.	2975 ν_4	2966(62)	2965(23) 2901(6)	0.3 dp	2965(66)	2965(19) 2901(3)	0.1 dp	
NH_2 def.	1617 ν_5	1615(60)br			[1231(81)br]			1.31
CH_2 def.	1456 ν_6 1424 ν_{19}	1454(88) 1420(10)	1455(21) 1417(14)	0.3 dp	1455(92) 1419(25)	1455(11) 1421(6)	0.27 dp	
CH bend (in-plane)	1374 ν_7	1370(98)	1372(17)	0.22	1379(100)	1371(16)	0.1	
ring breathing (gauche)	1214 ν_8 1220	1209(46)	1214(75)	0.12	1210(sh)	1215(60)	0.14	
CH_2 twist	1168 ν_9	1169(2)	1172(3)	dp	1170(4)	1179(8)	dp	
C-N str.	1150 ν_{10}	1145(38)	1146(15)	0.11	[965(40)]	[969(50)]	0.1	1.19
CH_2 twist	1104 ν_{20}	1105(32)			1110(30)			

Table 15 (Continued)

Assignment	Vibration		Infrared	Raman	ρ[c]	Infrared	Raman	ρ	ν_H/ν_D
CH_2 sym. wag	1045	ν_{21}	1040(65)			1044(71)			
CH bend (out-of-plane)	1026	ν_{22}^d							
CH_2 asym. wag	1020	ν_{11}	1014(100)	1014(16)	0.2	1014(93)	1014(8)	0.2	
ring def. (gauche)	989	ν_{12}		989(54)	0.11		975(43)	0.1	
	971			968(17)	0.15		969(50)	0.1	
NH_2 wag	940	ν_{23}^d	890[e]			[680(sh)][e]			1.31
ring def.	884	ν_{24}	878(31)	881(16)	dp	[840(sh)]	[833(11)br]	dp	1.05
CH_2 asym. rock	830	ν_{25}	826(84)br	826(16)	dp	829(49)br	833(11)	dp	
NH_2 rock	805	ν_{13}	826(84)br	806(18)[f]	dp	[630(91)br]	833(11)	dp	1.31
CH_2 sym. rock	762	ν_{14}		759(25)	dp		753(11)	dp	
			704(14)[f]						
CN bend (in-plane)	408	ν_{15}	403(59)	411(9)	dp	[390(64)]	[390(6)]	dp	1.07
CN bend (out-of-plane)	396	ν_{26}							
NH_2 torsion	254	ν_{27}							

a Symbols: br, broad; sh, shoulder; relative intensities in brackets.
b Data from reference 134.
c ρ, polarization ratios; dp, depolarized.
d Observed for solid only in reference 134.
e Possible assignment; see discussion of spectra.
f Unassigned.

Table 16. Vibrational spectra of cis-$PtCl_2(C_3H_5NH_2)_2$ and cis-$PtCl_2(C_3H_5ND_2)_2$ (cm^{-1})

Assignment	cis-$PtCl_2(C_3H_5NH_2)_2$		cis-$PtCl_2(C_3H_5ND_2)_2$		ν_H/ν_D
	Infrared	Raman	Infrared	Raman	
NH_2 asym. str.	3266(65) 3242(67)	3245(8) 3208(26)	[2432(100)]	[2422(21)]	1.34
NH_2 sym. str.	3205(72) 3138(60)	3197(23) 3135(12)	[2350(89)]	[2367(21)] [2325(10)]	1.36 1.35
CH_2 asym. str.	3080(29)	3085(21) 3082(29)	3080(19)	3081(35)	
CH_2 sym. str.	3062(32)	3070(51) 3059(33)		3069(48) 3059(29)	
CH str.	3001(8)	2997(72)	3005(32)	3000(60)	
NH_2 def.	1592(100) 1560(65)	1590(17) 1587(13)	[1180(50)] [1150(91)]	[1179(w)] [1158(15)]	1.35 1.36
CH_2 sym. def.	1456(30)	1462(21) 1453(14)	1462(47)	1462(15) 1449(15)	
CH_2 asym. def.	1433(34) 1414(21)	1430(14)	1430(55) 1420(72)	1427(8)	
CH bend (in-plane)	1388(44) 1385(40)	1382(18) 1378(22)	1370(sh) 1362(81)	1379(12) 1360(18)	
NH_2 twist	1267(17) 1260(19)	1262(12)	[975(55)]	[982(27)] [975(15)]	1.29 1.29
CH_2 twist	1240(38)		1240(sh)		

Continued.....

Table 16 (Continued)

Assignment	cis-$PtCl_2(C_3H_5NH_2)_2$		cis-$PtCl_2(C_3H_5ND_2)_2$		ν_H/ν_D
	Infrared	Raman	Infrared	Raman	
ring breathing	1230(sh)	1232(16) 1222(27)	1220(81)	1220(68)	
C-N str.	1215(34) 1204(90)	1210(73) 1204(100)	[1010(87)] [1000(91)]	[1012(95)] [1008(100)]	1.20 1.20
CH_2 twist	1169(12)	1175(4) 1169(9)	hidden under 1180 band.		
NH_2 wag	1122(24) 1110(47)	1113(15)	[887(77)] [880(71)]	[895(13)] [885(6)]	1.26 1.26
CH_2 twist	1094(31)	1095(8) 1087(4)	1094(w)		
CH_2 wag	1068(19)		1069(49)	1070(6)	
CH bend (out-of-plane)	1050(19)	1050(8)	1050(47)		
CH_2 wag	1034(73) 1029(79)	1032(7) 1028(10)	1034(83)	1034(23)	
NH_2 wag	958(20)	960(26)	[785(34)]	[790(23)]	1.22
ring def.	933(41) 921(27)	934(58) 920(38)	[850(41)] [815(60)]	[857(15)]	1.10 1.13
CH_2 rock	829(69) 820(57)	829(12) 822(21) 816(14)	830(48) 820(62) 815(16)	815(7)	

Continued.....

Table 16 (Continued)

Assignment	cis-$PtCl_2(C_3H_5NH_2)_2$		cis-$PtCl_2(C_3H_5ND_2)_2$		ν_H/ν_D
	Infrared	Raman	Infrared	Raman	
NH_2 rock		762(23)			
	757(43)	758(37)	[618(49)]	[622(21)]	1.22
CH_2 rock	744(42)	744(18)	740(58)	745(42)	
NH_2 rock	724(40)	726(13)	[592(w)]	[590(w)]	1.22
Pt-N str.	595(7)	601(55)	[540(w)]	[555(35)]	1.08
		593(18)		[549(13)]	1.08
Pt-N-C def.	406(40)		[353(53)]		1.15
	396(sh)				
Pt-Cl str.	332(88)	333(74)		331(74)	
	321(95)	326(88)	325(94)	328(85)	
		317(14)			
Pt-Cl str.	296(37)	302(61)		299(57)	
		291(31)		285(29)	
Pt-N def.	225(19)	233(40)		[217(16)]	1.07
Pt-N def.		201(12)		[192(7)]	1.07
(out-of-plane)		196(12)			
		190(11)		[181(15)]	1.06
Pt-Cl def.		163(83)		163(76)	
		123(45)		123(38)	
		111(40)		115(40)	
		78(46)		78(60)	

Relative intensities are in brackets.
Symbols sh, shoulder; w, weak.

the infrared band at 2965 cm^{-1}. There is no band in the complex in this region, but it is possible that, because of additional strain on complexation, the vibration occurs at higher wave number and is lost under the CH_2 deformations. The CH bend (out-of-plane) for cyclopropylamine (solid phase spectra) was assigned as 1026 cm^{-1},[134] but was not observed in the solution spectra. For the complexes, it could be hidden under the 1030 cm^{-1} bands which are broad in the infrared spectra.

The middle wave number range of the spectra ($\sim$ 1300 cm^{-1}-700 cm^{-1}) contains many bands with overlaps, intensity variations and deuterium shifts in several ratios. Reasonable assignments have been made for the observed bands, but there will, of necessity, be ambiguities and some of the assignments must be considered tentative.

The NH_2 twisting vibration is assigned to the 1267,1260 cm^{-1} bands (982,975 cm^{-1} in d_2-complex). This vibration is unique to the complexes. The corresponding motion in the ligand is a hindered rotation which was observed[134] at low frequency (254 cm^{-1}) in the infrared spectrum. The NH_2 wags for the complexes are assigned to bands at 1122 cm^{-1} (887 cm^{-1}) and 958 cm^{-1} (785 cm^{-1}). The NH_2 rocks are assigned to bands at 757,724 cm^{-1} (618,593 cm^{-1}). The corresponding ligand bands occur at 940 or 890 cm^{-1} and 820 cm^{-1}. The deuterium shift ratios for these modes are

roughly 1.2, and are less than those for the stretching vibrations (1.34). This would be expected as a result of moderately strong coupling with the skeletal motions.

The CH_2 twists, wags and rocks are assigned to bands that do not shift upon deuteration in accordance with previous assignments for the three-membered ring systems.[137] The CH_2 twist at 1170 cm^{-1} is not observed in the d_2-complex, but it could be under the band assigned to the ND_2 deformation at 1180 cm^{-1} which is quite strong and broad with weak components at 1179, 1172 and 1167 cm^{-1}.

The ring breathing mode for the ligand is observed at $\sim$ 1210 cm^{-1} in agreement with Kalasinsky[134] who assigned the band at this wave number to the more stable trans configuration and a vapour phase Raman band at 1220 cm^{-1} to the gauche conformer. In the complex, the ligand takes on the gauche configuration (Figure 7) and, therefore, an intense pair of bands (1220 cm^{-1}) which shows no shift on deuteration, is assigned to the ring breathing mode. This band is intensified in the d_2-complex by the overtone of 618 cm^{-1}. The other ring deformation modes are considerably more difficult to assign. For the complex, there should be considerable coupling between ring modes, CN stretching and NH_2 group deformations. In addition, a number of the peaks are extremely broad and could contain more than one band.

The intense pair of bands at 1215,1204 cm^{-1} (1010, 1000 cm^{-1}) is assigned to the C-N stretch. The 1215 cm^{-1} region in the h_2 complex is complicated by Fermi resonance and the first overtone of the Pt-N stretch, as well as coupling with the NH_2 twisting vibration and particularly the ring breathing mode. The ligand band (1145 cm^{-1}, 965 cm^{-1}) assigned to the C-N stretch also had a deuteration shift ratio ν_H/ν_D of 1.2 making this assignment reasonable.

The platinum-nitrogen stretching motions are exclusive to the complex, and occur at the high end of the frequency range for such vibrations.[135,136] The bands at 601,593 cm^{-1} (555,549 cm^{-1}) are assigned to the symmetric and asymmetric vibrations on the basis of Raman intensities with a shift on deuteration (ν_H/ν_D = 1.08) which would indicate moderately weak coupling with an NH_2 vibration.

The platinum-chlorine stretching vibrations are observed at 333 cm^{-1} (symmetric) and 302 cm^{-1} (asymmetric) with no shift on deuteration. The predicted chlorine isotope effect is a splitting into three components of relative intensity 9:6:1. A splitting is observed for the totally symmetric vibration (333,326,317 cm^{-1}) with a frequency separation of the components as predicted. The middle component, however, has the highest intensity. This increase in intensity can be attributed to coincidence with the first overtone of the Pt-Cl deformation at 163 cm^{-1}.

A C-N-Pt deformation is assigned to the band at 406 cm^{-1} (353 cm^{-1}) and the Pt-N and Pt-Cl deformations are observed at their usual frequencies.

4.2 The Crystal and Molecular Structures of cis and trans-dichlorobis(cyclobutylamine-N)platinum(II)[127]

4.2.1 Preparations:

cis-$PtCl_2(C_4H_7NH_2)_2$

The procedure of Connors et al.[26] was used. Cyclobutylamine (0.187 g) was added to an aqueous solution of K_2PtCl_4 (0.529 g in H_2O) and left at room temperature overnight. The yellow powder that precipitated was filtered and washed with cold acetone. Roughly one-third of the solid was dissolved in dimethylformamide (20 mL) at room temperature and any undissolved solid was removed by filtration. HCl (0.1 N) was added dropwise until the solution was faintly cloudy. A few drops of dimethylformamide were added to remove the cloudiness and the solution was placed in the refrigerator overnight. Pale yellow crystals were collected.

trans-$PtCl_2(C_4H_7NH_2)_2$

The same procedure[26] was used as for the cis compound (cyclobutylamine, 0.2 g, K_2PtCl_4, 0.58 g, water, 20 mL). The solid was recrystallized by dissolving in boiling acetone (30 mL) and removing any residual solid by filtration after the solid had cooled to room temperature. At this point,

three to four drops of acetone were added to the filtrate which was placed in an Erlenmeyer flask and covered with aluminum foil. A few holes were punched in the top of the foil to allow slow evaporation of the acetone in a refrigerator (0°C, 7 to 28 days). Pale yellow crystals were collected.

4.2.2 Solution of the Structures

cis-$PtCl_2(C_4H_7NH_2)_2$

Solution of the Patterson did not give an unambiguous set of results. A value of $y = \pm\frac{1}{4}$ was found. Peaks were expected at $2x,2y,2z$ and at $2x,\frac{1}{2},\frac{1}{2}\pm 2z$. Two peaks were observed with approximate coordinates 0.6,0.5,0.0 and 0.6,0.5,0.5. This meant that the z coordinate of the platinum atom could be either 0.5(0.0) or 0.25(0.75).

An initial solution with platinum at 0.299,0.25,0.25 was tried. The refinement seemed to progress satisfactorily although the weakness of almost all the reflections h,k,ℓ, $\ell \neq 2n$ made phasing difficult. The square plane around platinum was distorted, but the positional errors were large and the distortion was, therefore, insignificant. On adding the atoms of the cyclobutyl groups to the refinement, it became apparent that the C-C and C-N bond lengths showed unacceptable differences from the expected values (C-C, C-N bond lengths varied from 1.23 Å to 1.85 Å) and the refinement was abandoned. The solution with $z = 0.5$ for the platinum atoms was chosen and led to the structure discussed in this chapter.

The difference between the two solutions can be seen in Figure 9. If the position $x,\frac{1}{4},z$ is considered for both cases, the diagrams of Figure 9 can be drawn for the space group $P2_1/c$. Let the molecule be right-handed (R) (left-handed = L). In the first case, we have R at $x,\frac{1}{4},\frac{1}{4}$. The two-fold screw axis parallel to $\underset{\sim}{b}$ generates R at $1-x,3/4,1/4$. The inversion at $0,\frac{1}{2},\frac{1}{2}$ then generates L at $x,\frac{1}{4},-\frac{1}{4}$ (from $1-x,3/4,1/4$) and L at $1-x,3/4,-1/4$ (from $x,\frac{1}{4},\frac{1}{4}$). Within a row in the $\underset{\sim}{c}$ direction, alternating left-handed and right-handed molecules will be seen. In the $\underset{\sim}{a}$ direction, alternating rows have either right-handed or left-handed molecules only.

A similar operation on R at $x,\frac{1}{4},\frac{1}{2}$ will generate L at $1-x,3/4,1/2$ by inversion through $0,\frac{1}{2},\frac{1}{2}$ and the screw axis acting on these two positions will generate R at $1-x,3/4,0$ and L at $x,\frac{1}{4},0$. Now there are rows of molecules of alternating handedness in both the $\underset{\sim}{a}$ and the $\underset{\sim}{c}$ directions.

The fact that the wrong solution almost gave a satisfactory refinement can now be explained. The main effect of changing the atomic parameters by one-quarter in z is to change the handedness of the molecules with respect to each other. The effect this has on the square plane is minimal and becomes significant only when the rings are considered. For this reason, the refinement with the wrong solution progressed in a satisfactory manner until the carbon positions were added.

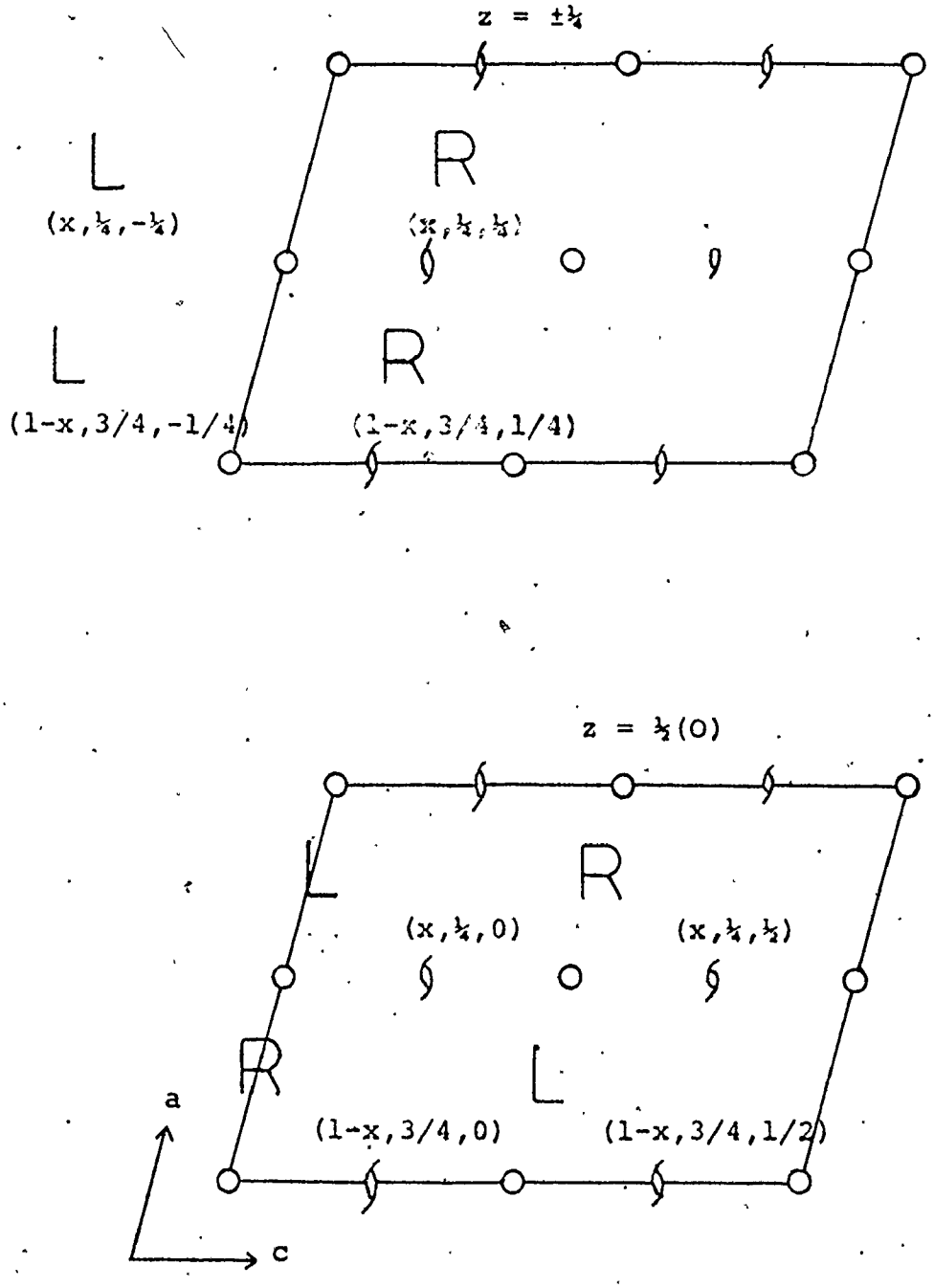


Figure 9

Two possible platinum positions in the space group $P2_1/c$ [139] for cis-$PtCl_2(C_4H_7NH_2)_2$

trans-$PtCl_2(C_4H_7NH_2)_2$

Solution of this structure followed the method outlined in Section 2.2, except that attempts were made to find the hydrogen atoms. A difference map showed a number of peaks with intensity about 1 $e^-/\mathring{A}^3$. Some were in geometrically acceptable positions, but others were not. In addition, it was not possible to find hydrogen atoms in all the expected positions. Ultimately, only the two hydrogen atoms which were attached to the nitrogen atom and could be involved in hydrogen bonding were included in the refinement. Only their positional parameters were refined; the temperature factors were fixed at approximately 50% greater than that of the nitrogen atom.

4.2.3 X-ray Studies:

Crystal data and other numbers pertaining to solution of the structures are presented in Table 17. The positional and thermal parameters are given in Table 18A for the cis complex and Table 18B for its trans analogue. Selected interatomic distances and angles are compared in Table 19 and the least squares plane, torsional and dihedral angles are given in Table 20.

Cis-dichlorobis(cyclobutylamine-N)platinum(II) is shown in Figure 11A and the corresponding trans compound in Figure 11B. In both cases, the ligands form a square plane about platinum with little or no distortion. Pt-N

Table 17

Compound	cis-$PtCl_2(C_4H_7NH_2)_2$	trans-$PtCl_2(C_4H_7NH_2)_2$
Formula weight	408.24	408.24
Crystal size	see Figure 10	plate $100, \bar{1}00$ 0.028 mm apart $1\bar{1}1, \bar{1}1\bar{1}$ 0.08 mm apart $011, 0\bar{1}\bar{1}$ 0.08 mm apart
Systematic absences	OkO $k \neq 2n$ hOl $l \neq 2n$	OkO $k \neq 2n$ hOl $l \neq 2n$
space group	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)
Unit cell parameters (Å and deg)	a = 5.975(2) b = 20.459(8) c = 11.512(2) β = 116.18(2)	a = 7.760(2) b = 9.319(3) c = 8.621(2) β = 97.61(2)
Volume (Å^3)	1262.9(7)	617.9(3)
Z	4	2
$\rho_{calc.}$ (gcm^{-3})	2.15	2.19
$\rho_{obs.}$ (gcm^{-3})	2.16(1)	2.17(2)
linear absorption coeff. (cm^{-1})	113	123
absorption coeff. limits	1.2996-1.4259	1.3889-2.7296
standard reflections, e.s.d.(%)	-1 -1 0, 3.4 1 -1 -2, 5.6 0 2 2, 4.5	1 0 4, 1.7 0 1 1, 1.8 0 3 -1, 1.7

Continued.....

Table 17 (Continued)

No. of independent reflections*	1852	1383
$I > 3\sigma(I)$	743	803
$3\sigma(I) > I > \sigma(I)$ $(F_o < F_c)$	84	38
$(F_o > F_c)$	281	105
$I < \sigma(I)$	744	437
Final R_1, obs. (all)	0.0457 (0.0515)	0.0269 (0.0281)
Final R_2, obs. (all)	0.0614 (0.0635)	0.0328 (0.0333)
Final shift in e.s.d. Max.	3.66×10^{-3}	5.75×10^{-1}
Ave.	1.88×10^{-4}	6.93×10^{-2}
g, extinction coefficient	1.52×10^{-8}	-4.52×10^{-9}
Final difference map:		
Highest peak, location	$1.9e^-/\AA^3$; 0.13,0.25,0 $1.9e^-/\AA^3$; 0.48,0.25,0	$0.8e^-/A^3$; 0.025,0.113,-0.05
Lowest valley, location	$-1.1e^-/\AA^3$; 0.36,0.25,0	$-0.9e^-/A^3$; 0.1,-0.005,-0.05
Weighting scheme**	$[\sigma^2 + (0.03\ F_o)^2]^{-1}$	$[\sigma^2 + (0.025\ F_o)^2]^{-1}$
Error in an observation of unit weight	1.347	0.909
Analysis, calc., obs. (%)	N 6.9, 6.7 C 23.5, 24.3 H 4.4, 4.8	N 6.9, 7.4 C 23.5, 23.7 N 4.4, 4.6

* Most of the unobserved reflections occurred above $2\theta = 35°$ for the trans compound. For the cis compound, most of the unobserved reflections occurred for $\ell = 2n + 1$.

** The values 0.03 and 0.025 were chosen to make $\langle\omega(|F_o| - |F_c|)^2\rangle$ locally independent of F_o and $\sin\theta/\lambda$.

Table 18A. Positional and thermal parameters $(\text{Å})^2$ for cis-$PtCl_2(C_4H_7NH_2)_2$ ($\times 10^3$)

Atom	x	y	z	U_{iso}
Pt	299.3(2)	249.3(1)	501.9(1)	
Cl(1)	105(2)	318.9(5)	325.8(8)	
Cl(2)	547(2)	208.0(5)	411.1(8)	
N(1)	84(5)	280(1)	590(3)	61(7)
N(2)	472(4)	187(1)	657(2)	49(6)
C(1)	- 23(7)	345(2)	567(4)	87(12)
C(2)	143(8)	404(2)	609(4)	88(12)
C(3)	- 49(8)	439(2)	654(4)	100(14)
C(4)	-138(8)	369(2)	660(4)	96(13)
C(5)	444(8)	120(2)	624(4)	95(13)
C(6)	506(10)	65(3)	718(5)	124(17)
C(7)	315(9)	17(3)	616(5)	130(18)
C(8)	214(10)	85(3)	551(5)	128(18)

Anisotropic temperature factors U_{ij} $(\text{Å})^2$ ($\times 10^3$)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	60.1(7)	69.7(8)	38.0(5)	- 2(2)	22.9(4)	- 2(1)
Cl(1)	88(7)	89(7)	50(5)	14(6)	33(5)	12(5)
Cl(2)	75(6)	105(7)	49(5)	- 3(5)	36(4)	-10(5)

Table 18B. Positional and thermal parameters ($Å^2$) for trans-$[PtCl_2(C_4H_7NH_2)_2]$

($\times 10^3$)

Atom	x	y	z	U_{iso}
Pt	0.0	0.0	0.0	
Cl	44.8(4)	243.8(3)	5.8(4)	
N	- 86(1)	6(2)	214.3(9)	
C(1)	-279(1)	1(2)	204(1)	
C(2)	-366(2)	15(2)	356(1)	
C(3)	-508(2)	105(2)	264(2)	
C(4)	-374(2)	144(2)	149(2)	
H(1)	- 45(27)	- 60(20)	273(26)	60
H(2)	- 50(28)	101(21)	251(27)	60

Anisotropic temperature factors U_{ij} ($Å^2$) ($\times 10^3$)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	34.5(3)	25.9(2)	21.9(2)	0.2(6)	7.4(1)	- 0.6(8)
Cl	72(2)	30(1)	37(1)	- 5(1)	15(2)	- 2(1)
N	47(5)	34(4)	26(3)	22(8)	8(3)	6(8)
C(1)	40(4)	48(5)	40(5)	- 4(11)	17(4)	16(12)
C(2)	53(6)	41(9)	51(5)	9(7)	27(4)	12(7)
C(3)	44(7)	69(9)	74(10)	11(6)	18(6)	- 6(7)
C(4)	52(7)	78(10)	53(8)	11(7)	15(6)	20(7)

Table 19. Interatomic distances (Å) and angles (deg) for cis- and trans-

$PtCl_2(C_4H_7NH_2)_2$

Distances

Atoms	cis	trans	Atoms	cis	trans	Atoms	cis
Pt-Cl(1)	2.326(9)	2.298(3)	N(1)-C(1)	1.45(5)	1.49(1)	N(2)-C(5)	1.41(5)
Pt-Cl(2)	2.32(1)		C(1)-C(2)	1.51(6)	1.56(2)	C(5)-C(6)	1.48(7)
Pt-N(1)	2.06(3)	2.047(8)	C(2)-C(3)	1.61(8)	1.52(2)	C(6)-C(7)	1.57(7)
Pt-N(2)	2.06(2)		C(3)-C(4)	1.54(6)	1.57(2)	C(7)-C(8)	1.56(7)
N-H(1)		0.8(2)	C(4)-C(1)	1.58(7)	1.57(3)	C(8)-C(5)	1.44(7)
N-H(2)		1.0(2)					

Hydrogen bond distances

cis		trans			
Cl(1)...N(2)[a]	3.41(2)	Cl...H(1)[d]	2.6(2)	Cl...N[b]	3.48(1)
Cl(1)...N(1)[b]	3.34(3)	Cl...H(2)[b]	2.7(2)	Cl...N[d]	3.42(1)
Cl(2)...N(1)[c]	3.30(3)				

a-d Atoms are related to those in Tables 18A and 18B by:

a $x-1, \frac{1}{2}-y, z-\frac{1}{2}$

b $x, \frac{1}{2}-y, z-\frac{1}{2}$

c $1+x, y, z$

d $-x, \frac{1}{2}+y, \frac{1}{2}-z$

Continued.....

Table 19 (Continued)

Atoms	cis	trans	Atoms	cis	trans	Atoms	cis
Cl(1)-Pt-Cl(2)	90.2(4)	180.0	Pt-N(1)-C(1)	121(3)	113.0(6)	Pt-N(2)-C(5)	115(2)
Cl(1)-Pt-N(1)	93.5(8)	91.2(5)	N(1)-C(1)-C(2)	120(3)	119.4(8)	N(2)-C(5)-C(6)	125(4)
Cl(1)-Pt-N(2)	179.3(8)	88.8(5)	N(1)-C(1)-C(4)	116(4)	115(1)	N(2)-C(5)-C(8)	127(4)
Cl(2)-Pt-N(1)	176.1(8)	88.8(5)	C(1)-C(2)-C(3)	89(4)	89(1)	C(5)-C(6)-C(7)	93(4)
Cl(2)-Pt-N(2)	89.3(9)	91.2(5)	C(2)-C(3)-C(4)	86(3)	88(1)	C(6)-C(7)-C(8)	79(4)
N(1)-Pt-N(2)	87(1)	180.0	C(3)-C(4)-C(1)	89(4)	86(1)	C(7)-C(8)-C(5)	95(4)
Pt-N-H(1)		113(17)	C(4)-C(1)-C(2)	88(3)	87(1)	C(8)-C(5)-C(6)	86(4)
Pt-N-H(2)		102(15)	C(1)-N-H(1)		108(15)		
H(1)-N-H(2)		114(18)	C(1)-N-H(2)		107(14)		

Table 20. Least squares plane, torsional and dihedral angles in cis- and trans-$PtCl_2(C_4H_7NH_2)_2$

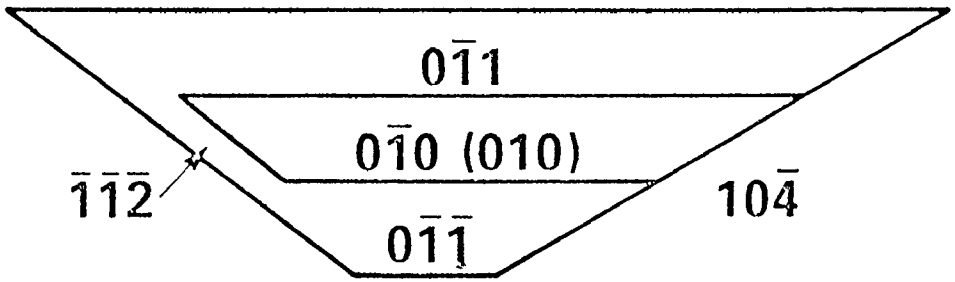
Plane [cis-$PtCl_2(C_4H_7NH_2)_2$]	Distance from Plane (Å)
Pt*Cl(1)Cl(2)N(1)N(2)	Pt, 0.02; Cl(1), 0.01; Cl(2), -0.01; N(1), -0.01; N(2), 0.01

Torsional Angles (deg)	cis	trans		cis
PtN(1)C(1)C(2)	64	-176	PtN(2)C(5)C(6)	-167
PtN(1)C(1)C(4)	-168	- 75	PtN(2)C(5)C(8)	53
N(1)C(1)C(2)C(3)	141	141	N(2)C(5)C(6)C(7)	-154
C(1)C(2)C(3)C(4)	- 22	- 24	C(5)C(6)C(7)C(8)	19
C(2)C(3)C(4)C(1)	20	24	C(6)C(7)C(8)C(5)	- 20
C(3)C(4)C(1)C(2)	- 22	- 24	C(7)C(8)C(5)C(6)	21
C(4)C(1)C(2)C(3)	21	24	C(8)C(5)C(6)C(7)	- 21
N(1)C(1)C(4)C(3)	-145	-145	N(2)C(5)C(8)C(7)	152

Dihedral angles (deg)

cis-$PtCl_2(C_4H_7NH_2)_2$

PtN(1)N(2)-PtN(1)Cl(1)	.3
PtN(1)N(2)-PtN(2)Cl(2)	1.5



0.05 mm.

Distance between 010 and 0$\bar{1}$0 faces = 0.03 mm.

Figure 10

The crystal shape of cis-$PtCl_2(C_4H_7NH_2)_2$

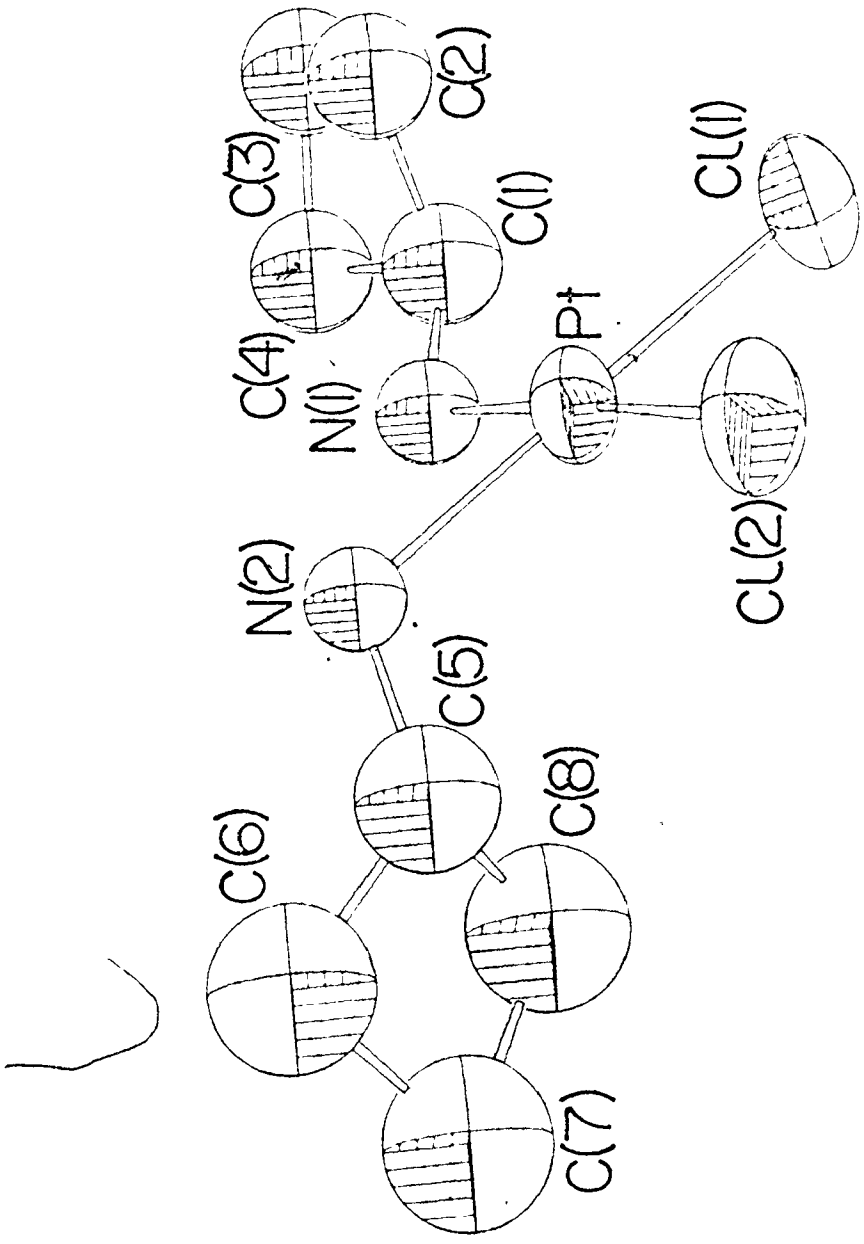


Figure 11A

The molecule cis-$PtCl_2(C_4H_7NH_2)_2$

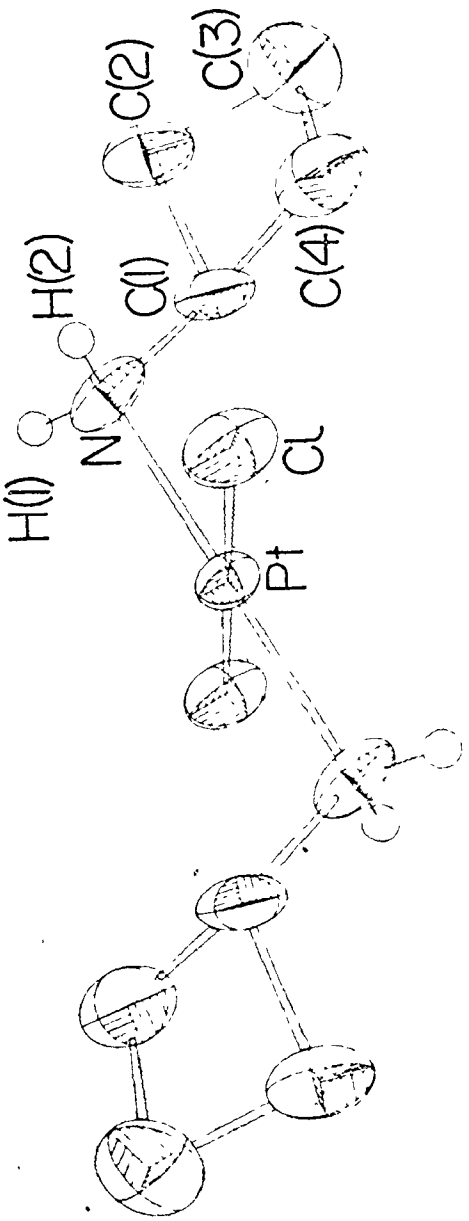


Figure 11B

The molecule trans-$PtCl_2(C_4H_7NH_2)_2$

distances are very similar for the two compounds, as are Pt-Cl distances, and both sets lie well within the range of distances observed previously.[75,104,105,125,128-132] The N-C distances are also insignificantly different and normal for an N-C single bond.[138] Distances and angles within the cyclobutylamine ring agree well with published values.[140] The dihedral angles between the C(1)C(2)C(4), [C(5)C(6)C(8)] and C(2)C(3)C(4), [C(6)C(7)C(8)] planes in the cyclobutylamine rings are 150° [153°] for the cis and 145° for the trans complex. The values for the cis compound do not lie far from the average for cyclobutane structures (157°),[140] but the angle for the trans compound is slightly lower than the bottom of the range (149(2)° - 168.1(2)°). Values from previous structures are evenly distributed within the range suggesting relatively easy folding of the ring and it is assumed that the angles observed here are determined primarily by packing forces.

The packing of the cis and trans molecules is shown in Figure 12A and 12B, respectively. In the cis complex, the molecules lie in chains along the $\underset{\sim}{c}$ direction roughly at $y = \frac{1}{4}$. The glide plane causes the square planes of adjacent molecules to be twisted about 90° with respect to each other. This arrangement maximizes both dipole-dipole interactions between the molecules and hydrogen bonding between $Cl(1)\ldots N(1)^{a}$ and $Cl(1)\ldots N(1)^{b}$. Packing in the $\underset{\sim}{a}$ direction is determined

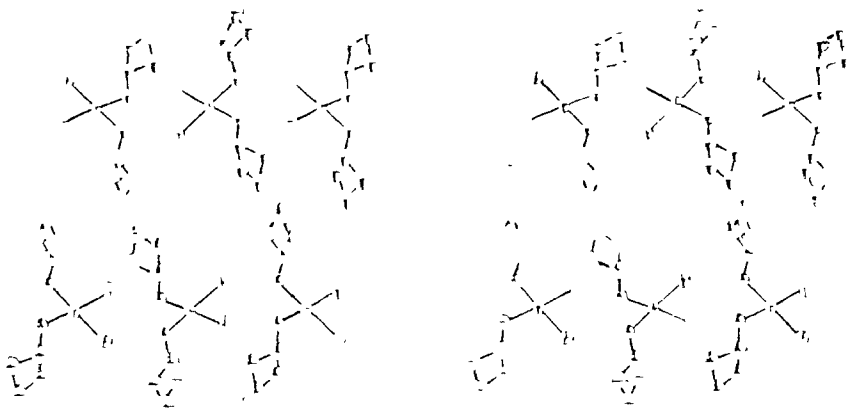


Figure 12A

The unit cell contents of cis-$PtCl_2(C_4H_7NH_2)_2$. $\underset{\sim}{c}$ and $\underset{\sim}{b}$ are parallel to the top and side of the page, respectively. The view is down $\underset{\sim}{a}^*$.

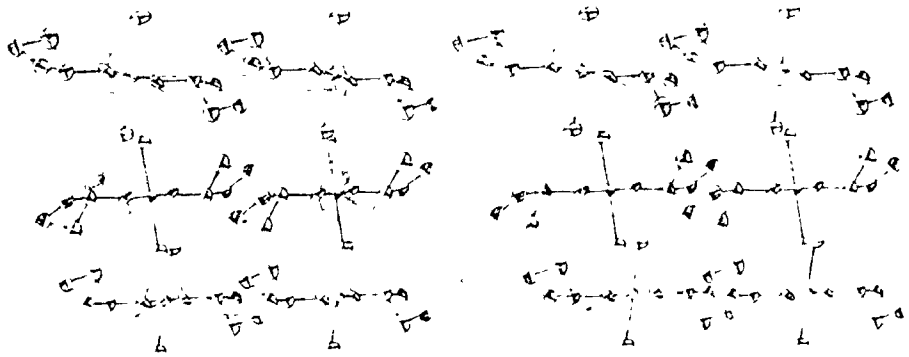


Figure 12B

The unit cell contents of trans-$PtCl_2(C_4H_7NH_2)_2$. $\underset{\sim}{a}$ and $\underset{\sim}{b}$ are parallel to the top and side of the page, respectively. The view is down $\underset{\sim}{c}^*$.

primarily by hydrocarbon ring contacts and hydrogen bonds, Cl(2)...N(1)^{c} (Table 21).

Molecules in the trans compound lie with the ligand atom plane almost in the $\underset{\sim}{bc}$ plane with the Pt-Cl axis roughly along $\underset{\sim}{b}$ and the Pt-N axis roughly along $\underset{\sim}{c}$. Hydrogen bonding (Cl...H(1)^{d}, Cl...H(2)^{b}) (Table 21) gives a two-dimensional network. Contact in the $\underset{\sim}{a}$ direction is between the hydrocarbon rings.

4.2.4 Vibrational Spectroscopy:

Tobe has suggested[141] that the standard spectroscopic technique for distinguishing cis and trans diamine complexes of platinum (the number of bands in the infrared and Raman spectra should differ for the two isomers) does not give unambiguous results. Confirmation of this suggestion can be obtained from the spectra of cis and trans-$PtCl_2(C_4H_7NH_2)_2$.

Vibrational spectra of both isomers were recorded and are presented in Table 21. They are sufficiently different to allow identification of the two compounds, but, because of coincidences of bands in the Pt-Cl stretch region, they would not allow one a priori to distinguish between the two compounds. The Pt-Cl stretches, both symmetric and asymmetric, would be expected to cause absorption in the 300-400 cm^{-1} region of the spectrum. Both modes should be active in the infrared and Raman spectra for the cis complex, while for the trans complex, only the asymmetric mode should be active

Table 21. Vibrational frequencies for cis- and trans-$PtCl_2(C_4H_7NH_2)_2$

cis-$PtCl_2(C_4H_7NH_2)_2$				trans-$PtCl_2(C_4H_7NH_2)_2$			
Infrared		Raman		Infrared		Raman	
Wavenumber (cm^{-1})	I	Wavenumber (cm^{-1})	I	Wavenumber (cm^{-1})	I	Wavenumber (cm^{-1})	I
				3260	vs		
~ 3200 br.	vs	3213	1.6	3222	vs		
3130	sh	3197	1.8	3145	vs		
2994	sh	2994	sh	2994	sh		
2981	vs	2976	3.6	2985	vs		
		2968	sh				
2951	vs	2962	3.3	2945	vs		
2938	sh	2942	3.3				
2899	m	2910	3.9	2900	sh		
2874	s			2878	s		
1662	w	1603	0.6				
1586	s	1582	0.9	1591 br.	s		
1562 br.	vs						
1468	m	1461	0.6	1462	w		
1447	m			1450	m		
1440	m	1442	2.5	1438	m		
1415	sh	1407	0.8				
1396	s			1395	s		

Continued.....

Table 21 (Continued)

Wavenumber (cm^{-1})	I	Wavenumber (cm^{-1})	I	Wavenumber (cm^{-1})	I	Wavenumber (cm^{-1})	I
1318	w	1309	0.9	1296	m	1290*	1.5
1286	m	1280	4.1	1273	w	1271	1.7
1245	s			1241	s		
1235	s	1231	2.0	1229	sh		
1222	sh	1222	2.5	1219	s	1210	1.8
1190	w	1195	0.7				
		1186	0.7	1188	m		
1162	m			1153	s		
1114	sh	1120	0.6				
1104	s	1109	0.6	1110	s		
		1098	0.9				
		1085	3.7				
		1077	sh				
1028	w	1020	1.2	1020	w		
				966	m		
956	sh	951	6.0	956	m	951	5.2
946	s	940	2.8			938	2.0
897 br.	m	904	5.5	900	m	901	3.9
790	sh			797	w		
776	m			775	w		
747	w			750	w		
728	m						

Continued.....

Table 21 (Continued)

Wavenumber (cm^{-1})	I	Wavenumber (cm^{-1})	I	Wavenumber (cm^{-1})	I	Wavenumber (cm^{-1})	I
637	m	634	1.7			631	1.8
627	w	623	1.2	622	m		
588	sh	590	3.4				
577	m	577	0.9	580	m	578	3.2
416	m	412	1.3	432	m		
311 br.	s	312	10.0	333 br.	m	329	10.0
		277	sh				
274 br.	w	270	3.4	288 br.	m	289	2.2
		232	1.3			226	1.8
		210	1.1				
		183	2.9			169	1.8
		128	1.8			130	1.1
		113	1.4			115	4.1
		97	0.9				
		75	1.2			79	4.6

* The Raman spectrum could not be obtained more than 1300 cm^{-1} from the exciting line because of an increasingly intense fluorescence background.

Symbols: v, very; s, strong; m, medium; w, weak; sh, shoulder; br., broad.

in the infrared and the symmetric mode in the Raman. Only one band is observed in both the infrared and the Raman for both compounds. The wave numbers of the bands in the infrared and Raman are almost the same, although the trans bands are ~ 20 cm^{-1} above those of the cis. Although the symmetric and asymmetric Pt-Cl stretches in PtL_2Cl_2 usually are well resolved, they may be as little as 8 cm^{-1} apart,[142] and on a geometric basis should have the same wave number.[143] Also, the resolution of the bands for the cis complex is not good. The width at half height for the infrared band is 30 cm^{-1} and for the Raman band is 13 cm^{-1}. Assuming a separation of the symmetric and asymmetric modes of 5-10 cm^{-1}, it is possible that no resolution of bands has taken place. Thus, although band position allows identification of the compounds, counting numbers of bands does not, in this case, allow differentiation.

4.3 The Crystal and Molecular Structure of trans-dibromobis-(cyclohexylamine-N)platinum(II)[128]

4.3.1 Preparation:

In a modification of Dhara's method,[126] cyclohexylamine (0.49 g) was added dropwise to the solution obtained from the reaction of K_2PtCl_4 (0.97 g) and KI (1.6 g) in water (10 mL). The yellow precipitate, $PtI_2(C_6H_{11}NH_2)_2$, was filtered and dried. Roughly half of the powder (0.66 g) was stirred with aqueous silver nitrate (0.34 g, 50 mL) in the dark for a week. AgI was removed by filtration and KBr solution (0.14 g, 20 mL)

was added dropwise to the filtrate. The pale yellow powder which precipitated was separated by filtration and dissolved in acetone. Slow evaporation of the solvent yielded the crystals used in this study.

4.3.2 X-ray Studies:

Crystal data and other numbers pertinent to solution of the structure are given in Table 22. The positional and thermal parameters are presented in Table 23. Selected interatomic distances and angles are given in Table 24 and the torsional and dihedral angles in Table 25.

The molecule is shown in Figure 13 and is very similar to that observed for the corresponding chloro-complex.[129] The bonded ligand atoms form a square plane around platinum with no distortion. The Pt-Br distance (2.388(2) Å) is normal[144] and 0.086 Å longer than the corresponding Pt-Cl distance, whereas the radii (both ionic and covalent) of bromine and chlorine differ by about 0.16 Å.[145] This implies that the Pt-Br bond is stronger than the Pt-Cl bond, which is consistent with the B-metal behaviour of platinum. The Pt-N distance (2.06(1) Å) does not differ significantly from that found in the chloro-complex (2.078(5) Å). Distances and angles within the hydrocarbon rings do not differ for the two complexes.

Despite the broad similarities in the two compounds, there are distinct differences in certain of the intramolecular

Table 22

Compound	trans-$PtBr_2(C_6H_{11}NH_2)_2$
Formula weight	553.26
Crystal size	cylinder of radius 0.07 mm length 0.25 mm
systematic absences	OkO k ≠ 2n hOℓ ℓ ≠ 2n
space group	$P2_1/c$ (No. 14)
unit cell parameters (Å and deg.)	a = 6.154(2) b = 8.823(3) c = 15.111(3) β = 96.79(2)
volume ($Å^3$)	814.7(3)
Z	2
$\rho_{calc.}$ (gcm^{-3})	2.26
$\rho_{obs.}$ (gcm^{-3})	2.25(2)
linear absorption coefficient (cm^{-1})	141.5
absorption coefficient limits	4.996→5.563
standard reflections, e.s.d. (%)	106, 1.7 142, 1.7

Continued.....

Table 22 (Continued)

No. of independent reflections	1885
$I > 3\sigma(I)$	1306
$3\sigma(I) > I > \sigma(I)$ $(F_o < F_c)$	42
$(F_o > F_c)$	149
$I < \sigma(I)$	388
Final R_1, obs. (all)	0.0505 (0.0516)
Final R_2, obs. (all)	0.0822 (0.0828)
Final shift in e.s.d., Max.	1.25×10^{-3}
Ave.	1.64×10^{-4}
g, extinction coefficient.	5.548×10^{-8}
Final difference map:	
Highest peak, location	$1.7e^-/\AA^3$; 0.01, 0.01, 0.03
Lowest valley, location	$-2.4e^-/\AA^3$; 0.36, 0.38, 0.57
Weighting scheme	$[\sigma^2 + (0.03\ F_o)^2]^{-1}$
Error in an observation of unit wt.	2.091
Analysis, calc., obs. (%)	C 26.1, 26.3 H 4.7, 4.7 N 5.1, 5.0

Table 23. Atom parameters for trans-$PtBr_2(C_6H_{11}NH_2)_2$ (x 10^3)

Atom	x	y	z
Pt	0	500	500
Br	292.6(4)	347.4(2)	569.2(2)
N	192(2)	691(1)	511.0(8)
C(1)	255(2)	752(2)	602(1)
C(2)	058(2)	794(2)	648(1)
C(3)	125(3)	856(2)	740(1)
C(4)	273(3)	993(2)	738(1)
C(5)	471(3)	958(3)	689(2)
C(6)	404(3)	891(2)	598(1)

Anisotropic temperature factors U_{ij} ($Å^2$) (x 10^3)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	36.7(4)	35.5(4)	33.4(4)	- 2.3(4)	8.8(3)	- 3.6(4)
Br	66(1)	71(1)	75(1)	7(1)	8.0(9)	2(1)
N	45(7)	40(7)	34(6)	- 7(5)	11(5)	- 7(5)
C(1)	40(8)	32(7)	46(8)	- 1(6)	12(6)	- 4(6)
C(2)	38(8)	73(11)	49(9)	-15(8)	16(7)	-17(9)
C(3)	59(10)	75(12)	45(9)	-18(10)	24(8)	-14(9)
C(4)	57(10)	55(10)	66(11)	2(9)	13(8)	-25(9)
C(5)	53(11)	81(14)	106(18)	-15(10)	17(12)	-44(13)
C(6)	45(8)	52(9)	60(10)	-16(7)	17(8)	-17(8)

Table 24. Interatomic distances (Å) and angles (deg) for trans-$PtBr_2(C_6H_{11}NH_2)_2$

Atoms	Distance	Atoms	Angle
Pt-Br	2.388(2)	Br-Pt-N	88.3(3)
Pt-N	2.06(1)	Pt-N-C(1)	117.3(9)
N-C(1)	1.49(2)	N-C(1)-C(2)	112(1)
C(1)-C(2)	1.51(2)	N-C(1)-C(6)	110(1)
C(2)-C(3)	1.51(2)	C(1)-C(2)-C(3)	111(1)
C(3)-C(4)	1.52(3)	C(2)-C(3)-C(4)	112(1)
C(4)-C(5)	1.53(3)	C(3)-C(4)-C(5)	111(2)
C(5)-C(6)	1.51(3)	C(4)-C(5)-C(6)	112(2)
C(6)-C(1)	1.53(2)	C(5)-C(6)-C(1)	112(2)
Br...N*	3.54(1)[a]	C(6)-C(1)-C(2)	110(1)

[a] N* is related to N in Table 23 by the inversion centre at ½,½,½.

Table 25. Torsional and dihedral angles (deg) in trans-$PtBr_2(C_6H_{11}NH_2)_2$

Torsional Angles

Group	Angle	Group	Angle
BrPtNC(1)	69.3	C(1)C(2)C(3)C(4)	60.2
PtNC(1)C(2)	-59.3	C(2)C(3)C(4)C(5)	-63.2
PtNC(1)C(6)	-178.2	C(3)C(4)C(5)C(6)	72.3
NC(1)C(2)C(3)	-173.0	C(4)C(5)C(6)C(1)	-53.5
NC(1)C(6)C(5)	179.5	C(5)C(6)C(1)C(2)	55.5
		C(6)C(1)C(2)C(3)	-64.2

Dihedral Angles

Planes	Angle
C(1)C(2)C(3)-C(4)C(5)C(6)	10.5
C(2)C(3)C(4)-C(5)C(6)C(1)	1.0
C(2)C(1)C(6)-C(3)C(4)C(5)	18.3
PtNC(1)-C(2)C(1)C(6)	56.6

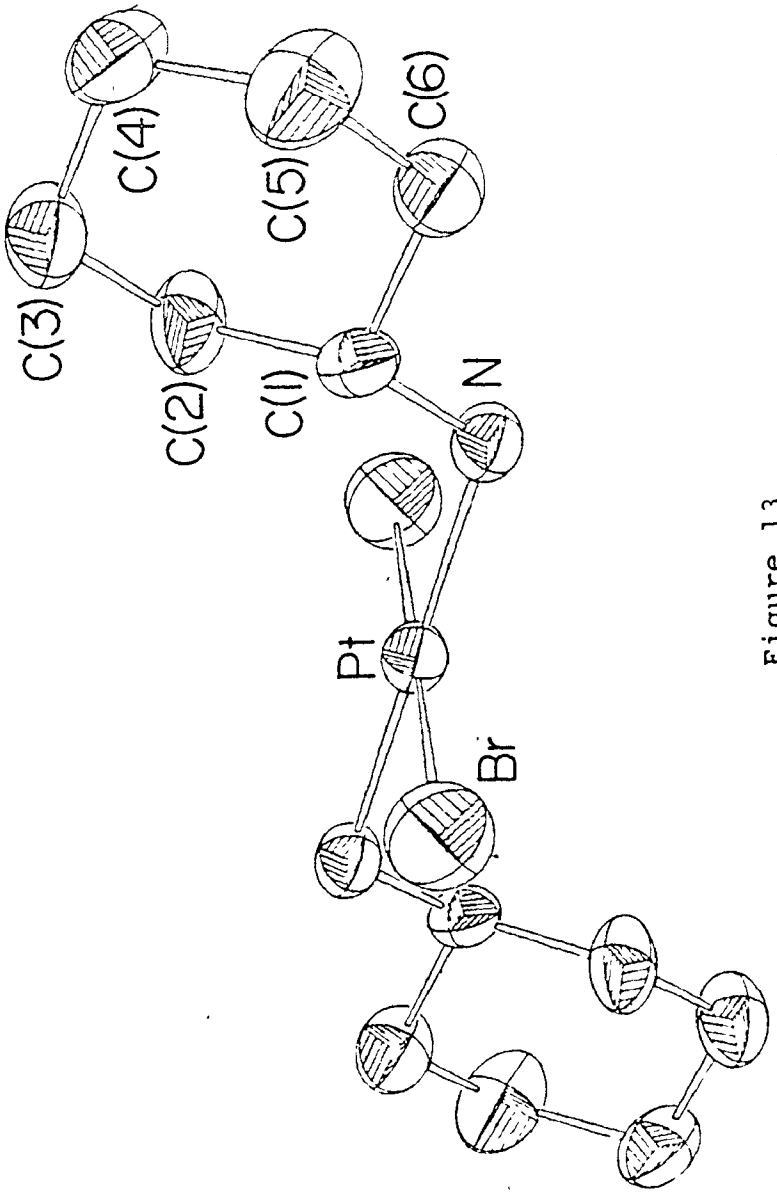


Figure 13

The molecule trans-$PtBr_2(C_6H_{11}NH_2)_2$

non-bonding distances and in torsional angles. This leads to different packing within the cell and even to a different space group. Thus, in the chloro-complex,[129] the torsional angle ClPtNC(1) is only 10.0°, which means that the C(1) atom is only slightly out of the ligand square plane and close to the Cl atom, while the torsional angle PtNC(1)C(2) of 66.5° means that C(2) lies roughly above C(1) (referred to the ligand square plane as base) and still close to the same chlorine atom. In the bromo-complex, the BrPtNC(1) angle is 69.3°, which means that C(1) is much more above the ligand plane and the C(1)-X distance is greater (3.63 Å vs. 3.30 Å). The PtNC(1)C(2) angle of 59.3° means that C(2) is now rotated away from the bromine atom. The two close contacts of C(1) and C(2) with the same chlorine atom were used to explain the inequality of the Cl-Pt-N angles (85.4°, 94.6°). The explanation is clearly reasonable since the Br-Pt-N angles (88.3°, 91.7°) are more nearly equal. The torsional angles in the ring (107.7° - 126.5°, ave. 118.5°) are generally smaller than in the chloro-complex (122.0° - 125.6°) giving a more compact ring and thus shorter C(1)-C(4) (2.92 - 2.95, ave. 2.93 Å vs. 2.94 - 2.97, ave. 2.95 Å) and C(1)-C(3) (2.49 - 2.52, ave. 2.51 Å vs. 2.51 - 2.57, ave. 2.53 Å) distances.

The crystal packing for the two compounds is clearly different as can be seen by comparing shortest Pt-Pt distances.

For the bromo-complex, these are 8.823 Å ($\underset{\sim}{b}$ translation), 6.154 Å ($\underset{\sim}{a}$ translation) and 8.75 Å ($\underset{\sim}{c}$ glide); for the chloro-complex, they are 4.95 Å ($\frac{1}{2}\underset{\sim}{b}$ translation), 6.673 Å ($\underset{\sim}{c}$ translation) and 13.50 Å ($\frac{1}{2}\underset{\sim}{a} + \frac{1}{2}\underset{\sim}{b}$ translation). The principal difference can be seen by considering the platinum atoms in the $\underset{\sim\sim}{bc}$ plane for the bromo-complex and in the (101) plane for the chloro-complex (Figure 14). The eclipsed arrangement along $\underset{\sim}{b}$ for the chloro-complex gives a somewhat longer $\underset{\sim}{b}$ axis than the staggered arrangement in the bromo-complex, whereas the n glide distance is shorter than the $\underset{\sim}{c}$ axis. The packing efficiency in the two space groups is very similar. The difference in molecular volume of 14.4 $Å^3$ is comparable to differences in volume of two chlorine and two bromine ions, ranging from 7.3 to 19.1 $Å^3$ calculated from such diverse structures as KX, NaX, $Pt(NH_3)_4 \cdot PtX_4$, K_2PtX_4 and K_2PtX_6 (X = Cl,Br).

The packing is illustrated in Figure 15. The molecules form chains along the $\underset{\sim}{a}$ direction at y = 0, z = 0 and y = ½, z = ½ with weak hydrogen bonds between N and Br of adjacent molecules (N...Br, 3.54 Å c.f. 3.47-3.51 Å in NH_4Br[146]). Contact between these chains in the $\underset{\sim}{c}$ direction is primarily between the hydrocarbon ring on one molecule and bromine atoms in molecules in the chain related by the $\underset{\sim}{c}$ glide. In the $\underset{\sim}{b}$ direction, the hydrocarbon rings are, therefore, interleaved. The other important contact in the $\underset{\sim}{b}$ direction is

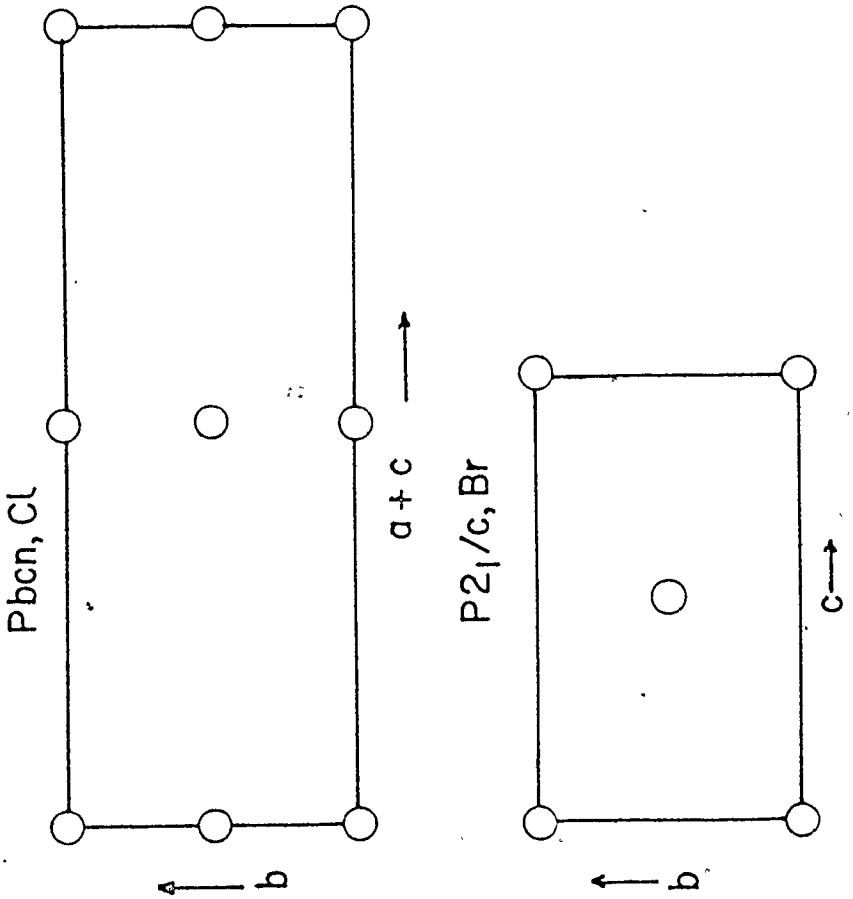


Figure 14

Comparison of the platinum arrangement in the bc plane for trans-$PtBr_2(C_6H_{11}NH_2)_2$ and the 101 plane for trans-$PtCl_2$-$(C_6H_{11}NH_2)_2$

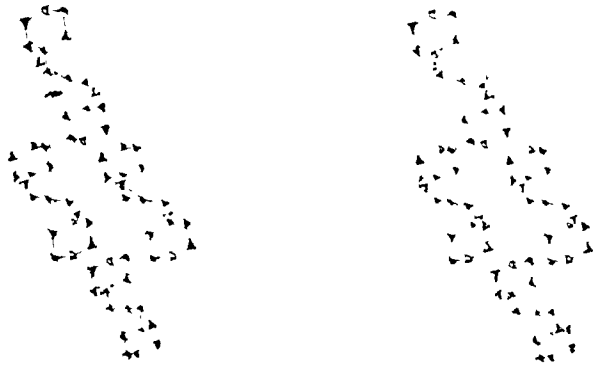


Figure 15

The unit cell contents of <u>trans</u>-$PtBr_2(C_6H_{11}NH_2)_2$. $\underset{\sim}{a}$ and $\underset{\sim}{c}$ are parallel to the top and side of the page, respectively. The view is down $\underset{\sim}{b}$.

between a bromine atom on one molecule and the hydrogen atoms attached to C(6) of the next.

4.4 The Crystal and Molecular Structure of cis-dichloro-di(cyclohexylamine-N)platinum(II)bis(hexamethylphosphoride)[130]

4.4.1 Preparation:

Cyclohexylamine (0.79 g) was added to K_2PtCl_4 (1.6 g) in water. The yellow precipitate was removed by filtration and washed sequentially with small amounts (2 x 10 mL) of water, methanol and diethyl ether and dried *in vacuo*. Crystals suitable for X-ray diffraction were recrystallized from hexamethylphosphoramide (HMPA) and stored with a small amount of HMPA at -5°C. It proved impossible to obtain satisfactory analysis as decomposition started immediately when the excess solvent was removed at room temperature. Analytical figures correspond to ratios of HMPA:Pt complex of 2.7:1 for a sample removed directly from the solvent to 0.2:1 for a sample allowed to stand two or three hours at room temperature. The density could not be determined because of crystal decomposition.

4.4.2 X-ray Studies:

Crystal data and numbers relevant to solution of the structure are summarized in Table 26. Positional and thermal parameters are presented in Table 27 and selected interatomic distances and angles in Table 28. The least squares plane and torsional and dihedral angles are given in Table 29.

Table 26

Compound	cis-$PtCl_2(C_6H_{11}NH_2)_2 \cdot 2[((CH_3)_2N)PO]$
Formula weight	823.24
Crystal size	polyhedron, with faces: {100} 0.065 mm apart {010} 0.095 mm apart {001} 0.095 mm apart
Unit cell parameters (Å and deg.)	a = 15.728(3) b = 12.030(3) c = 14.312(3) α = 123.89(2) β = 103.24(2) γ = 107.62(2)
volume ($Å^3$)	1852(1)
Z	2
$\rho_{calc.}$ (gcm^{-3})	1.48
linear absorption coefficient (cm^{-1})	42.5
absorption coefficient limits	2.339→1.476
g, extinction coefficient	6.75×10^{-8}
standard reflections, e.s.d. (%)	$2\bar{2}3$, 2.8 121, 2.8
No. of independent reflections	7277
$I > 3\sigma(I)$	4804
$3\sigma(I) > I > \sigma(I)$ ($F_o < F_c$)	566
($F_o > F_c$)	699
$I < \sigma(I)$	1208

Continued.....

Table 26 (Continued)

Final R_1, obs. (all)	0.0553 (0.0611)
Final R_2, obs. (all)	0.0690 (0.0710)
Final shift in e.s.d., Max.	8.56×10^{-3}
Ave.	7.04×10^{-4}
Final difference map:	
Highest peaks, location	$1.4e^-/\AA^3$; 0.07, 0.45, 0.38
	$1.6e^-/\AA^3$; 0.15, 0.44, 0.36
Lowest valleys, location	$-1.5e^-/\AA^3$; 0.7, 0.35, 0.31
	$-1.5e^-/\AA^3$; 0.20, 0.51, 0.45
Weighting scheme	$[\sigma^2 + (0.03\ F_o)^2]^{-1}$
Error in an observation of unit wt.	1.384

Table 27. Positional and thermal parameters ($Å^2$) for

cis-$PtCl_2(C_6H_{11}NH_2)_2 \cdot 2((CH_3)_2N)_3PO$ (x 10^3)

Atom	x	y	z	U_{iso}
Pt	117.82(3)	444.46(5)	407.90(4)	
Cl(1)	219.6(3)	351.0(4)	437.3(4)	
Cl(2)	- 28.9(2)	227.6(3)	333.9(3)	
N(1)	38.9(7)	549(1)	395.4(8)	39(2)
C(1)	- 72.8(9)	449(1)	288(1)	44(3)
C(2)	-111(1)	559(1)	305(1)	53(3)
C(3)	-221(1)	459(2)	193(2)	80(4)
C(4)	-228(2)	360(2)	67(2)	108(6)
C(5)	-195(1)	252(2)	48(2)	94(5)
C(6)	- 80(1)	347(2)	155(1)	59(3)
N(2)	248.5(7)	631(1)	470(1)	42(2)
C(7)	329(1)	747(1)	614(1)	50(3)
C(8)	427(1)	863(2)	640(1)	71(4)
C(9)	507(1)	979(2)	786(2)	95(5)
C(10)	467(1)	1068(2)	870(2)	103(6)
C(11)	367(1)	951(2)	840(2)	102(6)
C(12)	286(1)	832(2)	692(2)	84(4)
P(1)	186.6(2)	895.6(4)	389.6(3)	
O(1)	169.8(6)	756(1)	374(1)	57(2)
N(11)	83(1)	847(1)	278(1)	63(3)
C(13)	31(1)	695(2)	141(2)	93(5)
C(14)	49(1)	957(2)	294(2)	85(5)

Continued.....

Table 27 (Continued)

Atom	x	y	z	U_{iso}
N(12)	287(1)	962(1)	378(1)	61(3)
C(15)	307(1)	1071(2)	355(2)	83(4)
C(16)	360(2)	907(2)	375(2)	114(6)
N(13)	206(1)	1044(1)	528(1)	63(3)
C(17)	303(2)	1189(3)	630(2)	149(9)
C(18)	131(2)	1022(2)	572(2)	111(6)
P(2)	337.8(3)	428.1(4)	199.1(3)	
O(2)	352(1)	570(1)	313(1)	79(3)
N(21)	425(1)	393(2)	234(1)	82(4)
C(19)	464(2)	425(3)	361(2)	127(7)
C(20)	492(1)	368(2)	182(2)	101(5)
N(22)	341(1)	443(2)	91(1)	80(3)
C(21)	416(1)	594(2)	137(2)	102(6)
C(22)	288(2)	306(2)	- 49(2)	108(6)
N(23)	223(1)	266(2)	118(1)	88(4)
C(23)	214(2)	121(3)	77(3)	160(10)
C(24)	132(2)	277(3)	98(2)	128(7)

Anisotropic temperature factors U_{ij} ($Å^2$) (x 10^3)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	35.5(2)	32.1(2)	41.9(3)	19.3(2)	19.6(2)	25.9(2)
Cl(1)	56(2)	58(2)	108(3)	39(2)	38(2)	61(2)
Cl(2)	49(2)	34(1)	54(2)	19(1)	26(1)	28(1)
P(1)	48(2)	50(2)	59(2)	30(2)	31(2)	43(2)
P(2)	65(2)	61(2)	53(2)	43(2)	35(2)	38(2)

Table 28. Interatomic distances (Å) and angles (deg) for cis-$PtCl_2(C_6H_{11}NH_2)_2 \cdot 2((CH_3)_2N)_3PO$

Atoms	Distance	Atoms	Distance	Atoms	Distance
Pt-Cl(1)	2.305(5)	Pt-N(1)	2.07(1)	N(1)-C(1)	1.52(1)
Pt-Cl(2)	2.325(3)	Pt-N(2)	2.05(1)	N(2)-C(7)	1.52(1)
C(1)-C(2)	1.54(3)	C(2)-C(3)	1.52(2)	C(3)-C(4)	1.46(3)
C(7)-C(8)	1.53(2)	C(8)-C(9)	1.55(2)	C(9)-C(10)	1.52(3)
C(4)-C(5)	1.44(4)	C(5)-C(6)	1.57(2)	C(6)-C(1)	1.54(2)
C(10)-C(11)	1.52(3)	C(11)-C(12)	1.56(2)	C(12)-C(7)	1.49(3)
P(1)-O(1)	1.49(1)	P(1)-N(11)	1.65(2)	P(1)-N(12)	1.63(2)
P(2)-O(2)	1.45(1)	P(2)-N(21)	1.61(2)	P(2)-N(22)	1.66(2)
P(1)-N(13)	1.63(1)	N(11)-C(13)	1.49(2)	N(11)-C(14)	1.49(3)
P(2)-N(23)	1.67(1)	N(21)-C(19)	1.54(4)	N(21)-C(20)	1.43(3)
N(12)-C(15)	1.49(3)	N(12)-C(16)	1.49(3)	N(13)-C(17)	1.43(2)
N(22)-C(21)	1.46(3)	N(22)-C(22)	1.47(2)	N(23)-C(23)	1.44(5)
N(13)-C(18)	1.48(3)	N(23)-C(24)	1.46(4)		

Possible hydrogen bond distances

Atoms	Distance	Atoms	Distance	Atoms	Distance
Cl(2)...N(1)*	3.34(1)[a]	O(1)...N(1)	2.93(2)	O(1)...N(2)	2.89(2)
O(2)...N(2)	2.97(2)				

Angles

Atoms	Angle	Atoms	Angle	Atoms	Angle
Cl(1)-Pt-Cl(2)	91.8(2)	Cl(1)-Pt-N(1)	174.6(2)	Cl(1)-Pt-N(2)	86.9(4)

Continued.....

Table 28 (Continued)

Atoms	Angle	Atoms	Angle	Atoms	Angle
Cl(2)-Pt-N(1)	93.0(3)	Cl(2)-Pt-N(2)	178.3(4)	N(1)-Pt-N(2)	88.3(5)
Pt-N(1)-C(1)	120.4(8)	N(1)-C(1)-C(2)	108.7(9)	N(1)-C(1)-C(6)	109(1)
Pt-N(2)-C(7)	115(1)	N(2)-C(7)-C(8)	109(1)	N(2)-C(7)-C(12)	109(1)
C(6)-C(1)-C(2)	111(1)	C(1)-C(2)-C(3)	109(1)	C(2)-C(3)-C(4)	112(2)
C(12)-C(7)-C(8)	111(1)	C(7)-C(8)-C(9)	108(2)	C(8)-C(9)-C(10)	111(2)
C(3)-C(4)-C(5)	114(3)	C(4)-C(5)-C(6)	110(1)	C(5)-C(6)-C(1)	107(1)
C(9)-C(10)-C(11)	110(2)	C(10)-C(11)-C(12)	110(2)	C(11)-C(12)-C(7)	110(2)
O(1)-P(1)-N(11)	110.2(6)	O(1)-P(1)-N(12)	110.2(8)	O(1)-P(1)-N(13)	114.3(8)
O(2)-P(2)-N(21)	112.5(7)	O(2)-P(2)-N(22)	111.3(9)	O(2)-P(2)-N(23)	113.1(8)
P(1)-N(11)-C(13)	119(1)	P(1)-N(11)-C(14)	125.2(7)	C(13)-N(11)-C(14)	114(2)
P(1)-N(12)-C(15)	123(1)	P(1)-N(12)-C(16)	124(2)	C(15)-N(12)-C(16)	113(2)
P(1)-N(13)-C(17)	124(2)	P(1)-N(13)-C(18)	120.9(9)	C(17)-N(13)-C(18)	113(2)
P(2)-N(21)-C(19)	119(2)	P(2)-N(21)-C(20)	129(2)	C(19)-N(21)-C(20)	110(2)
P(2)-N(22)-C(21)	119(1)	P(2)-N(22)-C(22)	123(2)	C(21)-N(22)-C(22)	116(2)
P(2)-N(23)-C(23)	122(2)	P(2)-N(23)-C(24)	119(2)	C(23)-N(23)-C(24)	120(2)

[a] $N(1)^{*}$ is related to N(1) in table 27 by -x,1-y,1-z.

Table 29. Least squares plane, torsional and dihedral angles in cis-$PtCl_2(C_6H_{11}NH_2)_2$

Plane	Distance from Plane (Å)
Cl(1)Cl(2)N(1)N(2)Pt*	Cl(1), 0.03; Cl(2), -0.03; N(1), 0.04; N(2), -0.04; Pt, -0.01.

Torsional Angles (deg)

PtN(1)C(1)C(2)	0.7	PtN(2)C(7)C(8)	8.5
PtN(1)C(1)C(6)	53.9	PtN(2)C(7)C(12)	68.2
N(1)C(1)C(2)C(3)	176.3	N(2)C(7)C(8)C(9)	130.0
C(1)C(2)C(3)C(4)	125.4	C(7)C(8)C(9)C(10)	120.3
C(2)C(3)C(4)C(5)	121.6	C(8)C(9)C(10)C(11)	121.9
C(3)C(4)C(5)C(6)	120.9	C(9)C(10)C(11)C(12)	123.5
C(4)C(5)C(6)C(1)	122.9	C(10)C(11)C(12)C(7)	121.5
C(5)C(6)C(1)C(2)	123.4	C(11)C(12)C(7)C(8)	118.8
C(6)C(1)C(2)C(3)	124.1	C(12)C(7)C(8)C(9)	118.9
N(1)C(1)C(6)C(5)	176.6	N(2)C(7)C(12)C(11)	179.9

Dihedral Angle

PtCl(1)Cl(2)-PtN(1)N(2) 2.8°

* Pt given no weight in calculating the plane; other atoms given unit weights.

The molecule, which is shown in Figure 16, has a square planar arrangement around platinum with the structural parameters around platinum similar to those seen in other cis-$PtCl_2A_2$ compounds.[75,104,105,125,127,131] Pt-Cl (2.305(5), 2.325(3) Å vs. (range) 2.273(4)-2.333(9) Å) and Pt-N (2.07(1), 2.05(1) Å vs. (range) 1.85(6)-2.08(3) Å) distances are normal as are the Cl-Pt-Cl (91.8(2)° vs. (range) 90.2(4)-96.4(6)°) and N-Pt-N (88.3(5)° vs. (range) 73.2(2)-91.4(5)°) angles. The dihedral angle of 2.8° between $PtCl_2$ and PtN_2 planes is small and in the range (0-3°) normally observed for these structures. The rings are oriented so that the carbon atoms C(1), C(6), C(7) and C(12) are close to the square plane. The rings exist in the chair form and the ring bond lengths and angles and torsional angles are very similar to those obtained previously from trans-$PtCl_2(C_6H_{11}NH_2)_2$[129] and trans-$PtBr_2(C_6H_{11}NH_2)_2$.[128]

The packing of the molecules in the crystal is shown in Figure 17. The platinum-containing molecules are arranged so that they are hydrogen-bonded through N(1)*...Cl(2) into pairs related by the inversion centre at 0,½,½. The remaining hydrogen atoms on the amine groups are involved in bonding to the HMPA groups through N(1)...O(1), N(2)...O(1) and N(2)...O(2). Thus, we have six-molecule groups (two Pt-complexes, four HMPA units) bonded together, with the molecules so oriented that the hydrogen atoms of the hydrocarbon

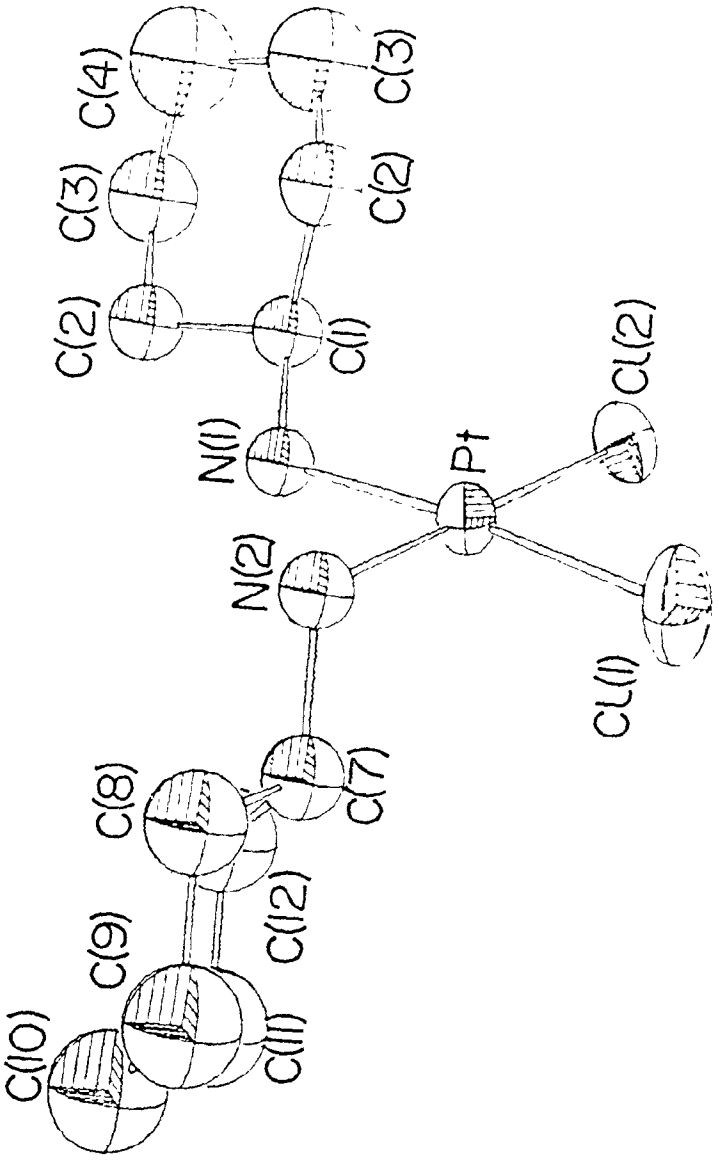


Figure 16A

The molecule cis-$PtCl_2(C_6H_{11}NH_2)_2$

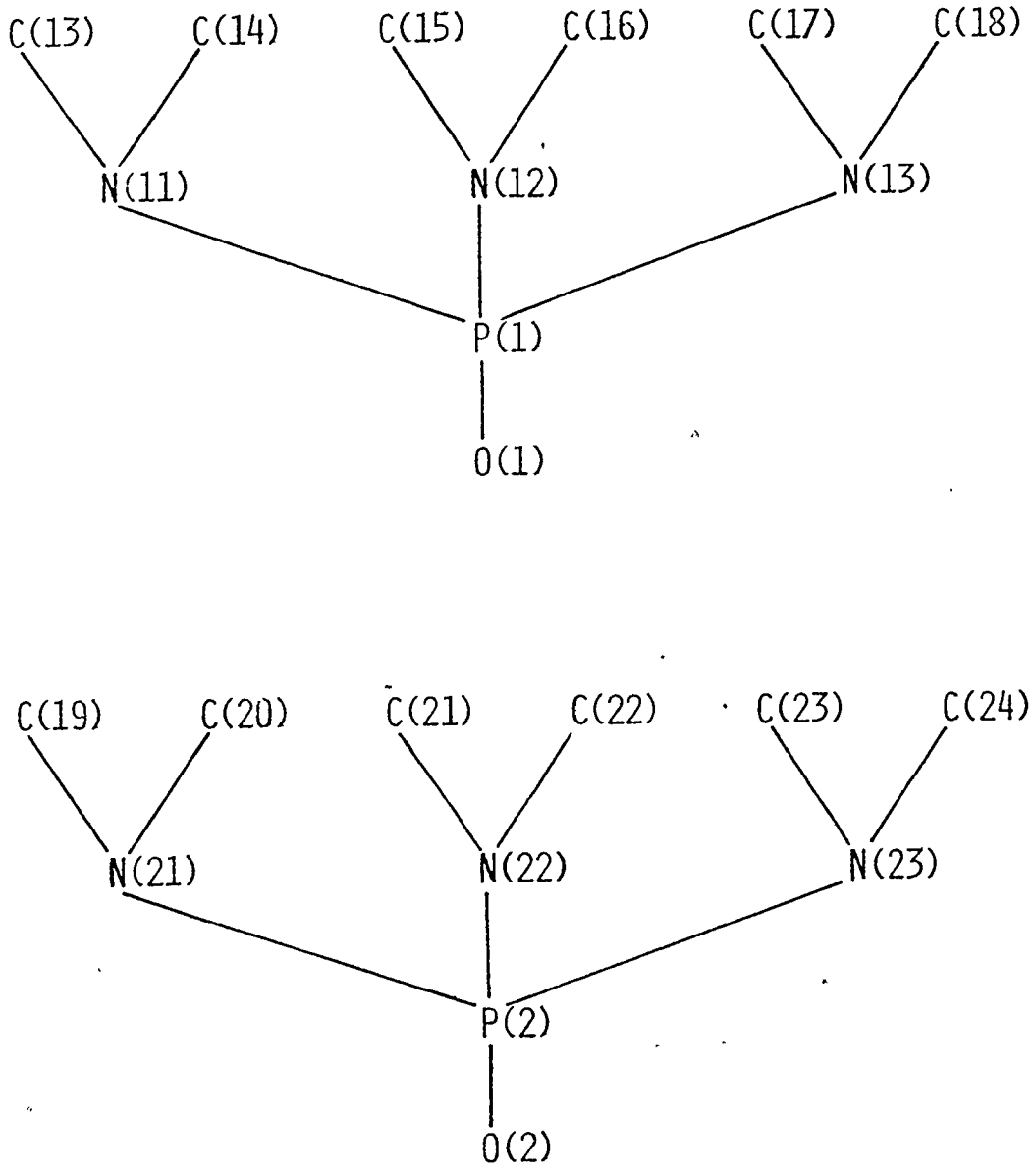


Figure 16B

The hexamethylphosphoramide labelling in cis-$PtCl_2(C_6H_{11}NH_2)_2 \cdot 2\{(CH_3)_2N\}_3PO$

Figure 17

The unit cell contents of cis-$PtCl_2(C_6H_{11}NH_2)_2 \cdot 2\{(CH_3)_2N\}_3PO$. $\underset{\sim}{a}$ and $\underset{\sim}{a} \times (\underset{\sim}{c} \times \underset{\sim}{a})$ are parallel to the bottom and side of the page. The view is down $\underset{\sim}{b}^*$.

cover the outside of the six-molecule group. The interactions between these groups are van der Waals.

4.5 The Crystal and Molecular Structure of cyclohexylammonium trichloro(cyclohexylamine-N)platinate(II)[147]

4.5.1 Preparation:

Cyclohexylamine (0.44 g) was added dropwise to an aqueous solution (20 mL) of K_2PtCl_4 (0.90 g). After a week, a light brown precipitate had formed and was removed by filtration. The residual yellow solution after one month yielded crystals of cyclohexylammonium trichloro(cyclohexylamine-N)platinate(II).

The product obtained was not the expected cis-$PtCl_2$-$(C_6H_{11}NH_2)_2$ but $[C_6H_{11}NH_3][PtCl_3(C_6H_{11}NH_2)]$. This fact suggests that the reaction conditions which have been used for the preparation of cis-diamine complexes of platinum(II) [148] are too acidic. Potassium salts with similar $[PtCl_3(amine)]^-$ anions have been produced in dimethyl formamide,[149] but not salts of the protonated amine.

4.5.2 X-ray Studies:

Crystal data and other numbers pertinent to solution of the structure are presented in Table 30. The positional and thermal parameters are given in Table 31. Selected interatomic distances and angles are given in Table 32 and the least squares plane and torsional angles are given in Table 33.

Table 30

Compound	$[C_6H_{11}NH_3][PtCl_3(C_6H_{11}NH_2)]$
Formula weight	500.81
Crystal size	cylinder of radius 0.1 mm height 0.6 mm
systematic absences	$0k0$ $k \neq 2n$ $h0\ell$ $\ell \neq 2n$
Unit cell parameters (Å and deg.)	a = 12.154(2) b = 7.940(2) c = 20.324(4) β = 115.28(1)
space group	$P2_1/c$ (No. 14)
volume ($Å^3$)	1773.7(6)
Z	4
$\rho_{calc.}$ (gcm^{-3})	1.88
$\rho_{obs.}$ (gcm^{-3})	1.89(2)
linear absorption coefficient (cm^{-1})	87.5
absorption coefficient limits	4.01→4.31
standard reflections, e.s.d. (%)	015, 2.30 $\bar{1}30$, 2.11
No. of independent reflections	4082
$I > 3\sigma(I)$	2703
$3\sigma(I) > I > 0.0$ $(F_o < F_c)$	442
$(F_o > F_c)$	576
$I < 0.0$	361

Continued.....

Table 30 (Continued)

Final R_1, obs. (all)	0.0416 (0.0494)
Final R_2, obs. (all)	0.0525 (0.0546)
Final shift in e.s.d., Max.	6.99×10^{-3}
Ave.	6.32×10^{-4}
g, extinction coefficient	6.669×10^{-8}
Final difference map:	
Highest peaks, location	$1.63e^-/\AA^3$; 0.0375, 0.295, 0.20
	$1.50e^-/\AA^3$; 0.145, 0.295, 0.16
	$1.31e^-/\AA^3$; 0.175, 0.325, 0.195
Lowest valleys, location	$-1.55e^-/\AA^3$; 0.0625, 0.285, 0.12
	$-1.26e^-/\AA^3$; 0.1125, 0.25, 0.12
	$-1.20e^-/\AA^3$; 0.10, 0.35, 0.225
Weighting scheme*	$[\sigma^2 + (0.03\ F_o)^2]^{-1}$
Error in an observation of unit weight	1.189
Analysis, calc., obs. (%)	N 5.6, 5.57 C 28.8, 28.52 H 5.4, 5.52

* The value of 0.03 was chosen to make $\langle \omega(|F_o| - |F_c|^2)^2 \rangle$ locally independent of F_o and $\sin\theta/\lambda$.

Table 31. Atom parameters for $[C_6H_{11}NH_3][PtCl_3(C_6H_{11}NH_2)]$ ($\times 10^3$)

Atom	x	y	z
Pt	87.44(3)	292.88(4)	179.70(2)
Cl(1)	- 12.4(2)	46.6(3)	128.8(1)
Cl(2)	97.4(3)	361.0(4)	71.9(1)
Cl(3)	177.4(2)	542.9(3)	232.1(1)
N(1)	80.5(7)	234.9(9)	276.5(4)
C(1)	197.2(9)	159(1)	334.6(5)
C(2)	178(1)	132(2)	403.3(5)
C(3)	297(1)	58(2)	464.2(6)
C(4)	329(1)	-103(2)	437.2(8)
C(5)	348(1)	- 72(2)	369.1(7)
C(6)	231(1)	1(2)	308.5(6)
N(1a)	867.0(9)	231(1)	923.9(6)
C(1a)	733(1)	180(2)	901.4(8)
C(2a)	733(1)	25(2)	944(1)
C(3a)	601(2)	- 20(4)	926(1)
C(4a)	518(2)	- 12(3)	856(1)
C(5a)	524(1)	137(4)	817(1)
C(6a)	657(2)	188(3)	835(1)

Anisotropic temperature factors U_{ij} $(\mathring{A})^2$ ($\times 10^3$)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	51.0(2)	43.2(2)	41.5(2)	2.6(2)	16.8(1)	2.4(2)

Continued.....

Table 31 (Continued)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(1)	81(2)	56(1)	59(1)	- 15(1)	25(1)	-11(1)
Cl(2)	116(2)	73(2)	50(1)	- 9(2)	39(1)	5(1)
Cl(3)	65(1)	52(1)	63(1)	- 11(1)	26(1)	- 5(1)
N(1)	55(4)	48(4)	43(4)	5(3)	17(3)	1(3)
C(1)	67(6)	60(6)	46(5)	19(5)	22(4)	16(4)
C(2)	82(7)	91(8)	49(5)	23(6)	29(5)	24(6)
C(3)	119(10)	122(12)	61(7)	43(9)	28(7)	21(7)
C(4)	118(11)	101(11)	92(9)	40(9)	31(8)	46(9)
C(5)	109(9)	122(12)	78(8)	66(9)	33(7)	20(8)
C(6)	104(9)	91(9)	71(7)	56(8)	23(7)	11(6)
N(1a)	65(5)	78(6)	104(8)	- 13(5)	31(5)	- 9(6)
C(1a)	69(7)	99(10)	109(11)	- 29(7)	17(7)	23(8)
C(2a)	101(11)	161(17)	142(14)	- 31(11)	- 3(10)	81(13)
C(3a)	141(17)	298(34)	256(30)	- 91(20)	- 1(18)	194(28)
C(4a)	107(13)	184(22)	172(19)	- 61(13)	2(12)	53(17)
C(5a)	82(10)	249(25)	153(17)	- 47(14)	-18(10)	94(18)
C(6a)	90(11)	340(34)	172(19)	- 77(16)	-12(12)	162(22)

Table 32. Interatomic distances (Å) and angles (deg) for

$[C_6H_{11}NH_3][PtCl_3(C_6H_{11}NH_2)]$

Atoms	Distance	Atoms	Distance	Atoms	Distance
Pt-Cl(1)	2.301(3)	C(1)-C(2)	1.52(2)	C(1a)-C(2a)	1.47(3)
Pt-Cl(2)	2.310(3)	C(2)-C(3)	1.56(2)	C(2a)-C(3a)	1.53(3)
Pt-Cl(3)	2.297(2)	C(3)-C(4)	1.51(2)	C(3a)-C(4a)	1.35(3)
Pt-N(1)	2.058(9)	C(4)-C(5)	1.52(2)	C(4a)-C(5a)	1.45(4)
N(1)-C(1)	1.53(1)	C(5)-C(6)	1.54(2)	C(5a)-C(6a)	1.55(3)
N(1a)-C(1a)	1.56(2)	C(6)-C(1)	1.48(2)	C(6a)-C(1a)	1.31(2)

Possible hydrogen bond distances

Atoms	Distance	Atoms	Distance	Atoms	Distance
Cl(1)...N(1)[b]	3.45(1)	Cl(2)...N(1a)[d]	3.26(1)	Cl(3)...N(1)[f]	3.422(9)
Cl(1)-N(1a)[c]	3.28(1)	Cl(2)...N(1a)[e]	3.28(1)		

Angles

Atoms	Angle	Atoms	Angle	Atoms	Angle
Cl(1)-Pt-Cl(2)	90.2(1)	N(1)-C(1)-C(2)	108(1)	N(1a)-C(1a)-C(2a)	109(1)
Cl(1)-Pt-Cl(3)	176.6(1)	N(1)-C(1)-C(6)	111.3(7)	N(1a)-C(1a)-C(6a)	116(2)
Cl(1)-Pt-N(1)	90.6(2)	C(6)-C(1)-C(2)	113(1)	C(6a)-C(1a)-C(2a)	117(2)
Cl(2)-Pt-Cl(3)	91.7(1)	C(1)-C(2)-C(3)	109(1)	C(1a)-C(2a)-C(3a)	108(2)
Cl(2)-Pt-N(1)	179.1(2)	C(2)-C(3)-C(4)	109(1)	C(2a)-C(3a)-C(4a)	118(3)
Cl(3)-Pt-N(1)	87.4(2)	C(3)-C(4)-C(5)	111(1)	C(3a)-C(4a)-C(5a)	115(2)
Pt-N(1)-C(1)	115.1(7)	C(4)-C(5)-C(6)	110(1)	C(4a)-C(5a)-C(6a)	112(2)
		C(5)-C(6)-C(1)	109(1)	C(5a)-C(6a)-C(1a)	116(2)

Continued.....

Table 32 (Continued)

b-f Atoms are related to those in Table 31 by:

b	-x,y-½,½-z	e	x-1,y,z-1
c	1-x,-y,1-z	f	-x,½+y,½-z
d	1-x,1-y,1-z		

Table 33. Least squares plane and torsional angles in

$[C_6H_{11}NH_3][PtCl_3(C_6H_{11}NH_2)]$

Plane	Distance from plane in Å
Cl(1)Cl(2)Cl(3)N(1)	Cl(1), 0.030(3); Cl(2), -0.028(4); Cl(3), 0.031(4); N(1), 0.033(9); Pt, -0.026(4); C(1), -1.41(1); C(2), -1.22(1); C(6), -2.36(2).

Torsional angles (deg)

Cl(1)PtN(1)C(1)	99.3(2)	Cl(3)PtN(1)C(1)	- 83.6(2)
PtN(1)C(1)C(2)	177(1)	PtN(1)C(1)C(6)	- 59(1)
N(1)C(1)C(2)C(3)	-180(1)	N(1a)C(1a)C(2a)C(3a)	174(1)
C(1)C(2)C(3)C(4)	- 57(1)	C(1a)C(2a)C(3a)C(4a)	61(2)
C(2)C(3)C(4)C(5)	60(1)	C(2a)C(3a)C(4a)C(5a)	- 64(2)
C(3)C(4)C(5)C(6)	- 62(1)	C(3a)C(4a)C(5a)C(6a)	64(2)
C(4)C(5)C(6)C(1)	59(1)	C(4a)C(5a)C(6a)C(1a)	- 62(2)
C(5)C(6)C(1)C(2)	- 58(1)	C(5a)C(6a)C(1a)C(2a)	65(2)
C(6)C(1)C(2)C(3)	57(1)	C(6a)C(1a)C(2a)C(3a)	- 65(2)
N(1)C(1)C(6)C(5)	180(1)	N(1a)C(1a)C(6a)C(5a)	-175(1)

The anion is illustrated in Figure 18. The configuration around platinum is the expected square plane with minor deviations from planarity (Table 33). Pt-Cl(2) is significantly longer than Pt-Cl(3), but not than Pt-Cl(1). On the basis of the trans influence,[150] there should be little difference in Pt-Cl distances; if anything, Pt-Cl(2) should be shorter than Pt-Cl(1) and Pt-Cl(3). The Pt-Cl distances do, however, correlate with the number of strong hydrogen bonds to the chlorine atoms. They are also within the range normally observed.[75,104,105,125,127,129-132,151] Similarly, the Pt-N distances agree with values previously found.[75,104,105,125,127-132,151] The torsional angles (Table 33) in the ring are very similar to those observed previously,[128-130] but the torsional angles involving platinum and distances of C(1), C(2) and C(6) from the square plane show that the arrangement of the ring is closer to that in cis-$PtCl_2(C_6H_{11}NH_2)_2 \cdot ((CH_3)_2N)_3PO$.[130] In this arrangement, C(6) is above the square plane only 3.38(2) Å from the platinum atom and 3.61(2) Å from Cl(1).

The packing of the ions in the unit cell is shown in Figure 19. The anions are arranged so that they form a double layer with the ligand square planes close to the $\underset{\sim}{bc}$ plane and the cyclohexyl rings on the outside of the double layer. Double layers related by the $\underset{\sim}{a}$ translation are separated by a zig-zag layer of cations centred at $x = \frac{1}{2}$. Within the

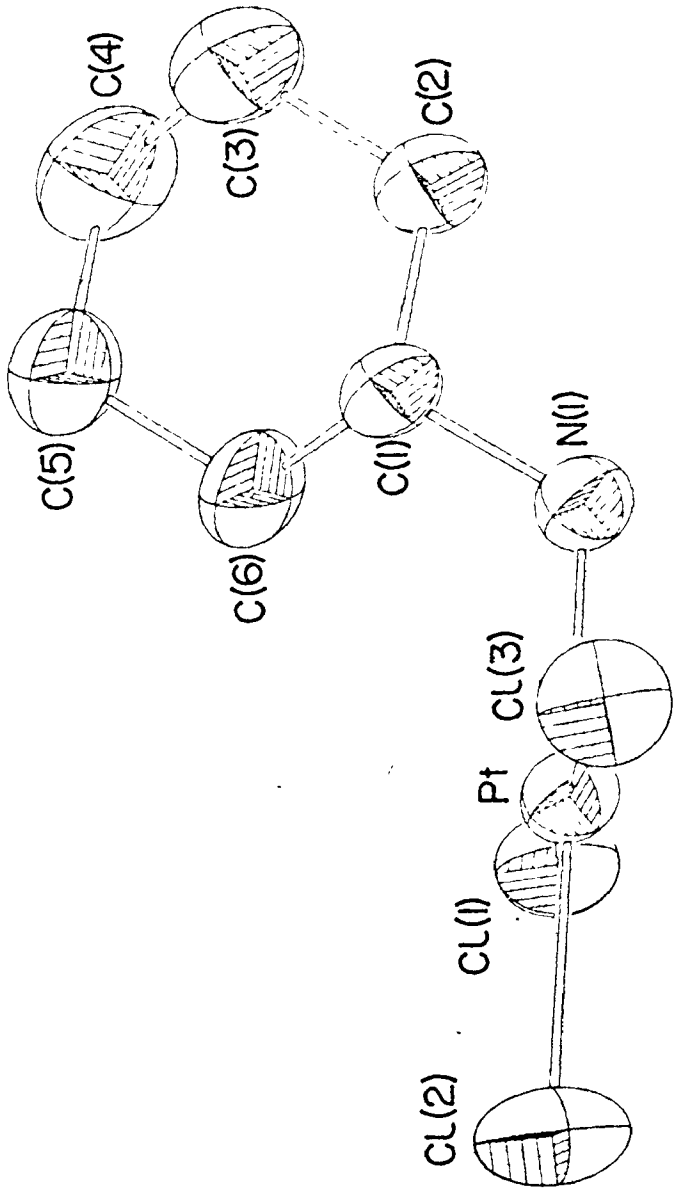


Figure 18

The molecular anion $[PtCl_3(C_6H_{11}NH_2)]^-$

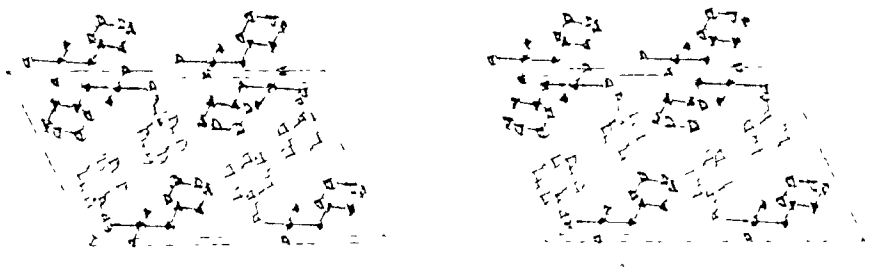


Figure 19

The unit cell contents of $[C_6H_{11}NH_3][PtCl_3(C_6H_{11}NH_2)]$. $\underset{\sim}{c}$ and $\underset{\sim}{a}^*$ are parallel to the bottom and side of the page, respectively. The view is down $\underset{\sim}{b}$.

double layer along the $\underset{\sim}{b}$ direction, there are spiral chains of molecules related by the 2_1 axis and bound to adjacent molecules by rather weak $N(1)\overset{b}{\cdots}Cl(1)$ and $N(1)\overset{f}{\cdots}Cl(3)$ hydrogen bonds (3.44(1), 3.42(1) Å). There are no direct hydrogen bonds between these chains along the $\underset{\sim}{c}$ direction, but hydrogen bonding to the NH_3 group of the cation holds adjacent chains together with strong hydrogen bonds $N(1a)\overset{c}{\cdots}Cl(1)$, $N(1a)\overset{d}{\cdots}Cl(2)$, $N(1a)\overset{e}{\cdots}Cl(2)$ (3.28(1), 3.26(1), 3.28(1) Å). This hydrogen bonding of the cation to the double layer means that the cyclohexyl ring of the cation is also pointing out of the double layer. Thus, any contacts near $x = \frac{1}{2}$ are H...H contacts and the forces are van der Waals.

4.6 The Crystal Structure of an Unknown Platinum Complex

4.6.1 Preparation:

Cyclobutylamine (0.183 g) was added dropwise to K_2PtCl_4 (0.535 g) in water (15 mL) and the solution left to stand overnight. The dark yellow crystals which formed were removed by filtration and washed with acetone.

4.6.2 X-ray Studies:

Crystal data and numbers pertinent to solution of the structure are listed in Table 34. Positional and thermal parameters are given in Table 35 and selected interatomic distances and angles are presented in Table 36.

The molecule is illustrated in Figure 20, and the packing of the molecules in the unit cell is shown in Figure 21.

Table 34

Compound	$PtCl_2(C_5H_7NC)$
Formula weight	359.10
Crystal size	$10\bar{1}$, $\bar{1}0\bar{1}$, 0.025 mm apart $10\bar{1}$, $\bar{1}01$, 0.028 mm apart 010, $0\bar{1}0$, 0.25 mm apart
Systematic absences	hOO $h \neq 2n$ OkO $k \neq 2n$ OOℓ $\ell \neq 2n$
space group	$P2_12_12_1$ (No. 19)
Unit cell parameters (Å)	a = 10.681(2) b = 6.3838(7) c = 11.456(2)
volume ($Å^3$)	781.1(2)
Z	4
$\rho_{calc.}$ (gcm^{-3})	3.05
$\rho_{obs.}$ (gcm^{-3})	not measured
linear absorption coefficient (cm^{-1})	194.1
absorption coefficient limits	2.401→3.330
standard reflections, e.s.d. (%)	$\bar{1}\bar{2}0$, 2.18 203, 1.86 $01\bar{3}$, 1.60

Continued.....

Table 34 (Continued)

No. of independent reflections	1318
$I > 3\sigma(I)$	1172
$3\sigma(I) > I > 0.0$ $(F_o < F_c)$	55
$(F_o > F_c)$	60
$I < 0.0$	31
Final R_1, obs. (all)	0.0242 (0.0260)
Final R_2, obs. (all)	0.0310 (0.0313)
Final shift in e.s.d., Max.	3.61×10^{-4}
Ave.	7.31×10^{-5}
g, extinction coefficient	1.56×10^{-7}
Final difference map:	
Highest peaks, location	$1.20e^-/\AA^3$; 0.13, 0.25, 0.64
	$1.04e^-/\AA^3$; 0.14, 0.59, 0.40
	$1.17e^-/\AA^3$; 0.15, 0.35, 0.17
	$-1.50e^-/\AA^3$; 0.14, 0.63, 0.61
Lowest valleys, location	$-1.37e^-/\AA^3$; 0.14, 0.59, 0.70
Weighting scheme	$[\sigma^2 + (0.02\ F_o)^2]^{-1}$
Error in an observation of unit weight	1.126
Analysis, calc., obs. (%)	N 3.90, 3.26
	C 20.07, 18.87
	H 1.96, 2.52

Table 35. Positional and thermal parameters ($Å^2$) for $PtCl_2(C_5H_7NC)$ (x 10^3)

Atom	x	y	z	U_{iso}
Pt	363.28(4)	626.53(6)	143.03(3)	
Cl(1)	389.2(3)	946.2(4)	52.4(2)	
Cl(2)	553.5(3)	506.2(5)	75.7(3)	
C	362(1)	356(2)	148.8(9)	48(3)
N	334.2(9)	355(2)	232.0(8)	41(2)
C(1)	208(1)	376(2)	286(1)	48(3)
C(2)	217(1)	583(2)	356(1)	47(3)
C(3)	223(1)	739(2)	258.2(9)	40(3)
C(4)	166(1)	649(2)	156.0(9)	45(3)
C(5)	121(1)	429(2)	189(1)	50(3)

Anisotropic temperature factors U_{ij} ($Å^2$) (x 10^3)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	30.3(4)	29.6(2)	24.5(2)	-2.4(2)	- 0.7(2)	1.7(1)
Cl(1)	59(3)	35(1)	42(1)	-6(1)	11(1)	6(1)
Cl(2)	28(2)	53(2)	45(1)	3(1)	3(1)	-4(1)

Table 36. Interatomic distances (Å) and angles (deg) for $PtCl_2(C_5H_7NC)$

Atoms	Distance	Atoms	Distance	Atoms	Distance
Pt-Cl(1)	2.306(3)	Pt-N	2.04(1)	C(1)-C(2)	1.54(2)
Pt-Cl(2)	2.305(3)	Pt-C	1.73(1)	C(2)-C(3)	1.50(2)
Pt-C(3)	2.12(1)	N-C	1.00(1)	C(3)-C(4)	1.44(2)
Pt-C(4)	2.12(1)	N-C(1)	1.50(2)	C(4)-C(5)	1.53(2)
				C(5)-C(1)	1.49(2)

Angles

Atoms	Angle	Atoms	Angle	Atoms	Angle
Cl(1)-Pt-Cl(2)	92.2(1)	Cl(2)-Pt-N	91.0(3)	C-N-C(1)	132(1)
Cl(1)-Pt-N	176.1(3)	Cl(2)-Pt-C	71.9(4)	N-C(1)-C(2)	104(1)
Cl(1)-Pt-C	154.5(4)	Cl(2)-Pt-C(3)	160.6(3)	N-C(1)-C(5)	105.6(9)
Cl(1)-Pt-C(3)	93.8(3)	Cl(2)-Pt-C(4)	157.4(3)	C(1)-C(2)-C(3)	100.9(9)
Cl(1)-Pt-C(4)	95.3(3)	N-Pt-C(3)	82.4(4)	C(2)-C(3)-C(4)	109(1)
C-Pt-C(3)	107.9(5)	N-Pt-C(4)	82.6(4)	C(3)-C(4)-C(5)	107.3(9)
C-Pt-C(4)	93.1(5)	Pt-C-N	93(1)	C(4)-C(5)-C(1)	102(1)
				C(5)-C(1)-C(2)	103(1)

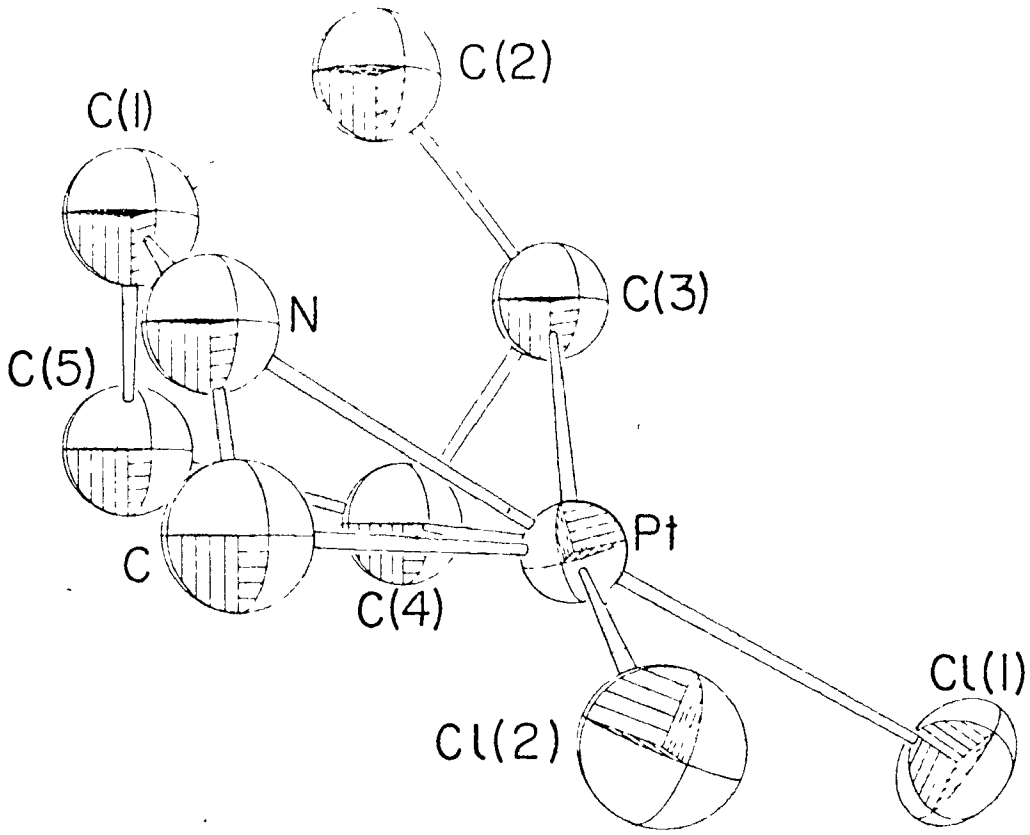


Figure 20

The molecule $PtCl_2(C_5H_7NC)$

Figure 21

The unit cell contents of $PtCl_2(C_5H_7NC)$. $\underset{\sim}{c}$ and $\underset{\sim}{a}$ are parallel to the bottom and side of the page, respectively. The view is down $\underset{\sim}{b}$.

The ring of the ligand is a cyclopentane ring with the platinum bonding to the double bond between C(3) and C(4). Bond lengths and bond angles for this part of the system are normal.[138] The acyclic group presents definite difficulties. This group seems to be an isonitrile which is bonded to platinum through the π system. All other platinum-isonitrile structures show the isonitrile group bonded either end-on through the carbon[152] with a carbon-nitrogen bond length of 1.12(1) to 1.22(5) Å and a carbon-nitrogen-carbon' angle of 170(2) to 179(2)° or bridging between two metal atoms[152] with a carbon-nitrogen bond length of 1.21(3) Å and a carbon-nitrogen-carbon' angle of 133(2)°. The angle C-N-C(1) in this structure (132(1)°) is close to that in the bridging isonitrile, but the carbon-nitrogen bond length of 1.00(1) Å is extremely short. As can be seen from the packing (Figure 21) there are no close contacts other than those from C to Cl(2) of the same molecule (2.41(1) Å) and from C to Cl(1) of the molecule at x,y-1,z (2.86(1) Å).

4.6.3 Discussion:

The compound which is discussed in this Chapter is not a product which was expected to form from the reactants that were used. Anomalies in the bond length and angle around nitrogen in the isonitrile group have been noted in the section on X-ray structure. Despite the low R-factor, this

compound must be further characterized before its structure can be considered to be solved. It has not been possible to repeat the reaction to yield this product and experiments are being performed at present to make the compound from K_2PtCl_4 and 4-isocyanocyclopentene.

The data presented in this chapter have been compiled for reference in case the same compound is accidentally or deliberately made and are not an integral part of this thesis, except that an unexpected product was formed.

CHAPTER 5

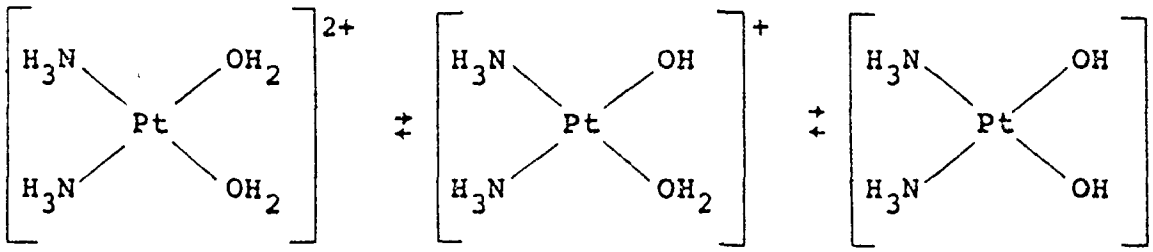
DISCUSSION

5.1 Aquation of Cisplatin:

Aquation of cisplatin is assumed to procede *via* the following mechanism[153]

$$\underline{cis}\text{-}[Pt(NH_3)_2Cl_2] \rightleftharpoons \underline{cis}\text{-}[Pt(NH_3)_2(OH_2)Cl]^+ \rightleftharpoons \underline{cis}\text{-}[Pt(NH_3)_2(OH_2)_2]^{2+}$$

with the final diaquo species in equilibrium with the two hydrolysis products shown.



At roughly neutral pH, such as is observed in the intracellular fluid, the monoaquo-monohydroxo species is expected to predominate.[154]

Because of the large difference between chloride ion concentration in blood plasma (103 mM) and in intracellular fluid (~ 4 mM), Lim and Martin[155] investigated the hydrolysis of $[enPtCl_2]$ under conditions of ambient chloride concentrations. Their results suggested that the predominant species present in the cell were the dichloro complex and the monoaquo-monohydroxo complex. They did, however, also postulate that the

latter compound formed a stable dihydroxo bridged dimer at physiological pH.

The actual existence of oligomeric forms of the platinum complexes was confirmed by a number of crystallographic studies by our group in collaboration with Rosenberg and Lippert,[35-38] and by Stanko and Hollis.[32]

The first compound isolated from reaction of cisplatin with silver nitrate at pH 6.55 was found to be the dihydroxo bridged dimer, $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2](NO_3)_2$,[35] shown in Figure 22A. With carbonate as a counterion at pH 10.65, another dimer, the structure of which is discussed in Section 3.2, was obtained (Figure 22B). This compound contains two dimeric cations which are held together by hydrogen bonding in the solid state, but which separate to discrete dimeric cations in solution.[38] During preparation of di-μ-hydroxo-bis[diammineplatinum(II)]nitrate, trimeric species were also observed and later shown to contain similar hydroxo bridges.[36,37] The trimer cations can exist in two different forms (Figure 23), one of roughly C_2 symmetry, the other, C_{3v}. These two forms interconvert in solution, as shown by the presence of only one ^{195}Pt nmr signal.[156] In an attempt to form $[Pt(NH_3)_2(H_2O)_2]^{2+}$, the pH was lowered and the solution concentrated. This procedure yielded crystals of cis-dinitratodiammineplatinum(II) rather than any monomeric aquo or aquohydroxo complex. The structure of cis-dinitratodiammineplatinum(II) is discussed in Section 3.1.

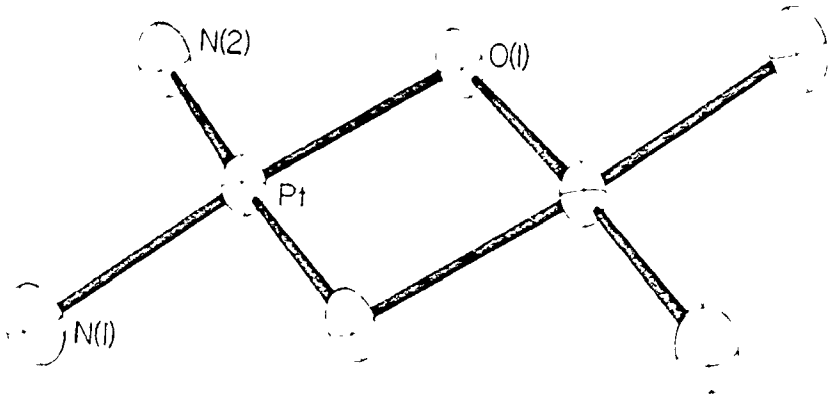


Figure 22A

The molecular cation $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ from $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2](NO_3)_2$.[35]

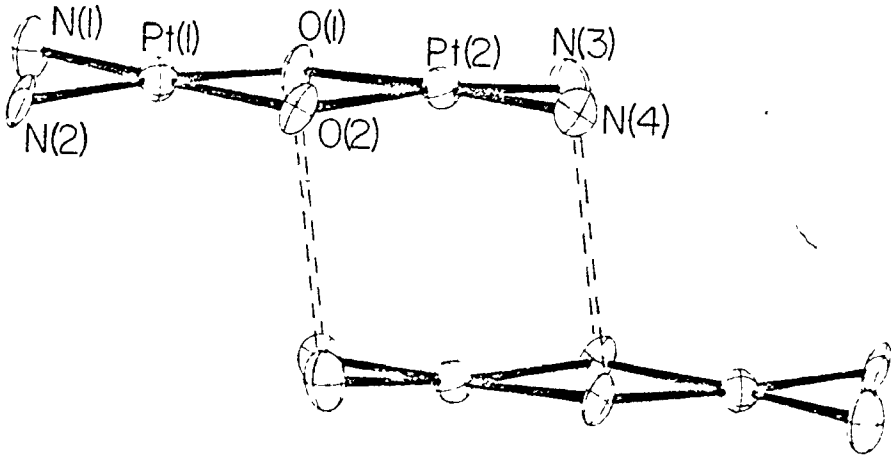
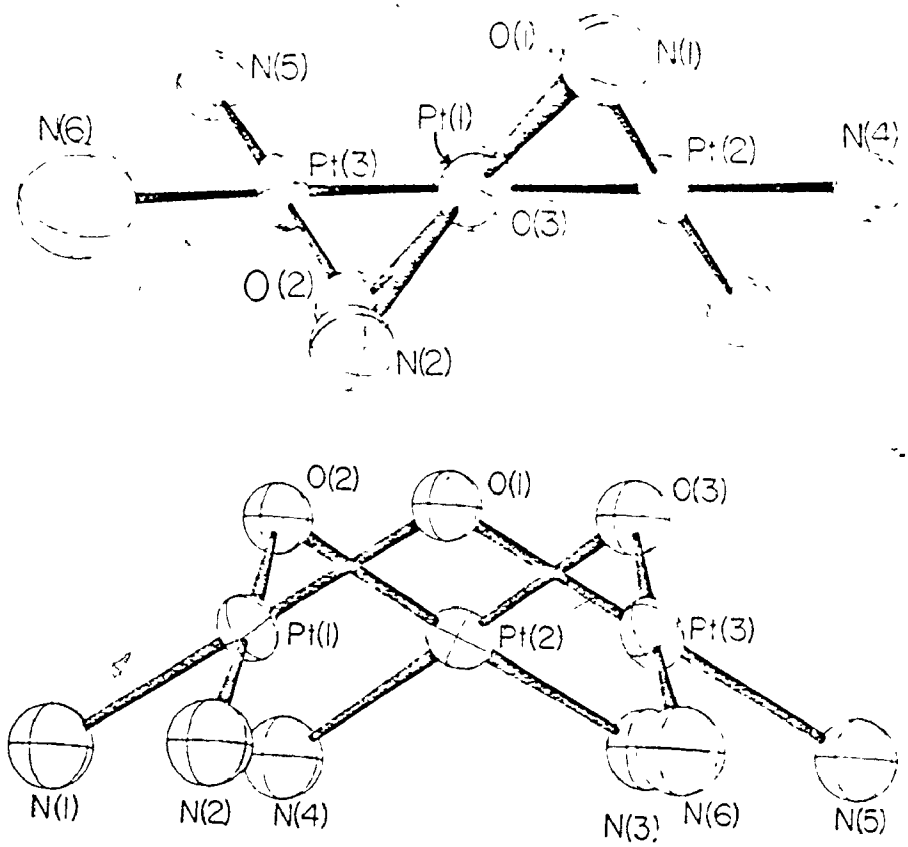


Figure 22B

The molecular cation $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ and its centrosymmetrically related neighbour from $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2]CO_3 \cdot 2H_2O$ (Section 3.2).



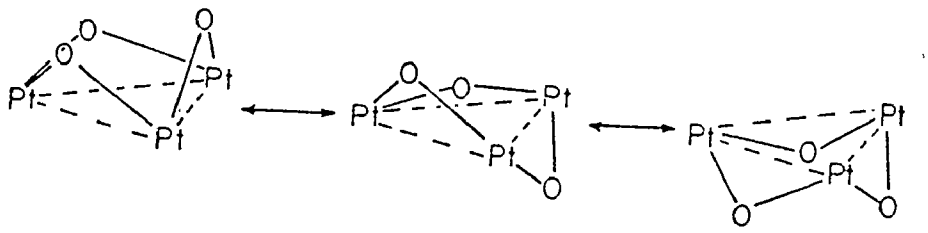


Figure 23

The two trimeric forms of the cation $[(NH_3)_3Pt(OH)]_3^{3+}$ and their probable rearrangement in solution.

Clearly, the aquation of cisplatin is far more complex than had been expected. Not only can a number of different dimeric and trimeric cations exist in solution, but they are the only species which have been isolated in the solid state. No monomeric aquo or hydroxo complexes have been crystallized, despite the fact that cis-$Pt(NH_3)_2(NO_3)_2$ rapidly releases NO_3^- in aqueous solution[34] to form a species which can be converted to the oligomers.

5.1.1 Bond Valence Approach:

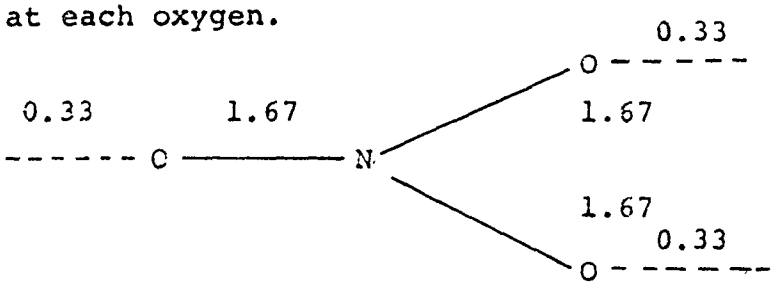
An explanation for the inability to crystallize monomer aquo or hydroxo species is based on Brown's acid-base model[157] which is an extension of Pauling's valence concepts. It is possible to use bond order (bond strength)-bond length relationships to give an order to any chemical bond. Brown and Shannon[158] tried to find a functional relationship which would relate bond strength to bond length for M-O bonds, regardless of structural type. The only constraint is that the sum of the bond strengths around an atom should equal the valence as defined by Pauling. This valence should always be integral (e.g., 2 for oxygen, 1 for hydrogen) and should encompass interactions of the atom under consideration with all neighbouring atoms. These interactions would include, for example, hydrogen bonding and van der Waals interactions.

In an extension of the bond valence model,[157] Brown considered individual ions and ligands, and defined their

residual bond valence as a measure of acid or base strength, depending upon whether the group is an electron acceptor or donor. As examples, consider nitrate ion, hydroxide ion and water as ligands around platinum(II).

5.1.1a Free Ligands:

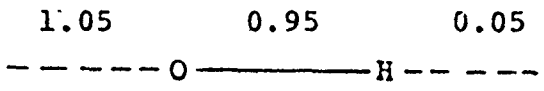
The bond valence around nitrogen must add up to five for the free nitrate ion since the sum of bond valences at each atom must be equal to the atomic valence.[157] Since the ion is symmetric, the bond valence or bond order of each nitrogen-oxygen bond must be 1.67. The valence around oxygen must add up to 2, leaving a residual valence of 0.33 at each oxygen.



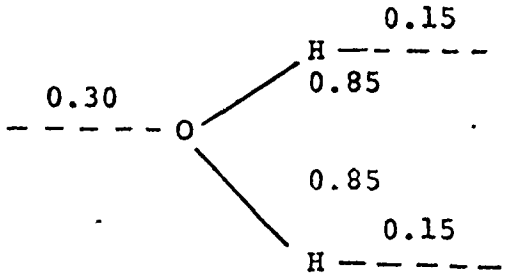
Since the nitrate ion is considered an electron donor, the residual valence is defined as the base strength of the oxygen atoms.

For the hydroxide ion, the absence of a central atom means that the value for bond valence between oxygen and hydrogen must be obtained from bond valence-bond length relationships. The hydroxide ion is a strong base, and the oxygen atom should thus have a large residual base strength. A value of 0.95 for the bond valence of the O-H bond leaves

oxygen with a residual base strength of 1.05 and hydrogen with a residual acid strength of 0.05.



Similar calculations for water lead to an oxygen-hydrogen bond valence of 0.85. This leaves a base strength of 0.30 for the oxygen atom and an acid strength of 0.15 for each hydrogen.



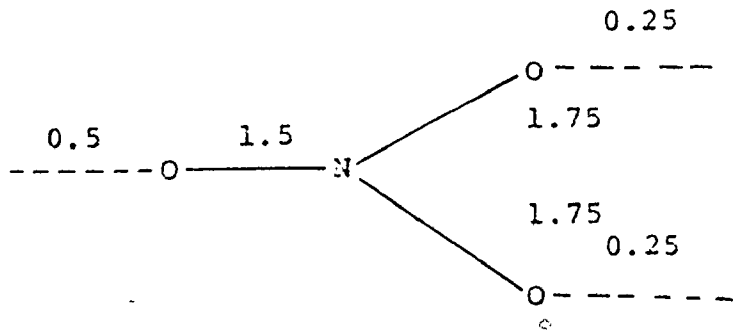
5.1.1b Platinum Complexes:

As previously mentioned, attempts to crystallize monomer aquo or hydroxo complexes starting with cisplatin have been unsuccessful. To eliminate the possibility of formation of oligomeric species which contain double hydroxide bridges, the aquation of platinum(II) complexes which have diethylenetriamine (dien) as a ligand was investigated.[159] No aquo or hydroxo species were isolated, but only $[Pt(dien)NO_3]NO_3$. Comparison of the platinum-nitrate part of this complex to the equivalent sections of the dinitrato compound of Chapter 3.1 shows that the bond lengths between equivalent atoms are not significantly different for the two compounds (Table 37). Because these two molecular fragments are so similar, it is possible to extend the calculations for each of the three

ligands considered previously to a system with the ligand bonded to the $[Pt(dien)]^{2+}$ moiety.

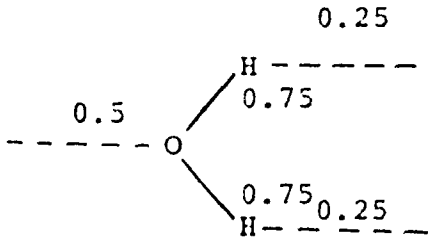
If Pt-O and Pt-N bond strengths are assumed to be equal, the bond order of each bond in square planar platinum(II) is 0.5. This means that the residual bond valence or acid strength of $[Pt(dien)]^{2+}$ is 0.5. The most stable structures will be formed when the acid strength of the cation most nearly matches the base strength of the anion,[157] since in all real structures the actual valence of a bond formed by the cation is necessarily the valence of the same bond at the anion. The base strengths of the ligands under consideration clearly do not match the acid strength of $[Pt(dien)]^{2+}$. Some arithmetic rearrangement is indicated.

For the nitrate group, this rearrangement is relatively straightforward. The residual valence at one oxygen which would bond to platinum can be raised from 0.33 to 0.5 with a drop in the corresponding O-N bond valence from 1.67 to 1.5. A valence of 3.5 remains and can be split between the other O-N bonds. The bond order of each of these bonds thus is increased to 1.75 and each terminal oxygen now has a residual bond valence or base strength of 0.25.



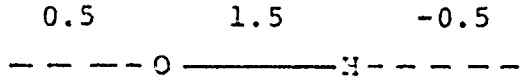
The bond lengths calculated for these bond orders (1.5 and 1.75) are 1.29 Å and 1.24 Å, respectively, and agree quite well with the observed O-N distances (Table 37).

When a similar operation is performed on the water molecule, the following results are obtained.



Here the acid strength of the protons increases from 0.15 to 0.25. This residual acid strength can be taken up by hydrogen bonding. The fact that aquo species do not crystallize suggests that in the crystal, nitrate as a counterion is not a sufficiently good hydrogen bond acceptor to stabilize the aquo complex and is itself coordinated instead. In aqueous solution, the solvent, water, is an excellent hydrogen bond acceptor and water can thus coordinate in preference to nitrate.

When the hydroxide ion is considered, certain difficulties are immediately obvious. Reduction of the residual valence on oxygen from 1.05 to 0.5 leads to the values shown below.



A negative residual bond valence at hydrogen is impossible. Consideration of the observed hydroxo structures suggests an

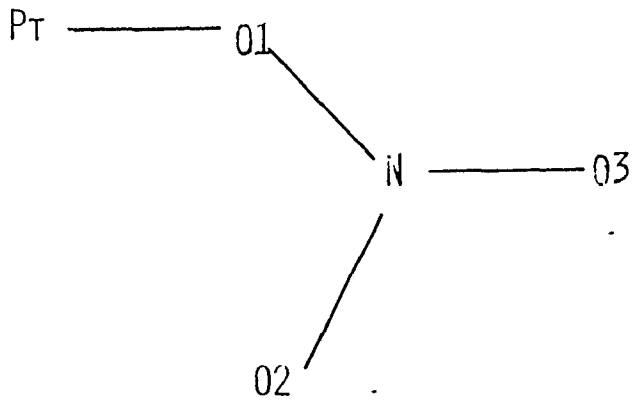
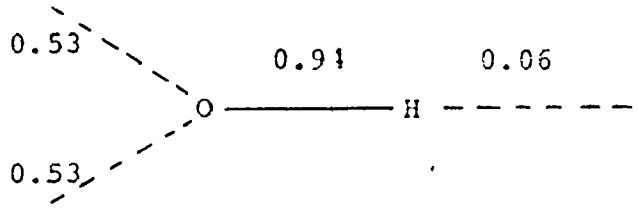


Table 37. Comparison of Pt-ONO_2 bond lengths for cis-$Pt(NH_3)_2(NO_3)_2$ and $[Pt(dien)NO_3]NO_3$

Bond	cis-$Pt(NH_3)_2(NO_3)_2$	$[Pt(dien)NO_3]NO_3$	
	Bond Lengths (Å)		
	NO_3	NO_3'	Coord. NO_3
Pt-O1	1.99(1)	2.03(1)	2.02(1)
O1-N	1.30(2)	1.28(2)	1.34(1)
N-O2	1.22(2)	1.19(2)	1.25(1)
N-O3	1.24(2)	1.22(2)	1.22(2)

acceptable alternative. The residual base strength at oxygen is 1.05. If the base strength is divided into two parts, each with a value of 0.53, the residual valence of 0.5 for Pt(II) is almost matched with no extreme effect on the bond valence at hydrogen.



This arrangement allows the hydroxide ion to form bridges between two platinum(II) species quite readily.

This approach explains why aquo complexes of platinum(II), although present in solution, have not been observed as solids, since their isolation would depend on the presence of a strong hydrogen bond acceptor as counterion. The lack of stability of monomeric hydroxy species and their tendency to oligomerize, even in solution, is also explained.

5.1.2 Reactions with Bases:

Chikuma et al.[156] studied the kinetics of the oligomerization using ^{195}Pt nmr and found that the reaction was fastest in the neutral pH region where the monoaquo-monohydroxo species is present. They concluded that the hydroxo-bridged dimers and trimers were extremely important in describing products of reactions of platinum complexes with the DNA bases, particularly for reactions done in vitro with

the pH adjusted to physiological levels.

The direct reaction of cisplatin with various bases seems fairly straightforward in that monomeric cis-$[Pt(NH_3)_2(base)_2]^{2+}$ species - some of which have now been characterized by X-ray crystallography[90-94] - are formed. There is also evidence for this type of product in the reaction between the bases and the complex aquation mixture.[116,160,161] This bis-base compound would arise from reaction of monomeric aquo complexes, present in the aquation mixture, with the bases.

The reactions of pure hydroxo-bridged dimer with bases give quite different compounds. The first crystals of a product between a dimer and a DNA base were obtained when $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2](NO_3)_2$ was reacted with 1-methylthymine.[119] The cation which was formed is shown in Figure 24. It consists of a dimeric unit with the two platinum atoms 2.974 Å apart and bridged by two 1-methylthyminato ligands arranged in a head-to-tail fashion. Similar compounds have been formed with 1-methyluracil[120b] and 1-methylcytosine[162] as the bridging ligand. Both show the same features of a short platinum-platinum distance and two bases, arranged head-to-tail bridging the distance between them.

Dimeric complexes with bases bridging in a head-to-head fashion rather than head-to-tail have also been isolated with 1-methylthyminate[120a] and 1-methyluracil[163] as bridging

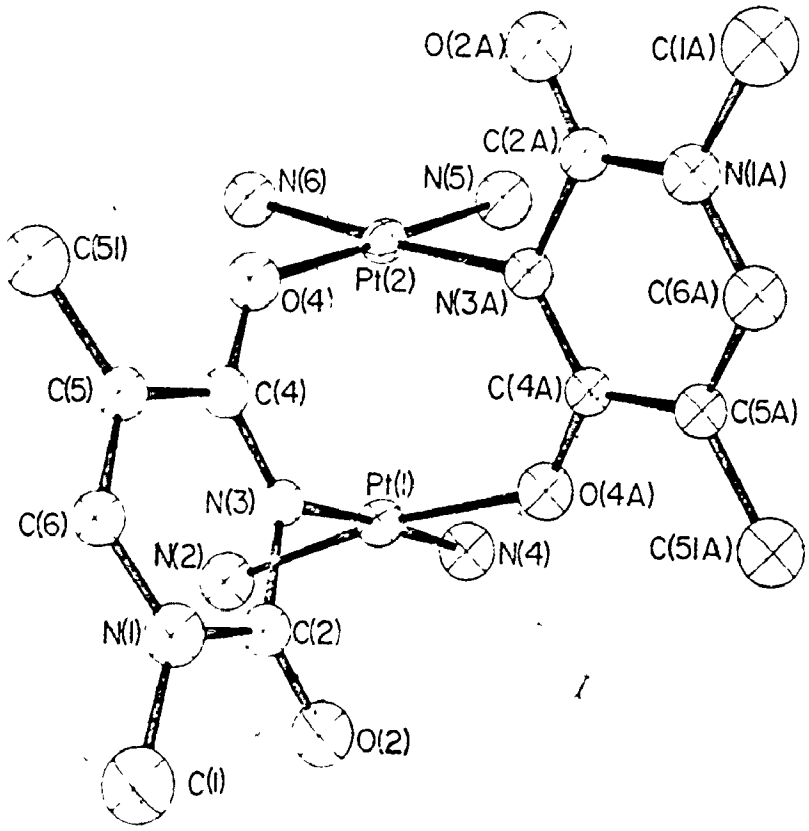


Figure 24

The molecular cation $[(NH_3)_2Pt(C_6H_7N_2O)_2Pt(NH_3)_2]^{2+}$ from reference 119.

ligands. The complex with 1-methyluracil is unstable and readily converts to a platinum blue when dissolved in water.

Such a conversion is not surprising considering the similarity of the above compounds to "Lippard's blue", the only crystallographically characterized[118b] blue platinum compound (Figure 25) which was obtained from the reaction of aquated cisplatin with α-pyridone. This structure consists of a four platinum atom chain composed of two dimeric units. Each unit is held together by a platinum-platinum bond (2.779 Å) and two α-pyridonate bridges bonded in a head-to-head manner. The two dimers are associated by a platinum-platinum bond (2.885 Å) and hydrogen bonding between the ammine groups of one dimeric unit and the α-pyridonate oxygen atoms of the other. The platinum formal oxidation state is 2.25.

5.1.3 Present Status:

When the complex nature of the aquation of cisplatin was confirmed, some of the animal tests were repeated with pure compounds. The monomeric complex obtained from the pure nitrate was found to be active while the oligomers were highly toxic.[164] This fact led to the suggestion that the toxicity of cisplatin is caused by formation, in the cell, of the toxic dimer from the active monomer.

An alternate explanation which has been set forth by Speranzini[165] involves binding of both monomer and dimer to

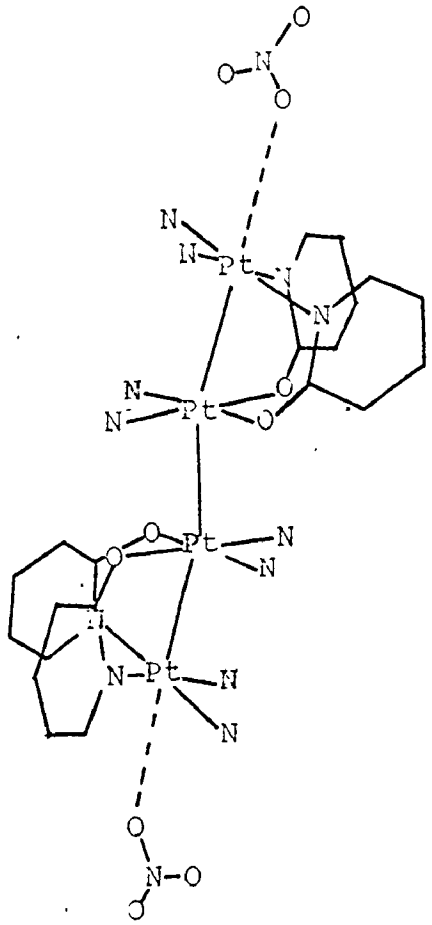


Figure 25

The molecule $[(NH_3)_2Pt(C_5H_4ON)_2Pt(NH_3)_2]_2(NO_3)_5$ from reference 118.

DNA with the type of bonding caused by the dimer (bis-base binding) responsible for the active lesion. Since only cis compounds can form such a dimer, this would effectively differentiate between the reaction of cis and trans with DNA.

A similar theory was proposed by Barton et al.[166] (Figure 26) after the solution of the α-pyridone blue structure, but was abandoned because EXAFS results showed that there was no platinum-platinum distance of less than 3.0 Å when cisplatin was reacted with DNA.[167] It has, however, been shown very clearly that cisplatin and the dihydroxo bridged dimer react differently with DNA bases, and would be expected to react differently with DNA itself. The definitive experiment would be reaction of the dimer with DNA and an EXAFS study of the product.

Whether a short platinum-platinum distance would be found in this study or not, many of the studies in the literature should be reinterpreted. It has become fairly common practice to attempt to mimic in vivo systems by reacting aquated cisplatin, rather than cisplatin itself, with DNA. While care has been taken by some researchers to minimize oligomer formation,[72] it has not been unusual to react DNA with aquation products that have been recrystallized[88,168] and are, therefore, almost certainly dimers or trimers. Most research falls in the area between these two extremes[169-174] and probably involves a mixture of monomers and oligomers. All the results, however, have been interpreted on the basis

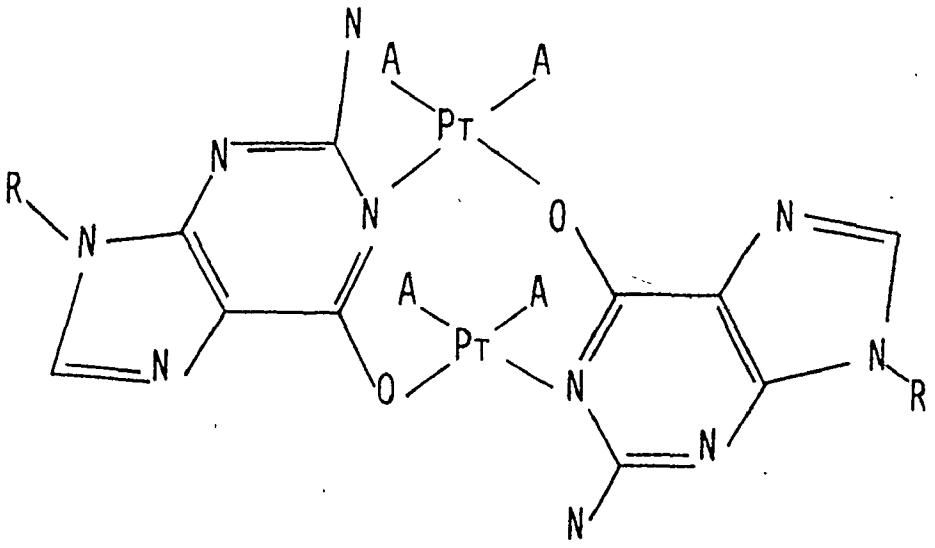


Figure 26

Postulated ligand bridged dimer formed by guanosine and platinum complexes.

of pure monoaquo-monohydroxo platinum(II) reacting with DNA or base homopolymers.

The existence of hydroxo bridged polymers has been proven both in the solid state and in solution.[32,33,35-38,155] There are enough spectral data to make it possible to examine the solution used before reacting it with the bases and be reasonably sure which species are present. Most of the work done using aquated cisplatin or cisplatin should be critically reexamined and, if necessary, repeated using pure compounds.

5.2 Alicyclic Amine Complexes:

The need for structural studies of the platinum alicyclic amine complexes was suggested after the original structure variation studies were made[26,27] and emphasized by the inconclusive kinetic and solubility results.[41] A partial solution of a structure of cisdichlorobis(cyclohexylamine-N)platinum(II) with ether of crystallization present in the lattice showed a distorted square plane aroung platinum,[175] but distortion caused by the presence of solvent could not be ruled out because the structure of cis-dichlorobis(cyclopropylamine-N)platinum(II) (Section 4.1) with no solvent of crystallization showed no unusual features. Attempts to recrystallize cis-dichlorobis(cyclobutylamine-N)-platinum(II) repeatedly gave the analogous trans complex, which also showed no distortion around platinum. The situation seemed ambiguous until the structure of cis-dichlorobis-

(cyclohexylamine-N)platinum(II) with no solvent of crystallization showed a marked distortion of the square plane.[176]

5.2.1 Distortion of the Square Plane:

The compound with the highest therapeutic index is cis-dichlorobis(cyclohexylamine-N)platinum(II). If some distortion exists, it is likely that it would be greatest for this complex.

Faggiani et al.[175] obtained an initial solution of the structure of cis-$[PtCl_2(C_6H_{11}NH_2)_2]\cdot(C_2H_5O)_2$ in P1; the platinum-containing molecule appeared to be half square-planar (Cl-Pt-Cl, 88.2(5)°) and half tetrahedral (N-Pt-N, 108(2)°) with a $PtCl_2$-PtN_2 dihedral angle of 35°. A Delaunay test showed that the true cell was C-centred and monoclinic, but attempts at refinement were unsatisfactory. The structure has not yet been solved and it is quite possible that the distortion is an artifact of a space group error.

The structure of cis-$[PtCl_2(C_6H_{11}NH_2)_2]$ did, however, seem to solve the problem. The distortion here is even greater than that in the above complex.[176] Both Cl-Pt-Cl and N-Pt-N angles are 151° and the $PtCl_2$-PtN_2 dihedral angle is 97° (Figure 27).

A new problem arose. Crystals of cis-dichlorobis-(cyclohexylamine-N)platinum(II) were obtained from HMPA and the structure of this compound, which does include solvent of crystallization, does not show any distortion of the

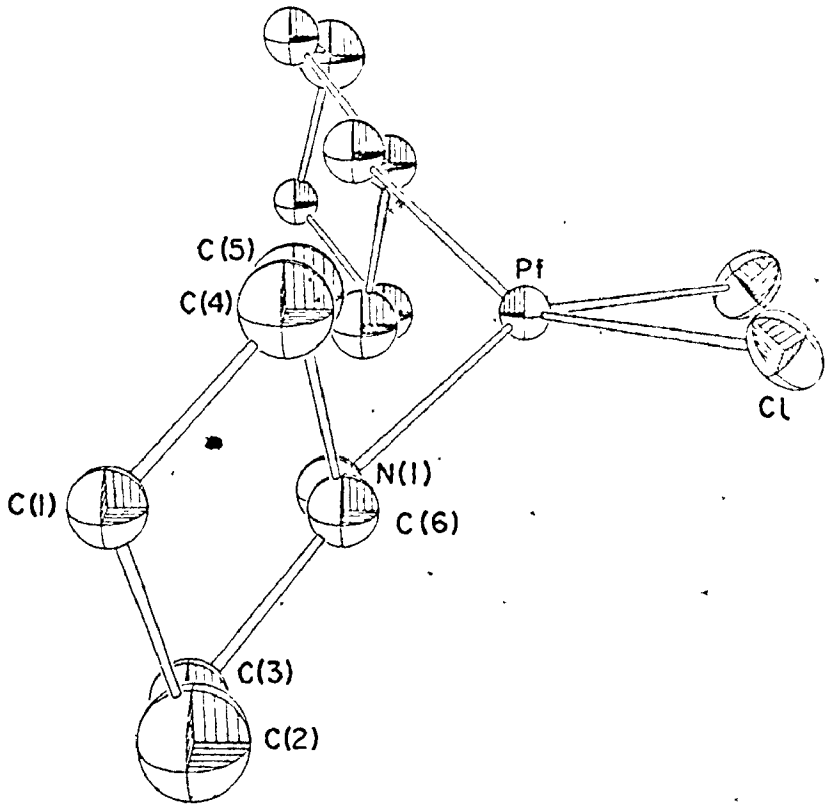


Figure 27

The published structure of cis-$PtCl_2(C_6H_{11}NH_2)_2$ from reference 176.

square plane. A reexamination of the bond angles around platinum (cis, 151°; trans, 97°) suggested that the published structure[176] was closer to that of a distorted trans complex than a distorted cis complex. The formation of the trans analogues during attempts to crystallize cis-dichlorobis(cyclobutylamine-N)platinum(II) and cis-dibromobis(cyclohexylamine-N)platinum(II) should have been a clue to the actual solution. A detailed comparison of the structures of cis[176] and trans-dichlorobis(cyclohexylamine-N)platinum(II)[129] shows that the space group (Pbcn) and the cell parameters are the same and that the atomic positions of the cis form can be converted roughly into those of the trans form by the operation $x,y,z \rightarrow x,-y,\frac{1}{4}+z$ with the carbon atoms renumbered (C(6) → C(1), C(5) → C(2), C(4) → C(3), C(2) → C(5), C(3) → C(6)). Thus, the reported structure of the distorted "cis" complex is an incorrect solution of the trans structure caused by an incorrect choice of the platinum position based on the presumed symmetry of the molecule. In the space group Pbcn with Z = 4, the platinum atom must be placed on a special position, either on a two-fold axis $(0,y,\frac{1}{4})$ or an inversion centre (0,0,0 or $0,\frac{1}{2},0$). Because the compound was presumed to have cis configuration around the platinum, the two-fold axis was chosen rather than the inversion centre which would automatically require the complex to be trans.

The low toxicity of these compounds is not, therefore, caused by a distortion of the square plane around platinum.

A different explanation has been suggested by Rosenberg[177] and will be discussed in Section 5.2.3.

5.2.2 Cis-trans Isomerization:

Crystals had been obtained in our laboratory of a compound which was supposedly cis-dichlorobis(cycloheptylamine-N)platinum(II), but attempts to refine the structure gave unsatisfactory results. Following the discovery that the correct solution of the reported cis-dichlorobis(cyclohexylamine-N)platinum(II) structure showed it to be the trans analogue, the platinum atom of the complex formed with cycloheptylamine was placed on an inversion centre rather than a two-fold axis. The structure then refined satisfactorily as a trans complex.[131] Crystals of cis-dichlorobis(cyclobutylamine-N)platinum(II) were eventually obtained (Chapter 4.2), but not before repeated attempts at recrystallization had yielded the trans analogue. Attempts to obtain crystals of complexes with cyclohexylamine in the cis configuration around platinum with no solvent of crystallization also led to trans compounds in our laboratory (Section 4.3) and in others.[129] The preparation of trans complexes from a procedure which is expected to yield cis compounds gives rise to some interesting problems. The procedure is that which has been used to prepare samples of cis-amine platinum complexes used in animal tests which showed that cis complexes were active against tumors and trans were not. Three obvious

possibilities exist:

1) The cis preparation procedure actually gives the trans complex;

2) The cis preparation procedure gives a mixture of cis and trans complexes, but in the recrystallization procedure, the trans complex is less soluble and crystallizes first, or both crystallize, but the trans crystals are better formed and are thus automatically selected for study;

3) The procedure gives the correct cis isomer, but in the process of recrystallization, the cis complex is converted to the trans.

Explanation (1) seems unlikely. Trans complexes prepared by conventional procedures were physiologically inactive, whereas the compounds from the cis preparations showed good activity.[26] This could only occur if the conventional trans preparation gave a product other than the trans complex. Explanation (2) is possible. If this were the case, the cis complexes used in animal tests would have been diluted with the inactive trans complexes and would thus have a greater physiological activity than reported. Explanation (3) is also possible, but less likely considering the mild conditions of recrystallization. It will, however, be shown to be the correct explanation.

The single crystal X-ray structure characterization of both the cis and trans isomers of dichlorobis(cyclobutylamine-N)platinum(II) allowed the calculation of powder patterns

for each compound. The product at various stages of the preparative procedure was then examined by X-ray powder diffraction and the observed powder patterns compared to the two sets of calculated d-spacings. Diffraction patterns were taken for

1) the product isolated using the literature procedure before recrystallization;
2) the product from stage (1), recrystallized from DMF/0.1 N HCl;
3) the product from stage (1), recrystallized from acetone.

The diffraction patterns from compounds (1) and (2) were identical and matched the pattern calculated using the cell parameters of the cis complex. The powder pattern of compound (3) corresponded to that calculated from the cell parameters of the trans complex. The results from the crude product (labelled cis) and the sample recrystallized from acetone (labelled trans) are presented in Table 38. The results are unambiguous in showing that the cis complex is the product of the preparative procedure but the process of recrystallization from acetone has converted the cis to the trans isomer. Such an interconversion in DMSO has been suggested before on the basis of infrared spectral results.[178]

5.2.3 Blocking of Axial Sites around Platinum:

The postulated mechanism for renal toxicity involves coordination of the platinum to the sulphur atoms in the kidney tubules.[179] Rosenberg[177] suggested that the flexibility of

Table 38. Powder data and calculated d-spacings[#] for cis- and trans-$PtCl_2(C_4H_7NH_2)_2$

trans					cis				
hkℓ	d-spacing		I^*_{obs}	I^*_{cryst}	hkℓ	d-spacing		I^*_{obs}	I^*_{cryst}
	calc.	obs.				calc.	obs.		
100	7.69	7.6-7.8	77	85	020	10.23	9.9-10.4	100	100
011	6.30	6.2-6.4	95	92	002	5.17	5.05-5.2	47	32
$11\bar{1}$	5.12	5.1-5.2	26	34	022	4.61	4.5-4.6	20	32
111	4.66	4.6-4.7	100	100	130	4.22	4.1-4.2	18	17
002	4.27	4.3	10	33	042	3.63	3.6	7	20
120	3.99	3.97-3.99	43	19	062	2.85	2.84-2.85	9	15
200	3.85	3.83-3.86	36	58	132	2.82			10
102	3.54	3.54-3.56	25	62	024	2.50	2.5	9	7
$21\bar{1}$	3.43	3.42-3.44	30	35					
211	3.15	3.16-3.17	16	24					
$20\bar{2}$	3.07	3.06-3.07	18	38					
031	2.92	2.90-2.92	19	24					
131	2.69	2.68-2.70	40	39					
$22\bar{2}$	2.56	2.56	6	6					
$31\bar{1}$	2.46	2.46	5	12					
$21\bar{3}$	2.37	2.37	24	35					
040	2.33	2.32-2.33	27	46					
140	2.23	2.24	18	44					
004	2.14	2.14	10	25					
$10\bar{4}$	2.13			37					

Continued.....

Table 38 (Continued)

hkℓ	d-spacing calc.	d-spacing obs.	I^*_{obs}	I^*_{cryst}	hkℓ	d-spacing calc.	d-spacing obs.	I^*_{obs}	I^*_{cryst}
302	2.09	2.08-2.09	10	14					
$20\bar{4}$	1.98	1.99-2.01	21	29					
142	1.95	1.93-1.94	13	17					
242	1.76	1.75-1.76	15	22					
044	1.57	1.57-1.58	6	14					
$14\bar{4}$	1.57			18					
$24\bar{4}$	1.51	1.51	13	13					
144	1.51			12					

≠ The d-spacings were calculated from the single crystal unit cell parameters.

* I_{obs} represents the measured intensity from the powder photograph recorded using CuK_α radiation and scaled to $I_{max} = 100$. I_{cryst} is the intensity of the single crystal reflection recorded using MoK_α radiation and scaled to $I_{max} = 100$.

the rings - especially the larger ones - would allow orientation of carbon atoms so that the hydrogen atoms attached to them could protect the axial positions above and below the square plane, thus preventing coordination of the sulphur atoms.

All the structures with alicyclic amines bonded to platinum (Chapter 4) have platinum-carbon distances of less than 4.0 Å (Table 39) and thus there exists a definite possibility that the hydrogen atoms bonded to these carbon atoms are close enough to platinum to block the axial positions.

The fact that such an arrangement is seen in the solid state does not prove that similar arrangements exist in solution, but it is clearly possible and provides a reasonable explanation for the reduction in toxicity on coordination of alicyclic amines. Solution studies could be carried out with the use of the Nuclear Overhauser Effect in nmr to determine the internuclear distances between platinum and various protons.

5.2.4 Platinum-DNA Binding:

The only postulated mechanism for platinum-DNA binding about which the studies on alicyclic amine complexes of platinum could give information is Eichhorn's co-stacking postulate[65] (Section 1.4.2a). Eichhorn suggested monofunctional coordination of each of a pair of platinum-containing molecules to adjacent bases on a DNA strand so that the platinum complexes and bases are "co-stacked", but he did not suggest a reason for this contact.

Table 39. Closest platinum-carbon distances for complexes with alicyclic amines

Complex	Pt-C	Distance
cis-$PtCl_2(C_3H_5NH_2)_2$	Pt-C(1)	2.97
	Pt-C(2)	3.87
	Pt-C(4)	2.93
	Pt-C(5)	3.76
cis-$PtCl_2(C_4H_7NH_2)_2$	Pt-C(1)	3.06
	Pt-C(2)	3.66
	Pt-C(5)	2.94
	Pt-C(8)	3.48
trans-$PtCl_2(C_4H_7NH_2)_2$	Pt-C(1)	2.96
	Pt-C(4)	3.59
trans-$PtBr_2(C_6H_{11}NH_2)_2$	Pt-C(1)	3.03
	Pt-C(2)	3.42
trans-$PtCl_2(C_6H_{11}NH_2)_2$[a]	Pt-C(1)	3.11
	Pt-C(2)	3.54
$[PtCl_3(C_6H_{11}NH_2)]^-$	Pt-C(1)	3.05
	Pt-C(6)	3.38
cis-$PtCl_2(C_6H_{11}NH_2)_2$	Pt-C(1)	3.13
	Pt-C(6)	3.47
	Pt-C(7)	3.03
	Pt-C(12)	3.43

[a] Data from reference 129.

It can be shown why stacking of this type could occur for cis complexes, but not trans complexes. As shown in Figure 28, amine-Cl hydrogen bonding can occur easily for the cis complex, but not the trans. It is interesting to note that cis complexes do not show activity unless there is at least one hydrogen atom on the amine group (Section 1.2.2).

In all the cis complexes studied in Chapter 4, there were no platinum-platinum distances less than 4.0 Å. The square planes, however, were always arranged to give possible hydrogen-bonding contacts. If we consider the fact that the backbone of DNA is a spiral, Figure 28A could be rearranged to give Figure 28B where there is still one hydrogen bond holding the pair of molecules together in the cis complex, but no hydrogen bonds in the trans. The structures studied in this thesis do not support this model completely, nor do they disprove it, but the existence of these close contacts, at least in the solid state, suggest that the model should be considered.

5.2.5 Present Status:

All the compounds studied in Chapter 4 were obtained from attempts to make cis-$[Pt(am)_2X_2]$ complexes with alicyclic amines. With cyclobutylamine as the amine, the trans complex clearly resulted from the method of recrystallization, but the trichloro complex (Section 4.5) and the "isocyanide" (Section 4.6) were obtained from the crude reaction product.

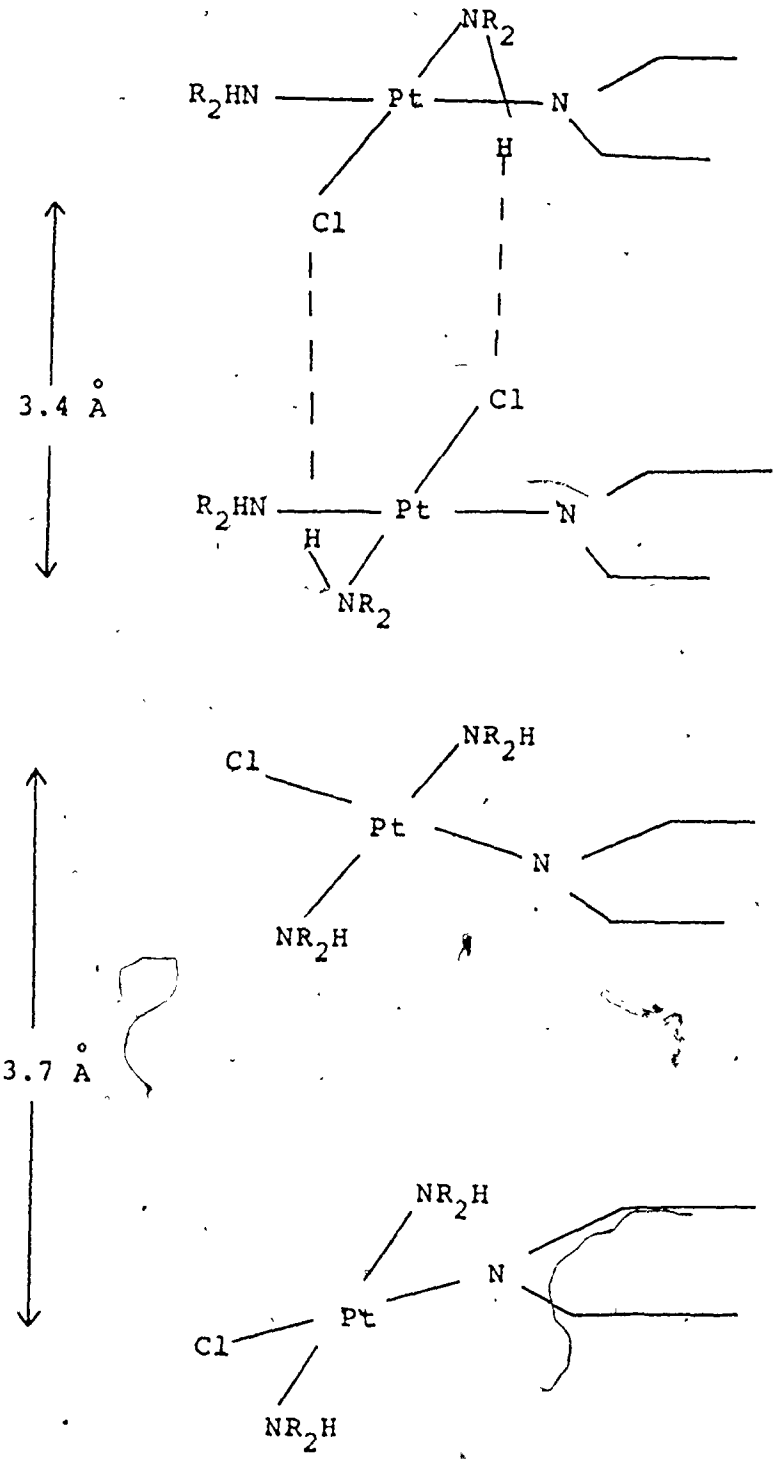


Figure 28A

Pairs of cis- and trans-$PtCl_2(NHR_2)_2$ molecules attached to adjacent bases on a DNA chain with the platinum atoms co-stacked.

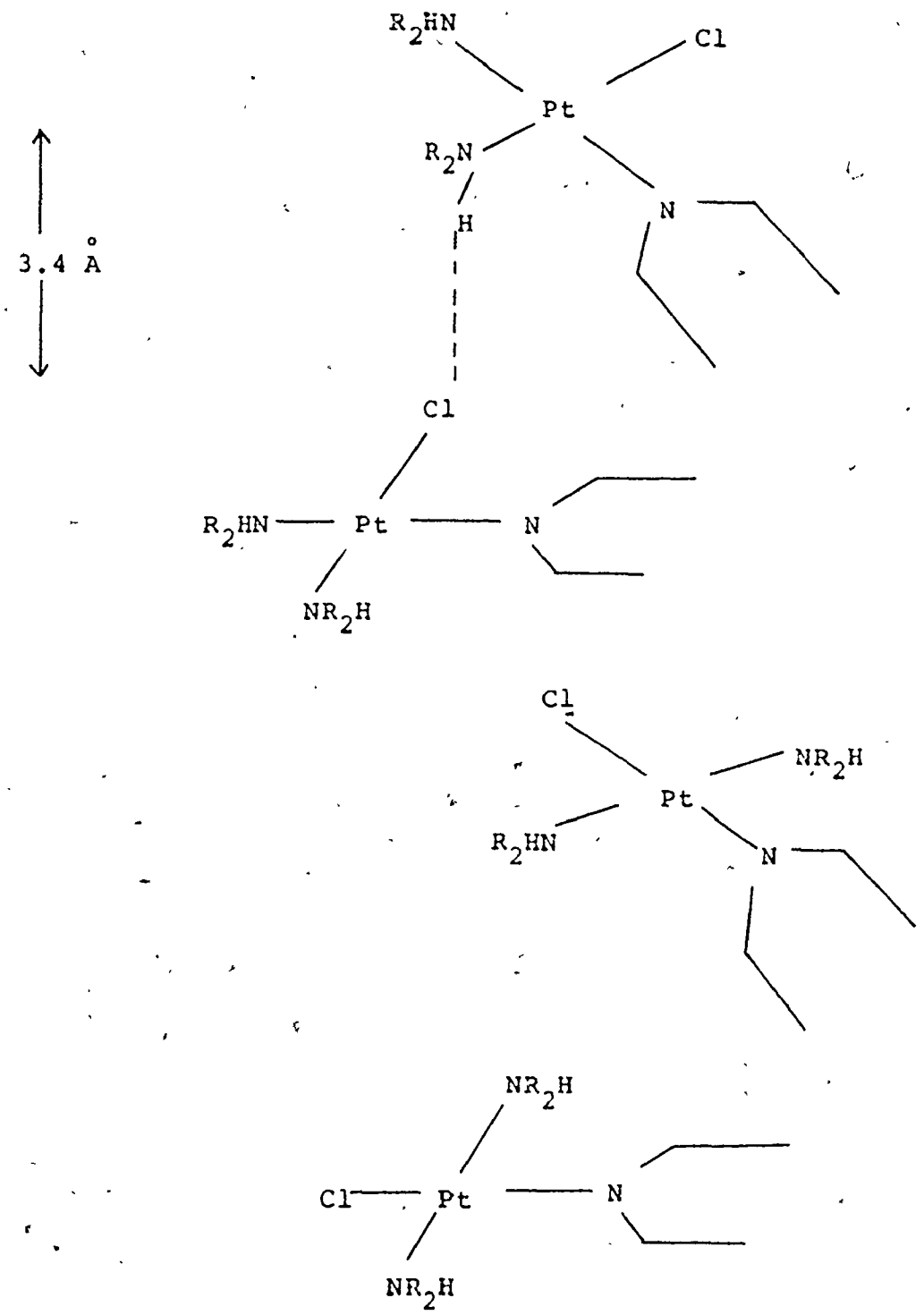


Figure 28B

Pairs of cis- and trans-$PtCl_2(NHR_2)_2$ molecules attached to adjacent bases on a DNA chain with DNA considered as a spiral.

The presence of such impurities in the compounds used for animal tests might lead to ambiguous results. Both spectral and powder data are needed for pure compounds to show that no cis-trans isomerization is taking place. Better purification methods should also be developed since the purity of the test material is vital.

X-ray and spectroscopic studies of pure cis-$[PtCl_2(C_5H_9NH_2)_2]$ and cis-$[PtCl_2(C_6H_{11}NH_2)_2]$ should be undertaken to provide accurate cell parameters and vibrational spectra for comparison. These would also serve to confirm whether any distortion of the square plane around platinum does exist or whether the ligands of all the complexes form a regular square plane as the studies here indicate.

CHAPTER 6

CONCLUSIONS

The major point made in this thesis is that the chemistry of platinum is not as simple as had been assumed previously. The aquation of cisplatin gave rise to hydroxo-bridged dimers; aquation at a pH low enough for formation of a monomer dihydroxo compound gave cis-dinitratodiammineplatinum(II). Studies of platinum complexes with alicyclic amines showed that a variety of products can be obtained from the crude reaction mixture, while recrystallization under fairly mild conditions can cause cis-trans isomerization.

These results can be directed at both the biochemist and the chemist. Most of the animal tests are performed by clinicians or biochemists. The compounds which are tested as drugs must be checked to determine unambiguously that they are pure compounds, i.e., not mixtures as in the first aquated cisplatin tests. They must also be the correct pure compounds (not pure trans when pure cis is needed). In order to check that their results are not inaccurate because of the starting compounds, the people doing the tests should interact with the chemists, who can determine the purity of the complex being tested.

The chemists themselves must also be careful. The

danger of preconceived ideas is very real. The existence of the dihydroxo-bridged dimer has caused reevaluation of the original animal test results and should cause reevaluation of the results obtained from reactions of aquated cisplatin with DNA and homopolymers of DNA bases. The so-called distortion of the cis-cyclohexylamine is another example of this danger. The compound was believed to be a cis isomer and, therefore, solved as a cis isomer. Once it was decided that platinum should be placed on a special position of the chosen space group, both possibilities, the two-fold axis (necessary for a cis complex) and the inversion centre (necessary for a trans complex) should have been tried. Consideration of both alternatives would have led to the correct solution.

The need for structural studies is also obvious. Once compounds have been purified and recrystallized, accurate cell parameters for powder data and good spectra of isomerically pure complexes can be stored for future reference.

Above all, the need for interdisciplinary cooperation stands out. The field of platinum anti-cancer drugs is wide and encompasses many areas of science. We cannot work unilaterally, but must cooperate. There is too much information, and as technology advances the method of gathering this information becomes more sophisticated until the person who understands more than is present in his own area is exceedingly rare. The only way to stay abreast of current knowledge

is to work, talk and argue with people whose area of expertise is different from our own, and in so doing, come to a better understanding.

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