STRUCTURAL STUDIES
OF PLATINUM COMPLEXES

BY

PIERRE PILON, B.Sc.

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OF PLATINUM COMPLEXES

TO KATHY

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AUTHOR: Pierre Pilon, B.Sc. (University of Guelph, Guelph, Ontario)

SUPERVISOR: Professor C. J. L. Lock

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ABSTRACT

The molecular and crystal structures of platinum complexes relevant to the cancer research field are investigated. The complexes whose structures have been studied, encompass many aspects of the chemistry of platinum(II): the preparation of starting materials, the solvolysis of the complexes in different solvents and the chemistry of the complexes with DNA bases. The important structural features of the complexes are outlined and, where possible, the molecular structures are related to previous information on the complexes which is available from animal studies, solution work or the interaction of the complexes with the DNA macromolecule.

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ABBREVIATIONS AND DEFINITIONS

metastasis	transference of bodily functions, disease, etc., from one part or organ to another
DDP	dichlorodiammineplatinum(II)
PtA_2X_2	platinum(II) complexes where A is an amine and X is a leaving group
1,2-dac	1,2-diaminocyclohexane
E. coli	*Escherichia coli*
DNA	deoxyribonucleic acid
UV	ultraviolet
G	guanine
C	cytosine
A	adenine
T	thymine
RNA	ribonucleic acid
cytotoxicity	toxicity to the cell
GpG	guanylyl (3'-5') guanosine
d(GpG)	deoxy[guanylyl(3'-5')guanosine] The same nomenclature is used for longer polynucleotides.
Nmr	nuclear magnetic resonance
ν	frequency

9-Et-G-H	N(1)-deprotonated 9-ethylguanine
9-Et-G	9-ethylguanine
1-MeC	1-methylcytosine
1-MeT	1-methylthymine
Å	Angstrom
trans-1,2-dac trimer	cyclo-tri-μ-hydroxotris[trans-1,2-diaminocyclohexane platinum(II)]nitrate hydrate
cis-1,2-dac $PtCl_2$	tris[cis-dichloro(cis-1,2-diaminocyclohexane platinum(II)]hydrate
cis-1,2-dac $PtBr_2$	cis-dibromo(cis-1,2-diaminocyclohexane)platinum(II)
λ	wavelength
h	hour
en	ethylenediamine
DMSO	dimethylsulfoxide
DMF	dimethylformamide
K	Kelvin
1-MeU-H	1-methyluracil anion, deprotonated at N(3)
PtN_4	best least squares plane through 4 nitrogen atoms attached to a central platinum atom

CHAPTER ONE

BACKGROUND

1.1 INTRODUCTION

Chemotherapy is now widely used for cancer treatment. It has the advantage over surgery and radiation therapy of being effective against tumours which have metastatized. Originally, most chemotherapeutic drugs were organic agents. In 1969, Rosenberg and his co-workers discovered that cis-dichlorodiammineplatinum(II) (cis-DDP) (Figure 1) was an effective anti-tumour agent against implanted cancerous cells in mice.[1] Since then, the number of inorganic complexes tested for anti-tumour activity has increased tremendously;[2] the majority of the studies carried out has involved cis-DDP and platinum-containing analogues.

Three major areas of research involving platinum anti-cancer drugs have been pursued:

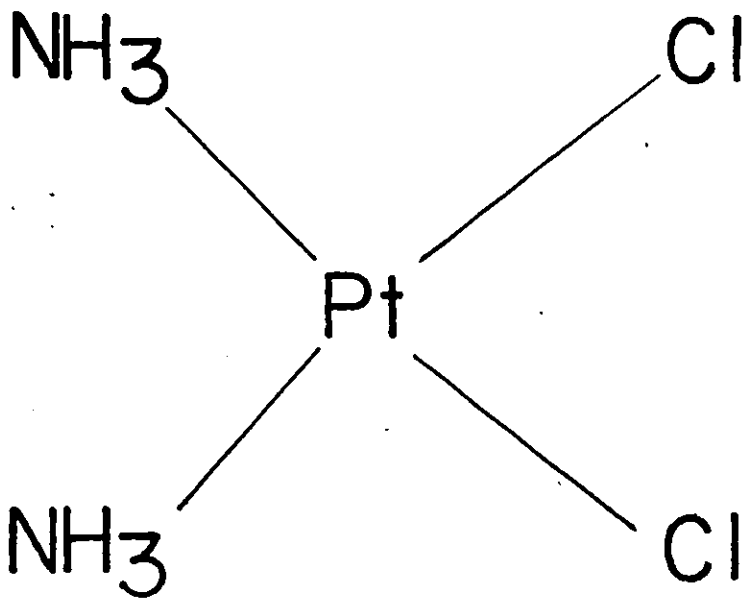
(1) Animal tests and human clinical trials of cis-DDP, alone or in combination with other chemotherapeutic agents to achieve better "cure" rates.

(2) Animal tests of platinum-containing analogues of cis-DDP (second-generation drugs) to obtain less toxic and more potent drugs.

(3) The study of the interaction of the drugs with their biological target to elucidate their mechanism of action.

Figure 1

Structure of cis-dichlorodiammine platinum(II) (cis-DDP)



This chapter is a review covering these three areas of research. The remaining chapters will deal with the structure determination of complexes involved in the last two areas.

1.2 ANIMAL STUDIES AND CLINICAL ASPECTS OF cis-DDP

Extensive investigations have shown that cis-DDP is an effective anti-tumour agent against a broad spectrum of cancer types.[3] The results of the animal tests prompted researchers to use cis-DDP in terminally ill patients. Early studies indicated that the long-term use of cis-DDP in man was prohibited by the high toxicity of the drug, particularly in causing kidney damage.[4]

Research advances in the administration of cis-DDP reduced the kidney toxicity of the drug without altering its activity.[5,6] Also, results of combination chemotherapy in mice showed that cis-DDP could act additively or even synergistically with a number of other chemotherapeutic agents.[7] Combination chemotherapy involves the administration of mixtures of anti-cancer agents which are active against the same type of cancer but show different toxicities. Thus it was possible to lower the dose of cis-DDP when administered with other drugs and therefore lower the toxicity.

The new methods of administration of cis-DDP and the use of combination chemotherapy permitted the continuation of clinical trials. Today, cis-DDP is used in combination chemotherapy in humans affected by ovarian and testicular cancer. The remission rate for ovarian cancer varies between 38% and 83%[8] while that for

testicular cancer is greater than 70%.[9,10]

1.3 SECOND - GENERATION DRUGS

1.3.1 Hydrolysis of PtA_2X_2 complexes

The search for cis-DDP analogues was originally undertaken to find platinum-containing complexes which would be less toxic, more potent and more versatile than the parent drug. Another impetus for this type of work was the discovery that certain types of tumours can become resistant to cis-DDP.[3] Because cis-DDP has two ammine ligands and two anionic ligands, complexes of the type PtA_2X_2, where A is an amine and X is a leaving group, have been surveyed extensively.

Kinetic studies of cis-$(NH_3)_2PtCl_2$ indicate that the platinum to nitrogen bond is inert and that the chloride ion is the reactive ligand [11,12]; this fact seems to dominate the chemistry of complexes of the type PtA_2X_2. Substitution reactions of platinum(II) complexes, as shown in equation 1.1

$$PtL_3X^n + Y^y \longrightarrow PtL_3Y^{n'} + X^x \quad (1.1)$$

generally follow the rate law:

$$\text{rate} = (k_1 + k_2[Y])([PtL_3X^n]) \quad (1.2)$$

where k_1 reflects the solvolysis pathway

$$PtL_3X^n + H_2O \xrightarrow{\text{slow}} PtL_3(H_2O)^{n+x} + X^x$$
$$PtL_3(H_2O)^{n+x} + Y^y \xrightarrow{\text{fast}} PtL_3Y^{n'} + H_2O \quad (1.3)$$

and k_2 is the second order rate constant appropriate for a bimolecular process where Y^y attacks the complex as X^x departs.[13] Because the

chloride ion concentration is high in the plasma (103 mM) the complexes remain unchanged, are neutral, and therefore can pass through the cell membrane. Once the drug enters the cell, because the chloride ion concentration is much lower (4 mM), hydrolysis products can form. This is suggested from substitution reactions of platinum complexes in dilute aqueous solutions; under these conditions, reactions of platinum(II) always proceed via a hydrolysis step (i.e. $k_1 > k_2$ in equation (1.2)).[12,14]

An overall reaction scheme for platinum(II) anti-tumour agents is shown in Figure 2. The drug (I) is administered as an uncharged species which remains intact until it enters the cell and undergoes hydrolysis. Complex II then reacts with the biological target, alone or in combination with other agents to form III.

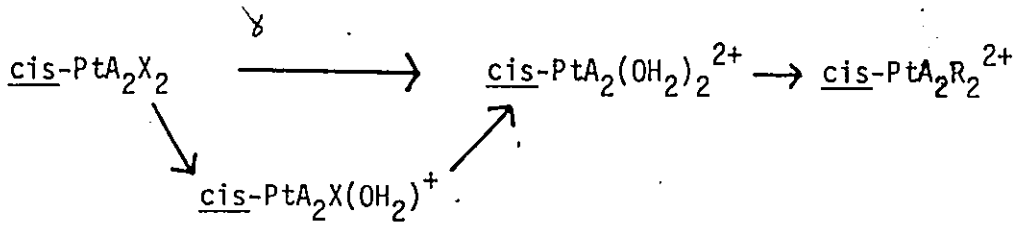
1.3.2 Structure - activity relationships

The search for second-generation drugs has provided the groundwork for relationships between the structure and the activity of inorganic chemotherapeutic agents. Complexes with metal centres other than platinum are active against certain cancer types; yet, the most effective drugs are those containing platinum.[16] Thus complexes of the type PtA_2X_2 have been studied most extensively.

Modifications in square planar diamine platinum(II) complexes can be accomplished in three ways: variations in the amine ligands, in the leaving group or of the geometry of the ligands around the platinum atom, i.e. the cis or trans arrangement shown in Figure 3.

Figure 2

Overall mechanism of action of platinum drugs[a]



A = amine ligand

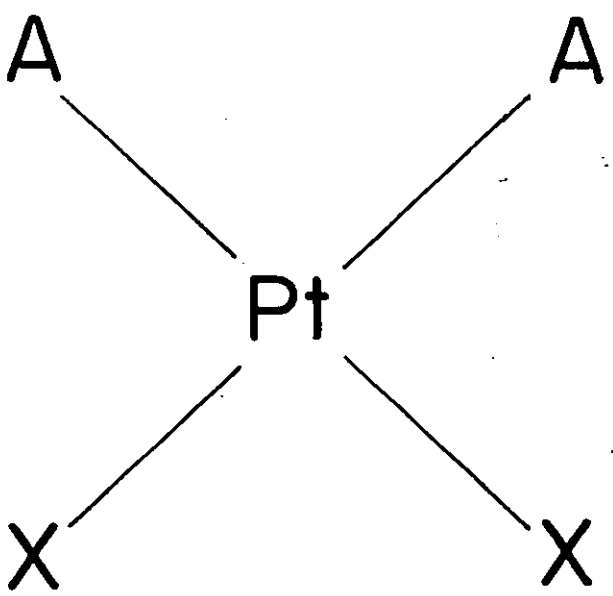
X = leaving group

R = ligand present on the biological receptor

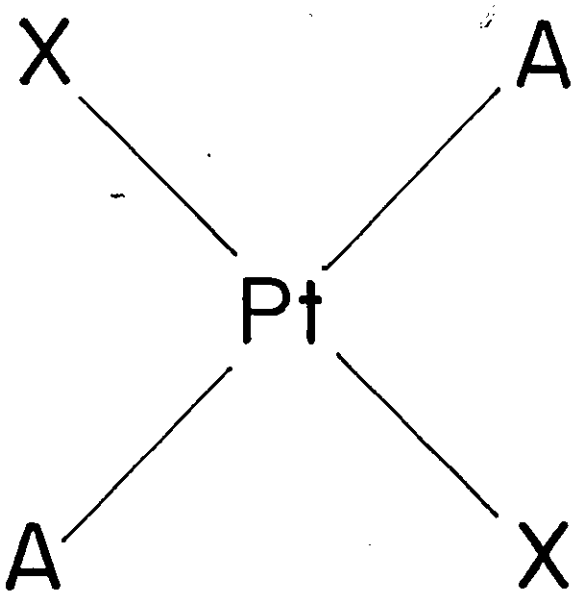
[a] adapted from reference 15

Figure 3

Geometric isomers of PtA_2X_2 complexes



cis



trans

The most important indication of a structure-activity dependence came from studies on the geometric isomers. For any PtA_2X_2 complex where the cis isomer is active against a certain tumour type, the corresponding trans isomer has no activity (Table 1).

Furthermore, charged species are never active, with the exception of platinum 'blues which are obtained from the reaction of aquated cis-DDP and pyrimidine-2,4-dione ligands, such as uracil or thymine.[18,19] Neutrality seems required for the penetration of the cell wall by the drug for subsequent reaction with the biological target.[20]

Varying the leaving group of cis-PtA_2X_2 affects the activity of the complex (see Table 2) in a manner reflecting the leaving ability of ligands in the reaction:

$$Pt(dien)X^+ + py \longrightarrow Pt(dien)(py)^{2+} + X^- \quad (1.4)$$

where dien is diethylenetriamine and py is pyridine. The order of leaving ability is $NO_3^- > Cl^- > Br^- > I^- > SCN^- > NO_2^-$.[14] The relationship between the activity of cis-PtA_2X_2 with different X groups and the leaving ability of ligand X should result if the rate-determining step in the mechanism of action of the anti-tumour platinum drugs is the hydrolysis of the complex. The order of activity expected from the reaction with pyridine is followed for Cl^-, Br^- and I^- (Table 2). The thiocyanate and nitrite complexes showed no activity; they contain ligands which are poor leaving groups. Although the complexes enter the cell, they cannot hydrolyze and show no activity since they cannot react with the biological target. The nitrate complex showed different

Table 1

Activity of cis-PtA_2X_2 and trans-PtA_2X_2 versus Sarcoma 180 in swiss white mice [a]

Complex	T/C [b]
cis $(NH_3)_2PtCl_2$	1
trans $(NH_3)_2PtCl_2$	83
cis $(NH_3)_2PtBr_2$	30
trans $(NH_3)_2PtBr_2$	110
cis $(C_2H_5NH_2)_2PtCl_2$	14
trans $(C_2H_5NH_2)_2PtCl_2$	106

[a] Values in the table are from reference 17.

[b] $T/C = \frac{\text{weight of a treated tumour}}{\text{weight of tumour in control animal}} \times 100\%$,
T/C values less than 50 are considered significant.

Table 2

Activity of cis-PtA_2X_2 complexes against Sarcoma 180 tumour [a]

X	T/C
NO_3^- in water	54
NO_3^- in saline	8
Cl^-	1
Br^-	30
I^-	110
SCN^-	70
NO_2^-	99

[a] Values are from reference 21

levels of activity: when administered in saline, the activity was similar to that of cis-DDP. This occurs because the nitrate anion, a good leaving group, is replaced by a chloride ion before the drug penetrates the cell wall. When administered as an aqueous solution, the nitrate complex was toxic. Later work by Rosenberg (personal communication) showed that cis-$(NH_3)_2Pt(NO_3)_2$ was more active than cis-DDP. The toxicity previously seen is caused by hydroxo-bridged species formed in the hydrolysis step (see Chapter 4).

Because the amine ligand has very little effect on the reaction rate of substitution reactions of platinum(II) complexes,[22] it was originally believed that it would have a secondary role in determining the activity of the drugs. As seen in Table 3, the amine group plays an important part in the structure-activity relationship. There are general trends in activity with variations in amine ligands. Firstly, the most effective complexes are those containing a primary amine, with the exception of the alicyclic amines. In some cases, complexes with lesser alkyl- substituted amines are active against several tumour systems while those with more substituted amines are only active against the most sensitive systems.[24] Secondly, the therapeutic index for the complexes containing alicyclic amines increases with ring size, up to the six-membered ring. The increase in the therapeutic index is caused by a decrease in the toxicity of the drugs and not by their greater efficacy. Finally, when the platinum atom is bound to a tertiary amine, all activity of the drug is lost.

In summary, the following requirements must be met in order

Table 3

Anti-tumour activity of cis-PtA_2X_2 complexes against ADJ/PC6 tumour

Complex	LD_{50} [a]	ID_{90} [b]	T.I. [c]
$(NH_3)_2PtCl_2$ [d]	13.0	1.6	8.1
$(CH_3NH_2)_2PtCl_2$ [d]	18.5	18.5	1.0
$(CH_3CN)_2PtCl_2$ [d]	27.0	>27.0	<1.0
(▷ NH_2)$_2PtCl_2$ [d]	56.6	2.3	24.6
(◇NH_2)$_2PtCl_2$ [d]	90	2.9	31.0
(▱NH_2)$_2PtCl_2$ [d]	565.4	2.4	235.7
(⬡NH_2)$_2PtCl_2$ [d]	>3200	12.0	>267
(⬡NH_2)$_2PtCl_2$ [e]	1000	7.7	130
(⬡NH_2)$_2PtCl_2$ [e]	660	230	2.9

[a] LD_{50} is the dose required to kill 50% of the test animals

[b] ID_{90} is the dose required to cause tumour regression in 90% of the test animals

[c] T.I. = $\frac{LD_{50}}{ID_{90}}$, therapeutic index

[d] Values are from reference 20

[e] Values are from reference 23

to prepare active anti-cancer platinum drugs: the complex must be neutral, and have two non-tertiary amine ligands and two labile groups in the cis configuration. The most active complexes have labile groups of intermediate leaving ability. When bulky amines are present, the toxicity of the complex is lowered.

Of all the second-generation drugs tested, a few have been deemed worthy of advancing to phase I clinical trials. One of these is the drug containing 1,2-diaminocyclohexane as the amine ligand.

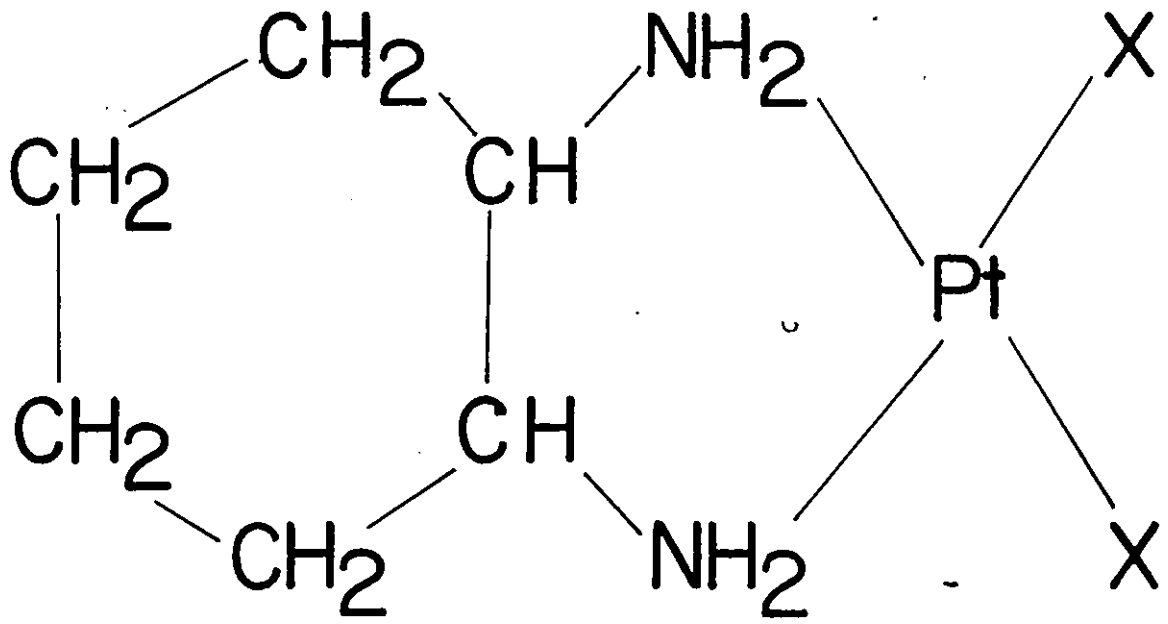
1.3.3 1,2-diaminocyclohexane platinum complexes

Platinum complexes of 1,2-diaminocyclohexane (1,2-dac) (Figure 4) fulfill the requirements needed for a good second-generation drug: in animal tests platinum drugs containing the 1,2-dac ligand are more potent than the parent drug against many tumour types;[25-35] they have low nephrotoxicity and show no serious side effects[35-37], and are active against tumour types which have become resistant to cis-DDP.[35,38-41] Combination chemotherapy using (1,2-dac) platinum(II) complexes shows synergistic action with a variety of other agents.[26,27,33,34,42-45] Thus, (1,2-dac) platinum compounds have been identified as potential second-generation drugs for clinical trials.[25,29,37,46]

The early work with 1,2-diaminocyclohexane platinum drugs was carried out on compounds containing a mixture of isomers of the ligand; it was not realized that the amine could exist in three isomeric forms: cis and the two trans configurations, RR and SS. In 1977, it was shown that complexes of the separated isomers behaved differently

Figure 4

Structure of 1,2-diaminocyclohexane platinum(II) complexes



physiologically.[47] As a result, several studies have concentrated on the activity of complexes of the stereoisomers of the ligand.[48-50] The first structural determination of a platinum complex containing a separated isomer of 1,2-dac will be discussed in Chapter 3.

1.4 PLATINUM COMPLEXES - DNA INTERACTIONS

The first indication that the interaction of platinum complexes with DNA is the lesion responsible for their anti-tumour activity was the discovery that low concentrations of cis-DDP inhibit the cell division in E. coli without affecting the growth rate of the bacteria; this results in filamentous growth.[51] The same effect on bacterial cultures has been observed with other agents [52,53] and is thought to be caused by the inhibition of DNA synthesis.[52,54,55]

Active platinum complexes have the ability to cause phage DNA to be released and phage particles to be synthesized in lysogenic strains of E. coli.[56] The release of phage DNA is usually a rare event but agents which react with DNA can cause this effect to occur. Studies of the interaction of cis-DDP with DNA, RNA and proteins indicate that low doses of the drug selectively inhibit DNA synthesis;[57] high doses of the drug inhibit the synthesis of all three components but only DNA synthesis is prevented irreversibly.[58] In its interaction with the SV40 virus, cis-DDP attacks the viral DNA rather than the protein coating.[59] Active anti-cancer platinum complexes are carcinogenic,[60] mutagenic[61-65] and affect the repair mechanism of DNA in certain types of cells, suggesting that DNA is the biological

target of the drugs.[66]

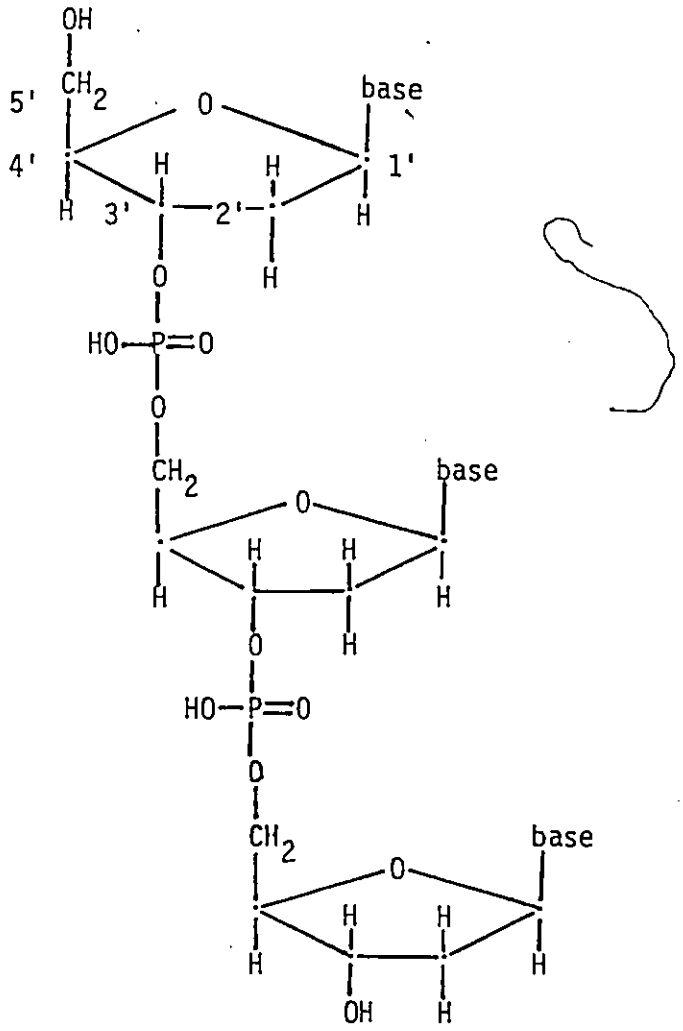
1.5 PLATINUM - DNA BASES INTERACTIONS

DNA is a macromolecule made up of a backbone of phosphate groups and ribose sugars joined together by phosphodiester bridges (Figure 5). Attached to this backbone are the four DNA bases, guanine, adenine, thymine and cytosine, shown in Figure 6. The purine bases are bonded to the sugar moiety through N9 and the pyrimidine bases bind through N1. It has been argued that there are three general areas which the platinum drug can attack.[13] The phosphate groups and ribose sugars forming the backbone have oxygen atoms which do not have a strong affinity for platinum. The DNA bases on the other hand, offer the most likely sites of attack for the platinum complexes. Some positions on the DNA bases are not easily accessible however since they form hydrogen-bonded pairs on the inside of the molecule. The most open position is the N7 of the purine bases which is not involved in hydrogen bonding (Figure 7).

UV absorption spectroscopy has been used to monitor the reaction of platinum complexes with DNA. The reaction caused a shift in the absorption band associated with the bases of DNA while the bands attributed to the phosphate and ribose groups remained unchanged; this points to the DNA bases as the site of attack of the drug.[67,68] The platinum complexes react preferentially with G - C rich regions of DNA;[69] this would not be expected to occur if the platinum atom were bonding to the phosphate or ribose moieties.

Figure 5

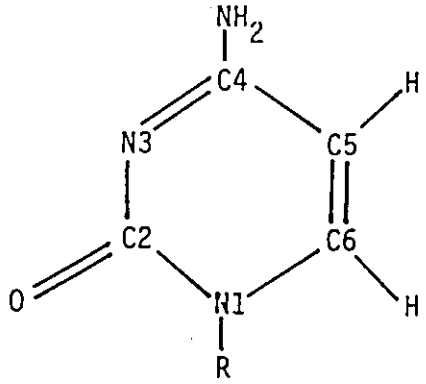
Covalent backbone structure of deoxyribonucleic acid (DNA)



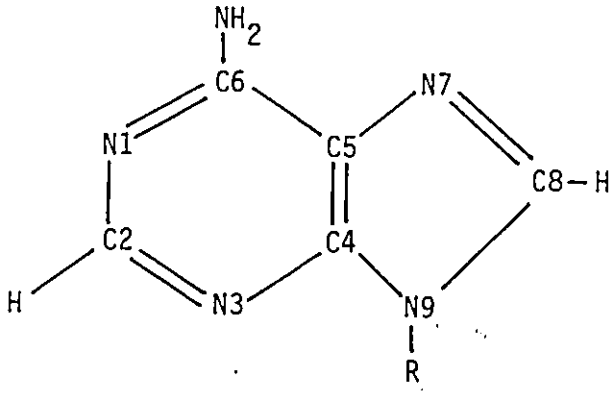
3'

Figure 6

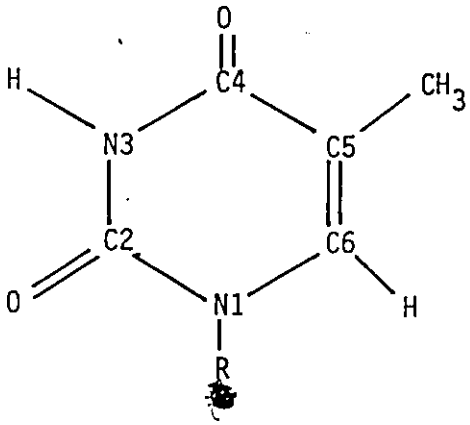
Labelling and numbering of DNA bases



Cytosine

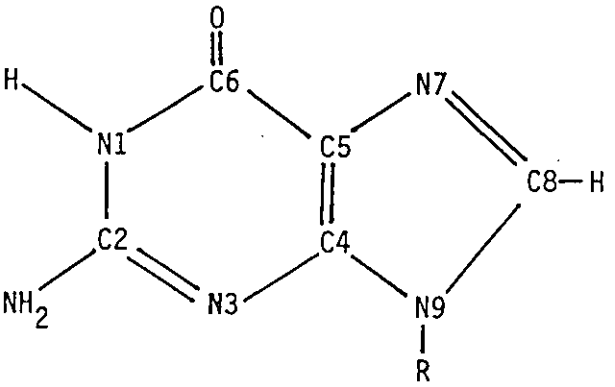


Adenine



Thymine

Pyrimidine Bases



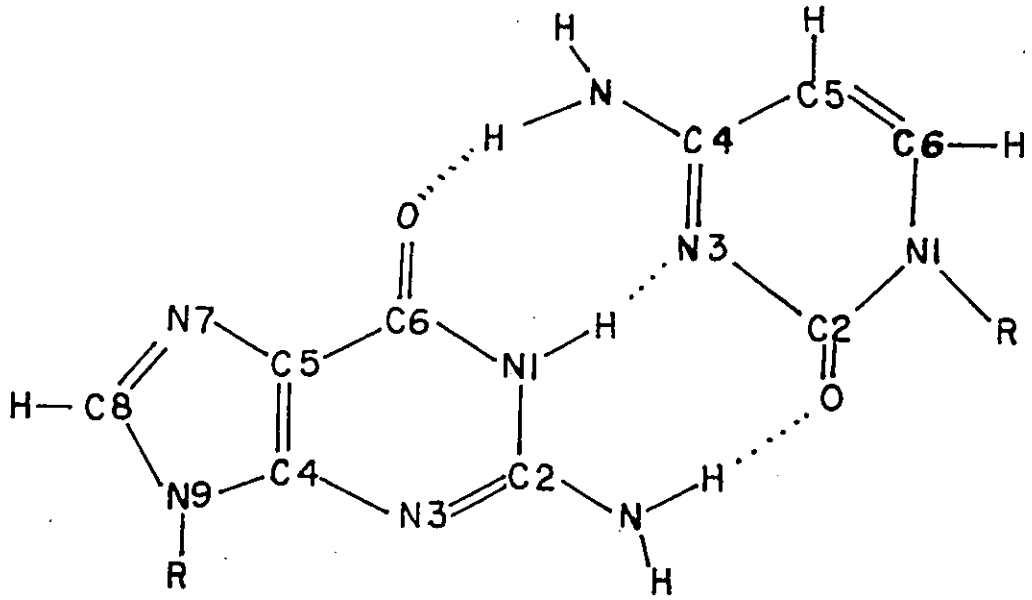
Guanine

Purine Bases

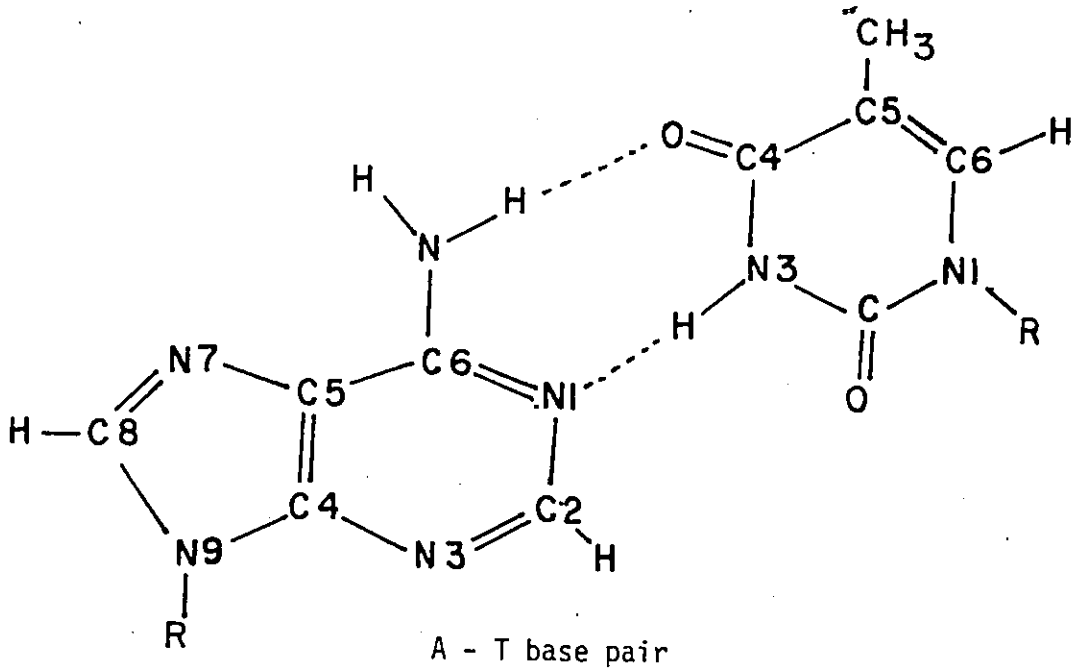
R denotes the position to which the backbone is attached

Figure 7

Watson - Crick base pairs in DNA



G - C base pair



A - T base pair

Theoretically, there are many nucleophilic sites on the DNA bases which a positively-charged platinum complex could attack. These are, at neutral pH (refer to Figure 6): The N7 and O6 atoms of guanine, the N7 and N1 positions of adenine, the O2 and N3 atoms of cytosine and the O2 and O4 atoms of thymine in its keto form. If the pH is raised, more nucleophilic sites become available: N1 and N2 of guanine, N6 of adenine, N4 of cytosine and N3 of thymine.

Experimentally, with model complexes of ethylated or methylated bases, with nucleosides, nucleotides and polynucleotides, the interactions of platinum complexes with many of the ring positions have been observed in solution and in the solid state. For N9-blocked guanine and its derivatives, the bonding of platinum has been observed to N7 only.[70-88] Adenine forms bonds at N7,[82,89-91] and at N7 and N1 where the adenine molecule bridges two platinum atoms.[92] Reactions of platinum complexes with N1 blocked cytosine have yielded bonds to platinum at the N3 position,[82,84,93-99] and at the N3 and the deprotonated N4 positions, where cytosine bridges two platinum atoms.[100] Studies with 1-methyluracil or 1-methylthymine show attack of the platinum at N3[101] and bridging of platinum atoms by the ligand through N3 and O4.[102-105] When the thymine or uracil base is not blocked at N1, this position is the preferred site of attack of the platinum atom.[93,106]

Although there are many good nucleophilic positions on the bases, the reaction of a mixture of the nucleosides with platinum complexes suggests that the guanine base reacts more readily than

the others in a competitive environment.[107] For this reason, the bonding of the platinum complexes to the N7 position of guanine is regarded as the primary lesion on DNA.

1.6 POSSIBLE MECHANISMS OF ACTION OF PLATINUM ANTI - TUMOUR DRUGS

Numerous mechanisms of action have been proposed to account for the activity of platinum anti-cancer drugs. The suggested mechanisms must consider the results of the structure-activity research previously mentioned. The difference in activity between the cis and trans isomers of $(NH_3)_2PtCl_2$ cannot be linked to their ability to penetrate cell membranes or to react with biological acceptors; the trans isomer reacts with DNA, RNA and protein to a greater extent than its cis counterpart.[108] The major difference between the two isomers is the distance between the two leaving groups and thus, the distance between any two incoming ligands(Figure 8). The cis platinum complexes could therefore chelate to DNA in a manner which is not possible for the trans isomer. The variation in chelating behaviour of the two isomers, based on internuclear distances, has given rise to three possible mechanisms of action; these differ in the way in which DNA chelates to cis-platinum complexes (Figure 9). The interstrand crosslink involves the chelation of DNA to platinum through atoms on separate strands of the macromolecule. The intrastrand crosslink occurs via chelation of the platinum atom by two ligands on the same strand of DNA. Finally, bifunctional bonding could occur through two atoms on the same DNA base.

Figure 8

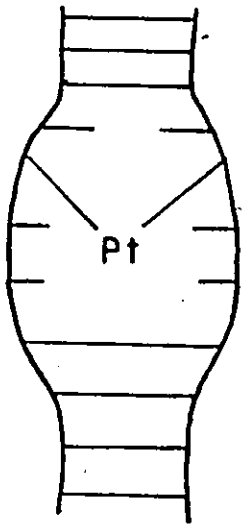
Bonding of cis and trans isomers of platinum complexes

cis trans

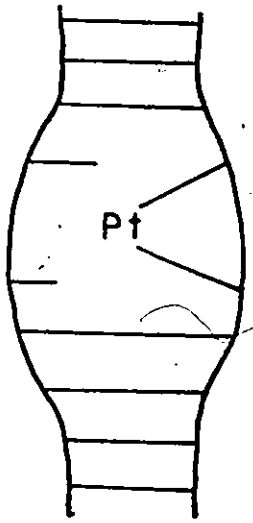
The platinum - R distance is given as "r ". Since the angles around the platinum atom in square-planar complexes are approximately 90°, the distance between R groups in the cis complex is $\sqrt{2r^2}$ while that in the trans complex is 2r.

Figure 9

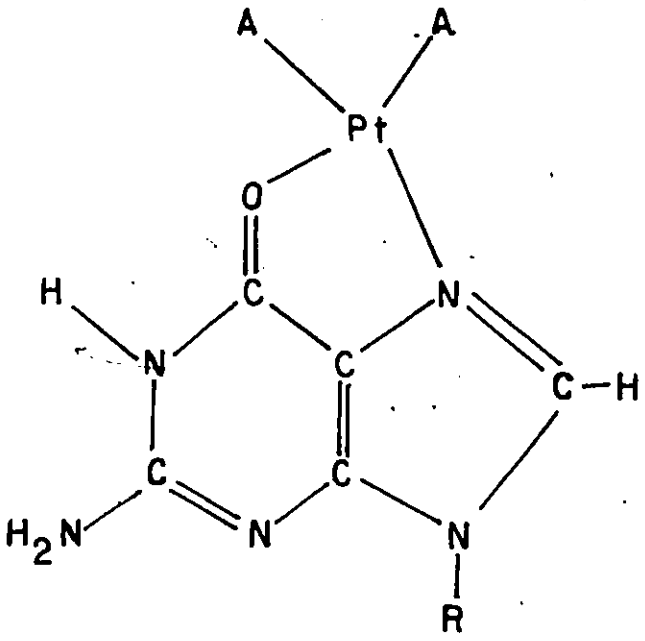
Different types of bifunctional bonding of DNA to cis-platinum complexes



a) Interstrand crosslink



b) Intrastrand crosslink



c) N7 - O6 chelation

Two other mechanisms of action have been postulated. The first one deals with the stacking of cis-platinum complexes 3.4 Å apart in the solid state; this distance is the same as that separating the bases in helical DNA. The second mechanism of action involves the facile deprotonation of guanine at N1 after platination at the N7 position; the loss of the proton at N1 would interfere with the hydrogen-bonding pattern in DNA(refer to Figure 7).

The remainder of this section will review the evidence obtained for each postulated mechanism of action of the platinum drugs.

1.6.1 Interstrand crosslink

A qualitative correlation between the cytotoxicity of platinum complexes and their ability to form interstrand crosslinks has been established. In vivo, cis-DDP forms approximately ten times more interstrand crosslinks than trans-DDP;[108,109] similar results were obtained by Zwelling and his co-workers.[110] Their conclusions are reported here briefly: both cis and trans-DDP form interstrand crosslinks and there is a correlation, in both cases, between the survival of cell colonies and the amount of interstrand crosslinking; the dose required to get the same amount of crosslinking with trans-DDP is ten times higher than that required for cis-DDP. Reactions of thiourea with cell colonies which have been incubated with platinum(II) complexes confirm the correlation between crosslink formation and cytotoxicity: thiourea is an avid ligand for platinum(II) and is thought to prevent crosslink formation by reacting with platinum

complexes which are monofunctionally bound to DNA;[110] crosslink inhibition and survival enhancement of cell colonies depend in a similar manner on the thiourea concentration and on the time interval between platinum drug and thiourea treatment.

A number of studies have shown that interstrand crosslinks account for only a small fraction of the total drug-DNA products.[111-115] Harder [116] studied the denaturation and renaturation of DNA after reaction with cis-DDP and suggested that there are at least two types of interactions present. The first type aids the renaturation of DNA; this could involve an interstrand crosslink, helping to keep the complementary strands in close proximity. The second type, which destabilizes the DNA helix, could be one of the other two crosslinking models.

1.6.2 Intrastrand crosslink

The intrastrand crosslink is one of the most attractive hypotheses for the mechanism of action of the platinum anti-tumour drugs; it involves the binding of the platinum atom to two adjacent guanine bases on the same strand of DNA. Indirect evidence for this model includes the result that shows preferred binding to GpG sequences by cis-platinum complexes, as evidenced by the unexpectedly large buoyant density exhibited by poly(dG)·poly(dC) nucleotides when reacted with cis-DDP.[117] Platinum drugs alter the enzymatic digestion of DNA at GpG sequences[118-120] and inhibit the interaction of intercalating agents with DNA.[121,122]

N7-N7 chelates to the platinum atom by GpG,[73] d(GpG) [77] have been observed in solution using proton Nmr spectroscopy. The same type of interaction has also been observed in longer polynucleotides, for example d(CpCpGpG) [85] and $[d(ApGpGpCpCpT)]_2$.[75]

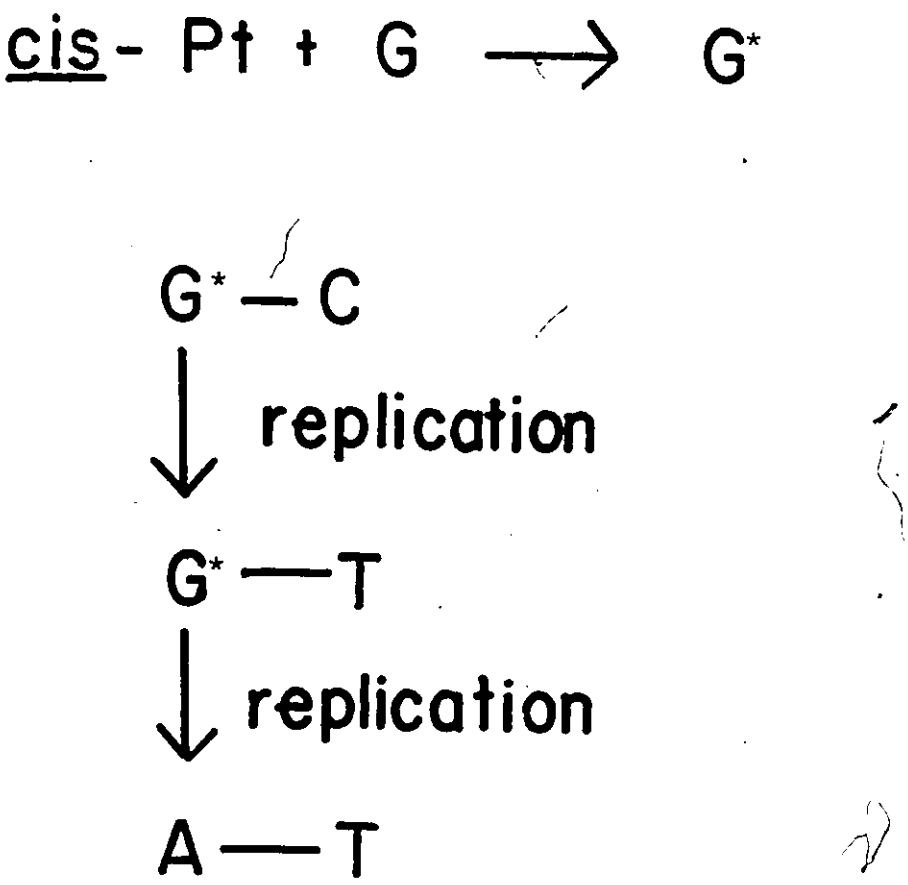
This mechanism of action will be investigated in more detail in Chapter 5.

1.6.3 N7 - O6 chelation

This mechanism of action has received much attention because chelation of a guanine molecule through the N7 and O6 positions involves one of the normal hydrogen-bonding positions of the base in DNA (refer to Figure 7). It has been argued [123] that chelation of the platinum atom would disrupt the hydrogen bonding pattern seen in native DNA and could eventurally lead to a guanine - thymine base pair. The scheme shown in Figure 10 shows how a G-C base pair in native DNA would become an A-T pair after reaction with a platinum drug and replication of the platinated DNA. This mechanism of action, leading to base mispairing and eventual cell death, would be similar to that involved when methylating agents interact with DNA; [123,124] these agents, which are known carcinogens, methylate the O6 position of guanine and interfere with the hydrogen bonding of guanine to cytosine (Figure 11a). The same type of G-T base pair can be obtained when a guanine moiety is deprotonated at N1 (Figure 11b). It has been shown however that deprotonation at N1 of guanine is facilitated by a simple coordination of the N7 position of the DNA base to platinum (see below

Figure 10

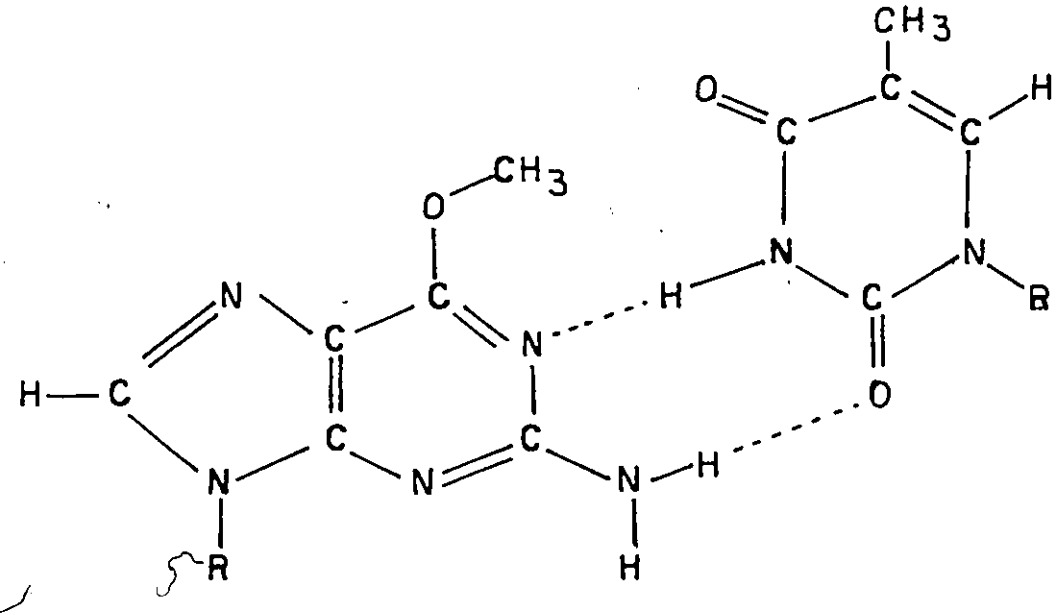
Reactions leading to base substitutions in DNA[a]



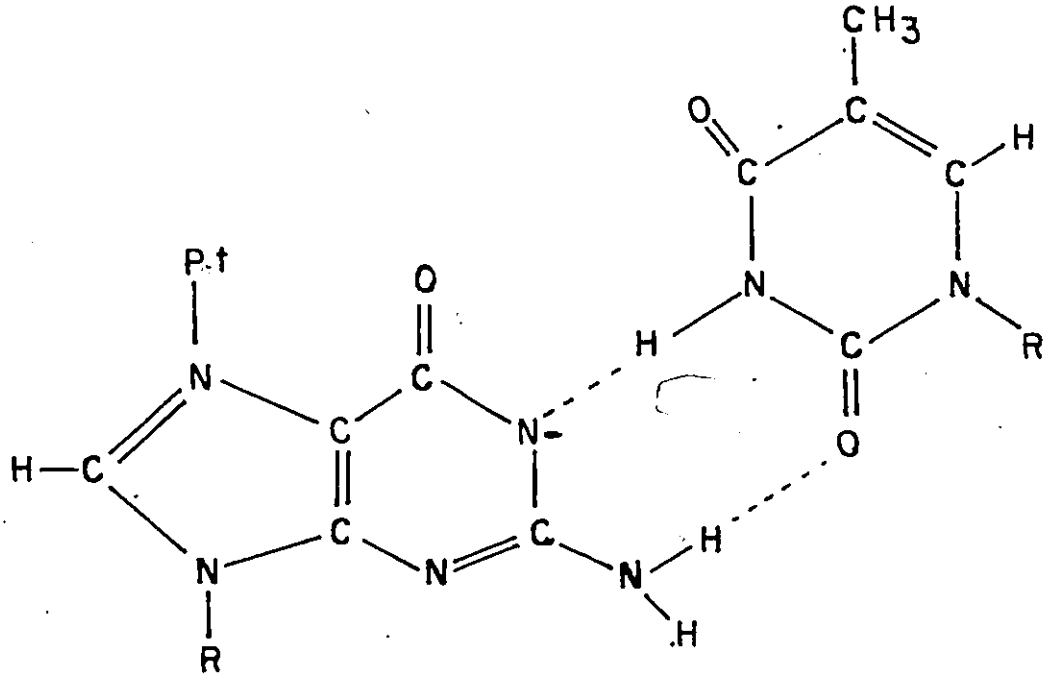
[a] From reference 123

Figure 11

G - T base mispairing



a) upon methylation at O6 of guanine



b) upon platination at N7 and deprotonation at N1 of guanine

and Section 1.6.4). This could lead to G-T base mispairing without chelate formation at N7 and O6.

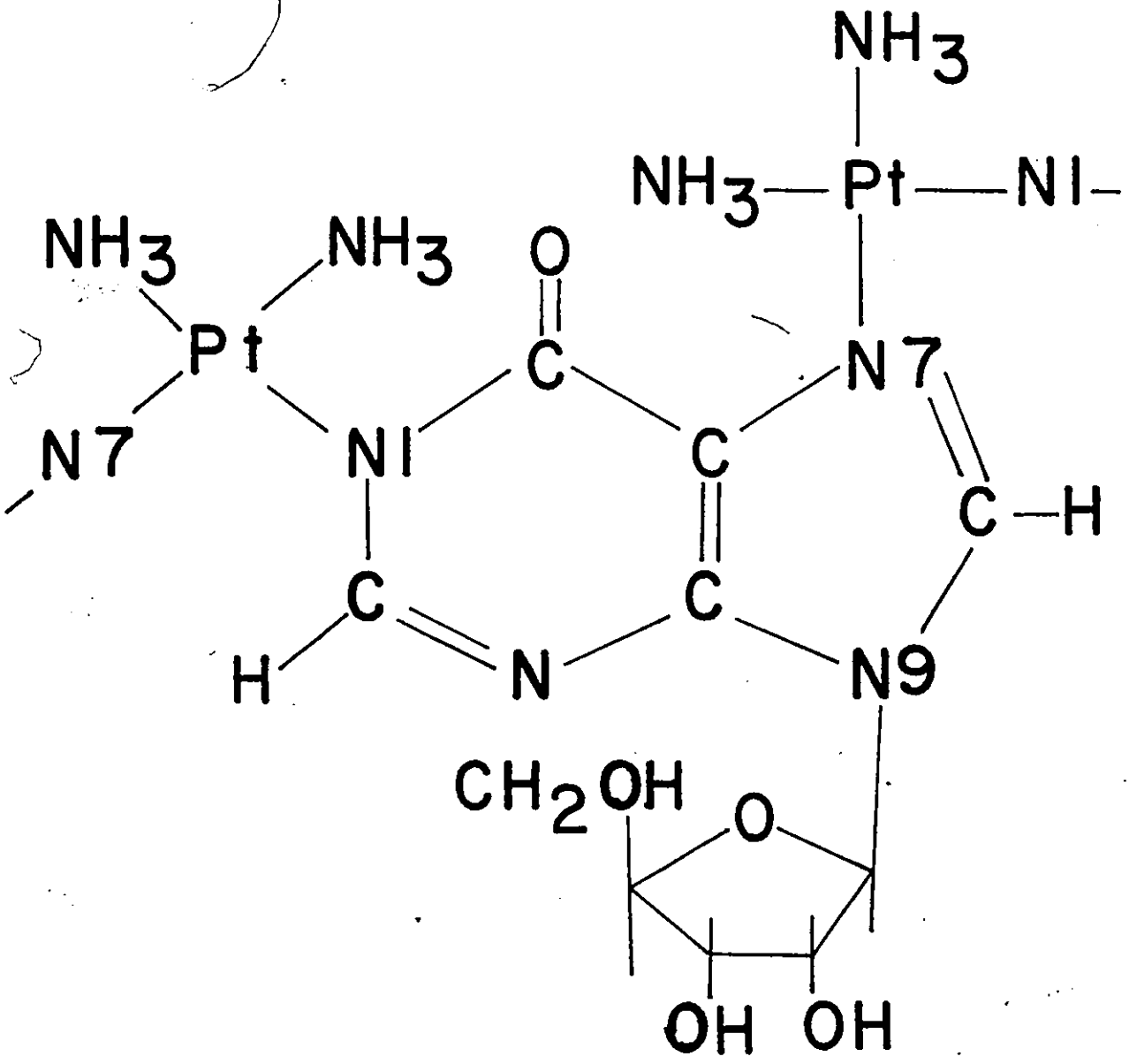
No direct evidence for the formation of an N7-O6 chelate is available and for this reason, this mechanism of action has been widely criticized. As has been mentioned previously, interaction of platinum with N9-blocked guanine and its derivatives has been observed at N7 only.[70-88] Evidence suggesting a Pt-O6 interaction consists of a shift in the 1s binding energy of the oxygen atoms in DNA.[125] The shift indicates a change in the chemical environment of some of the oxygen atoms, but not necessarily a change at the guanine O6 position.

A shift in the carbonyl frequency in the infrared and Raman spectra is observed when guanine derivatives react with palladium [126] and platinum complexes.[83,127,128] Bond formation between O6 of guanine and the platinum atom would cause a decrease in the stretching frequency of the carbonyl group. Yet, it has been shown that shifts in ν(C=O) of 20 to 30 cm^{-1} can be caused by changing hydrogen bonding patterns.[129] Even larger shifts can be obtained when N1 is deprotonated; the solution of the crystal structure shows no interaction between O6 and the platinum atom.[70] Similar shifts in the carbonyl stretching frequencies have been observed for deprotonated inosine complexes of platinum.[130] These shifts occur because of the formation of the polynuclear species shown in Figure 12. The same type of results have been obtained for the reaction of cis-DDP with guanine monophosphate.[131]

Chelation of platinum through the N7 and O6 positions of

Figure 12

Polynuclear species formed between deprotonated inosine and cis-DDP



guanine has also been proposed to account for the inhibition of the intercalation of ethidium bromide in DNA. The N7-O6 chelate would disrupt the hydrogen bonding of guanine to cytosine, causing local distortions in the DNA helix and preventing the intercalator from fitting between stacked bases.[121,132,134,135] The same results can be explained by the formation of an intrastrand crosslink.

Lastly, 1:1 reactions of cis-DDP and analogues with guanine nucleotides or nucleosides (G) show no N7-O6 chelation but yield [cis-$(NH_3)_2Pt(G)Cl]Cl$.[136]

1.6.4 N1 pK_a shift model

The formation of a bond between platinum and the N7 position of guanine results in a lowering of the pK_a of the N1 proton by approximately 1.6 pK units.[70-74,77,80,85] This is of interest because of the change in the hydrogen bonding behaviour of guanine when N1 is deprotonated. For example, it is possible to get mispairing of a deprotonated, platinated 9-ethylguanine (9-Et-G-H) with a normal 9-ethylguanine moiety (9-Et-G).[70-72,80] The normal G-C hydrogen bonding pattern (refer to Figure 7) can be replaced by the 9-Et-G-H --- 9-Et-G interaction shown in Figure 13. This is seen in a solution of $[(NH_3)_2Pt(9\text{-Et-G-H})(1\text{-MeC})]$ with excess 9-ethylguanine[80] and in the crystal structure[72] of $[Pt(NH_3)_2(9\text{-Et-G})(1\text{-MeC}):Pt(NH_3)_2(9\text{-Et-G-H})(1\text{-MeC})]^+$ where 1-MeC is 1-methylcytosine. The structure of the cation and its hydrogen bonding behaviour is important because the species was crystallized from a solution of pH=7.0, indicating

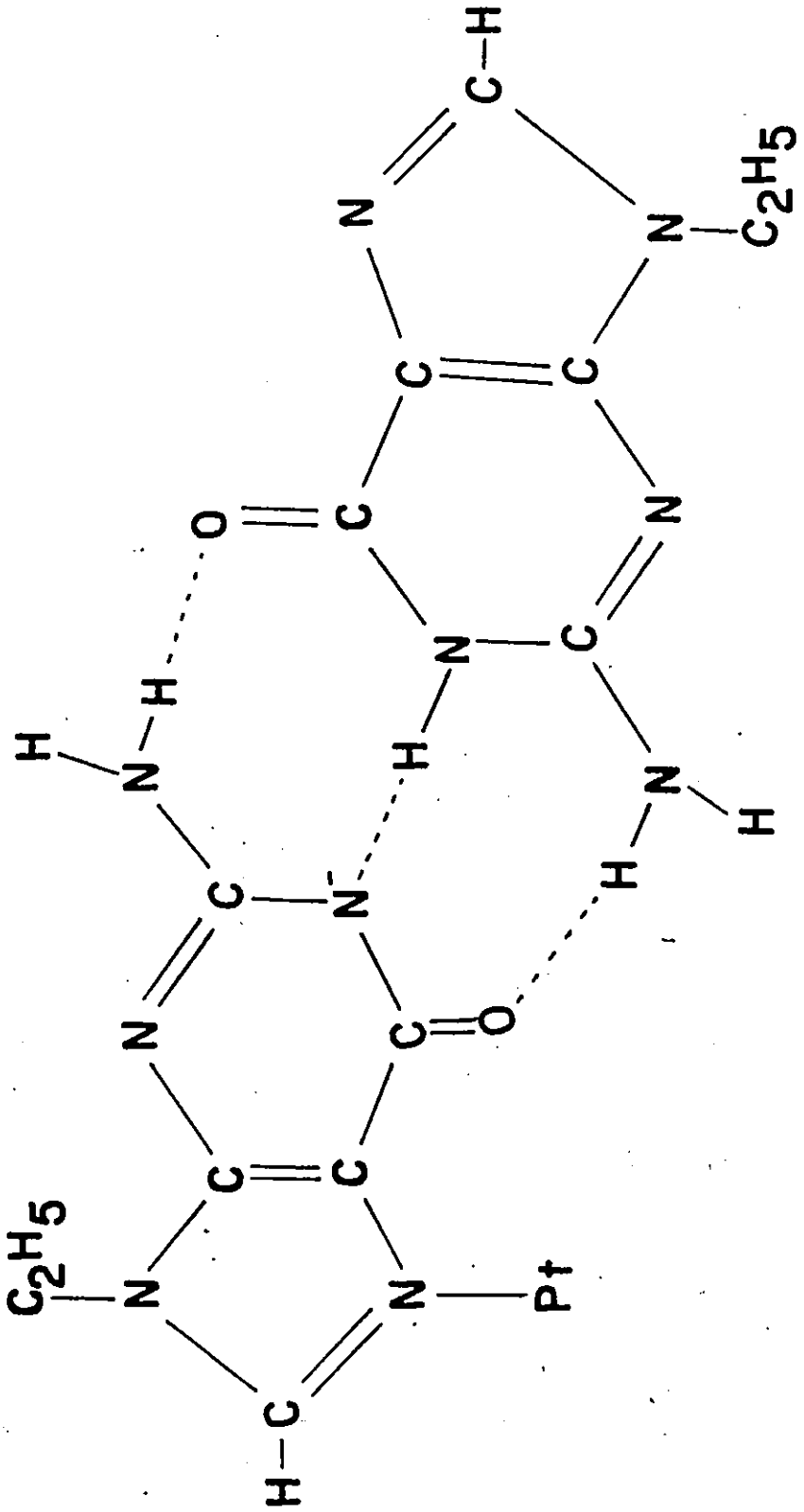


Figure 13

Base mispairing (9-Et-G-H---9-Et-G) caused by deprotonation of 9-Et-G at N1

that at physiological pH, a certain amount of deprotonated guanine bases could be present, after bonding to platinum at the N7 position. Thus this mechanism of action is a viable alternative to the N7-O6 chelate mentioned in the previous section; it is possible to get base mispairing by attaching a platinum atom to a position on guanine removed from the hydrogen-bonded region in native DNA. Another type of hydrogen bonding pattern, between two 9-ethylguanine anions, has been observed in the solid state[70] (Figure 14).

The 9-Et-G-H ---9-Et-G and 9-Et-G-H ---9-Et-G-H pairs cannot fit into the DNA double helix because the deoxyribose groups are on the opposite side of the base pair compared to the G-C pair in DNA (refer to Figures 13, 14 and 7). Lippert[80] has proposed that it is possible to get at 9-Et-G-H ---1-MeT pair in solution (1-MeT = 1-methylthymine). A similar hydrogen bonded pair has been proposed for N7-alkylated guanine and thymine.[137] As can be seen from Figure 15, mispairing of 9-Et-G-H with 1-methylthymine gives the proper orientation of the ribose sugars.

1.6.5 Eichhorn co-stacking

This mechanism of action is based on the observation that cis-DDP and cis-dichloroethylenediamine platinum(II) pack in the solid state with the square planes around the platinum atom at a distance of 3.4 Å.[138,139] This stacking distance, as observed by Eichhorn and his co-workers,[140] corresponds to the distance between bases in DNA. Other workers postulated that the cis-complexes may co-stack

Figure 14

Hydrogen bonding between 9-Et-G-H---9-Et-G-H

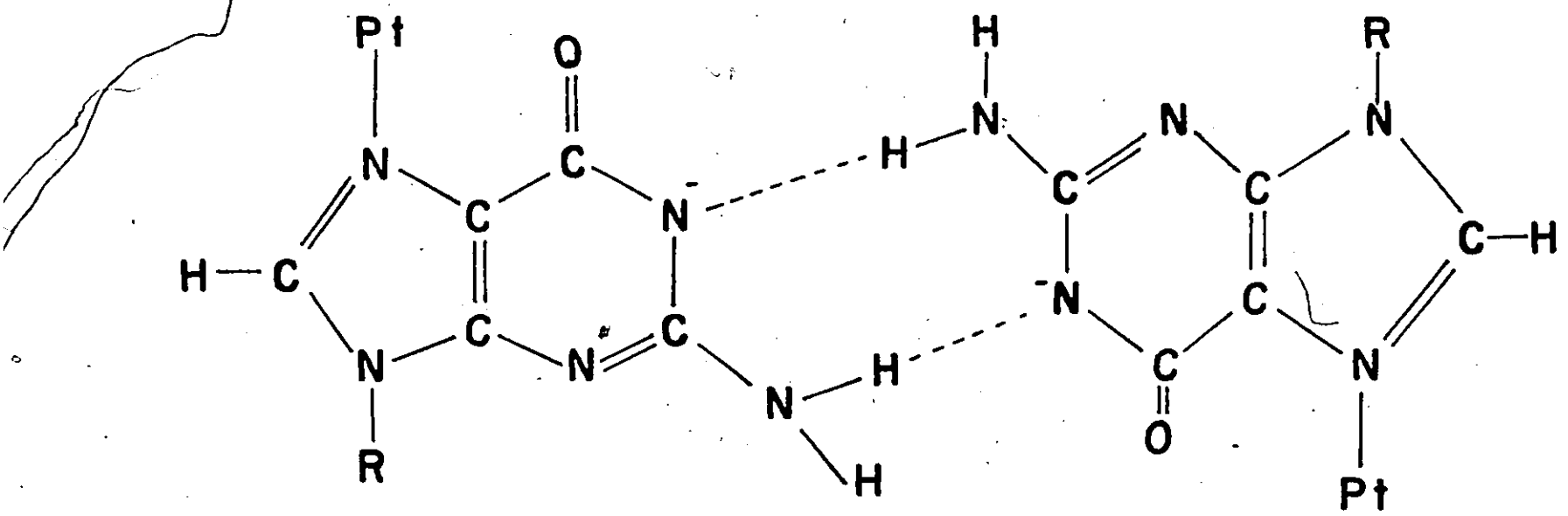
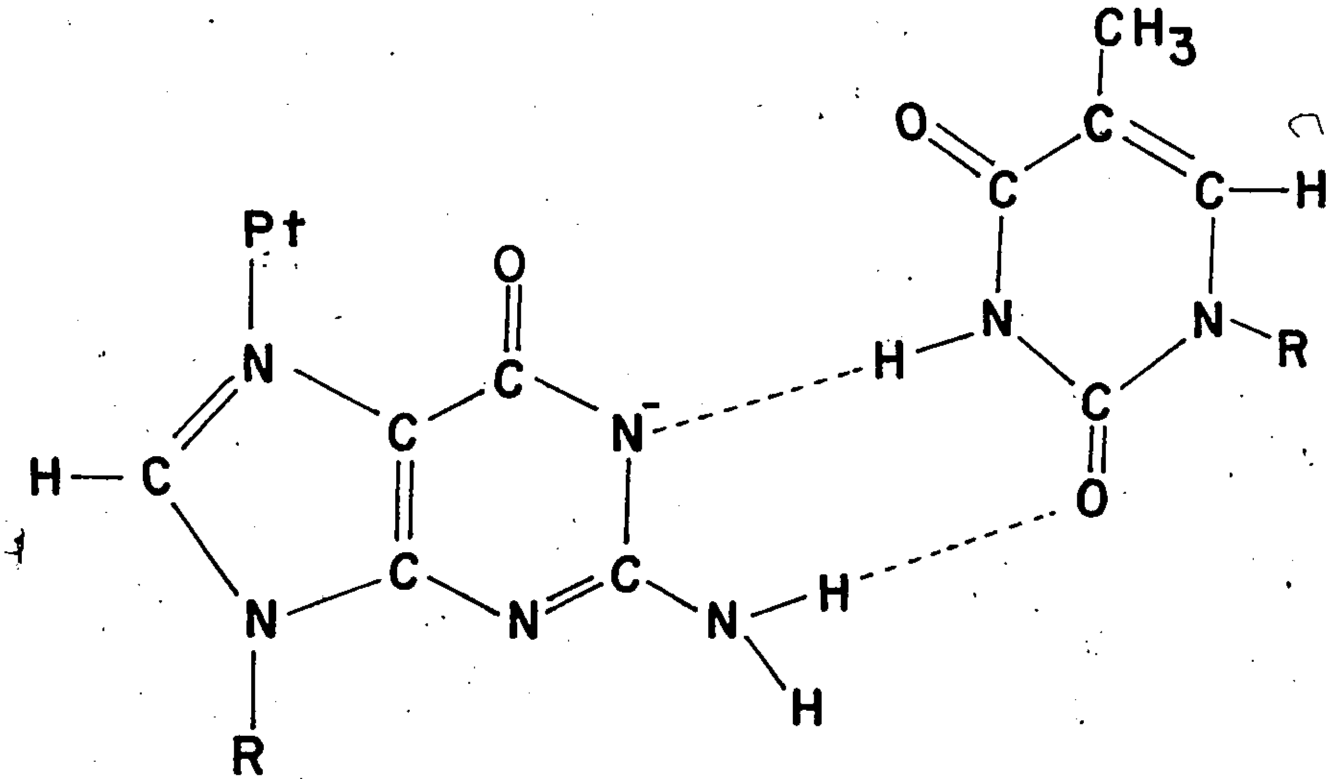


Figure 15

Base mispairing of 9-Et-G-H and 1-MeT



with each platinum atom binding to a DNA base.[129] The trans complexes cannot co-stack in this manner (Figure 16). The packing of the molecules 3.4 Å apart is stabilized by hydrogen bonding between a chloride ligand on one molecule and the amine group on the next molecule. In the trans complex, the chloride ligands lie above one another and the square planes must be skewed with respect to one another.

The stacking of square planes at 3.4 Å in cis complexes has been observed in a number of structures.[138,139,141] Yet, other cis-complexes do not stack in this way, although they have been shown to be active anti-cancer agents.[142,143] That is the main drawback for this mechanism of action. Another is that the energy of a single hydrogen bond may not be enough to stabilize the system.[129]

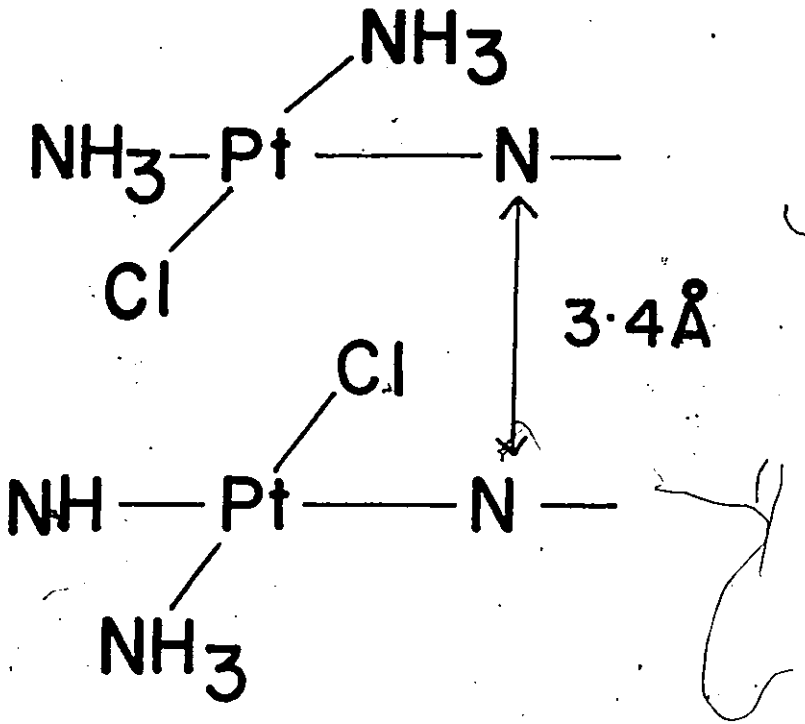
1.7 CONCLUSIONS AND OBJECTIVES

Although cis-DDP is presently used as an anti-cancer agent in humans, its mechanism of action is not known. In order to gain a clearer understanding of the reasons why some cis-platinum complexes are active anti-tumour drugs, the structure determination of relevant platinum compounds was undertaken and will be presented in the remainder of this work.

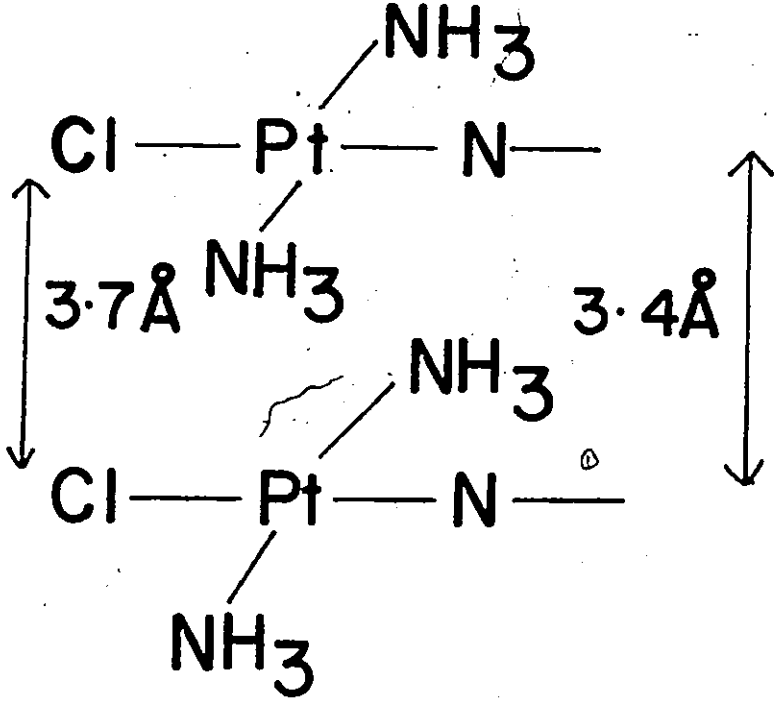
The first section deals with the structure determination of platinum complexes of 1,2-diaminocyclohexane. The platinum complexes of the separated isomers of the ligand show different activities against animal tumours, it was of interest to investigate whether there is a correlation between the structure of these complexes and their activity.

Figure 16

Eichhorn co-stacking



co-stacking of cis complex



co-stacking of trans complex

The second section is concerned with the hydrolysis products of platinum anti-cancer drugs. Aqueous solutions of platinum complexes yield a large number of species, some of which have never been isolated. The objective was to determine the structure of some of these complexes. The structural studies of the solvolysis products in other solvent systems was also of interest in the cases where hydrolysis products cannot be isolated.

The last section deals with the interaction of platinum complexes with the DNA bases. We wanted to see whether the structural information in these model systems is consistent with the results obtained on the interaction of platinum complexes with the DNA macromolecule using other techniques.

CHAPTER TWO

EXPERIMENTS

2.1 PREPARATIONS

Most of the complexes studied in this work were prepared by Dr. B. Lippert, Institut fur Anorganische Chemie, Technische Universitat, Munchen, 8046 Garching, FRG. Cyclo-tri-μ-hydroxotris [trans-1,2-diaminocyclohexane platinum(II)]nitrate·hydrate (trans-1,2-dac trimer) was prepared by D. S. Gill, Michigan State University, East Lansing, Michigan, 48824. Tris[cis-dichloro(cis-1,2-diaminocyclohexane) platinum(II)]hydrate (cis-1,2-dac $PtCl_2$) and cis-dibromo(cis-1,2-diaminocyclohexane)platinum(II) (cis-1,2-dac $PtBr_2$) were prepared in this laboratory. The preparation of the latter two complexes will be given in detail in chapter 3.

A powdered sample of the trans-1,2-dac trimer was recrystallized in this laboratory by evaporating an aqueous solution (pH = 6.4) of the sample slowly at 5°C.

The density measurements on all the complexes were carried out in this laboratory by flotation in a chloroform/bromoform mixture with the exception of cis-1,2-dac $PtBr_2$ and potassium thyminate trihydrate where chloroform/diiodomethane and dichloromethane/carbon tetrachloride mixtures were used respectively.

The elemental analyses for the complexes prepared in this laboratory were carried out by A. B. Gygli, Microanalyses Laboratory, Toronto, Ontario.

2.2 X - RAY CRYSTALLOGRAPHY

2.2.1 Preliminary experiments and data collection

The crystals were examined under a polarizing microscope and the best possible crystal was chosen for data collection. When necessary, the crystals were cut or ground to the shape of a cylinder. The crystals were glued to the end of a glass fiber or wedged inside a capillary tube. The latter method was used when the crystals decomposed because of the loss of solvent from the lattice.

The crystal system, the lattice dimensions and the possible space groups of the crystals were determined by alignment and full-layer photographs on a Buerger precession camera. In the case of the triclinic system, a Delaunay reduction was carried out to look for any hidden symmetry.

The crystals were then transferred to a Nicolet P3 or a Syntex $P2_1$ diffractometer for data collection. For crystals which were unstable at room temperature (see X-ray data tables in the appropriate chapters) , the Syntex $P2_1$ diffractometer, adapted for low temperature, was used. The crystals were cooled by directing a stream of cold nitrogen gas over the sample, along the ϕ axis. To avoid frost build-up on the capillary tube, two heaters were used, one located at the stream outlet to warm the perimeter of the cold stream and the other to disperse the cold stream once it has passed beyond the crystal. The temperature was controlled by adjusting the flow of nitrogen gas.

The data collection procedure was the same regardless of

temperature with the exception that, at low temperature, the software was programmed to transform reflections with $75° \leq \chi \leq 90°$ to their Friedel equivalent reflections.

The crystals were centered optically and an orientation matrix was obtained using a Polaroid film. The unit cell parameters were obtained by a least-squares refinement of 15 well-centered, medium angle reflections ($16° \leq 2\theta \leq 34°$).

Intensities were measured using graphite-monochromated MoKα radiation (λ = 0.71069 Å) for the appropriate hemisphere or quadrant to a maximum 2θ value of 45° or 55°. The upper 2θ limit was set according to the number of reflections with $I < \sigma(I)$ for $35° \leq 2\theta \leq 45°$. Intensities were measured with the use of a coupled θ (crystal) - 2θ (counter) scan for all crystals. The scan rate for each reflection was chosen by the program supplied with the instrument and the choice of limits for the scan rate has been described in detail elsewhere [144,145]. The stability of the crystals was monitored by measuring two standard reflections after every 48 reflections. The intensity of a reflection (I) and its error ($\sigma(I)$) were calculated as follows:

$$I = \left[\text{total scan count} - \underline{\text{sum of background counts}}\right] \times \text{scan rate}$$

$$\sigma(I) = \left[\text{total scan count} + \underline{\text{sum of background counts}}\right]^{\frac{1}{2}} \times \text{scan rate}$$

2.2.2 Data processing

2.2.2.1 Absorption correction

The attenuation of an X-ray beam by absorption effects can be expressed by

$$I = AI_o$$

where I is the measured intensity and I_o is the incident beam intensity. A is the absorption factor which can be determined by

$$A = e^{-\mu x}$$

where μ is the linear absorption coefficient and x is the pathlength of radiation through the crystal. For crystals of spherical or cylindrical shape, the absorption factor has been determined analytically. Tables of A* values (A* = transmission factors = A^{-1}) as a function of μR (R = radius of the crystal) and θ can be found in the International Tables, Volume II p. 291 (1967). This correction is applied because the average path length of the radiation is reduced as θ increases. This type of absorption correction was applied in the structure determination of the crystal of hydroxo-cis-diammine (1-methylcytosine-N^3) platinum(II) nitrate dihydrate where the crystal was ground to a cylinder.

The potassium thyminate trihydrate crystal contained no heavy elements and μ was calculated as 5.5 cm^{-1} which does not warrant an absorption correction. The crystals of cis-1,2-dac $PtCl_2$ and cis-1,2-dac $PtBr_2$ were thin plates with faces which were very hard to identify. No absorption corrections were made; this introduced a maximum error of 2% (Cl) and 3% (Br) in $|F_o|$.

For all the other complexes, the total absorption factor A_T, was separated into two parts:

$$A_T = A_S \cdot A_{2\theta}$$

where A_S is determined empirically and is dependent on the crystal shape and $A_{2\theta}$ is the absorption factor for cylindrical or spherical crystals.

The empirical method made use of the fact that the variation in absorption of the X-ray beam could be assessed by measuring the variation in the intensity of a Bragg reflection as the crystal rotated 360°, in increments of 10°, about the normal to the corresponding reflecting plane. Since 2θ is fixed for diffraction to occur from a particular plane, the variation in intensity is a function of ϕ, χ, and ω. The normal to the reflecting plane was calculated in terms of these three angles by the equation

$$\phi_{corr} = \phi - \omega\cos(\chi).$$

One then obtained a curve of intensity versus ϕ_{corr} for a particular 2θ value. The curve was normalized so that the maximum value of the curve was 1.0. Experimentally, a number of reflections of increasing 2θ values spanning the 2θ range of the data collected were measured and a normalized curve of intensity vs. ϕ_{corr} was obtained for each of these reflections. To carry out the absorption correction for a given reflection, ϕ_{corr} was calculated for that reflection, the absorption curve with the closest 2θ value was chosen and the corresponding interpolated value for the correction was used to determine A_S.

Since each curve described above was normalized at different 2θ values, the absorption factor did not correct for the progressive reduction in the average path length in the crystal as θ increases. This was taken into account by considering the correction needed for a cylindrical or spherical crystal of diameter equal to the mean thickness of the crystal.

2.2.2.2 Lorentz, polarization and secondary extinction corrections

Unscaled structure factors, F_o, and their standard deviations, $\sigma(F_o)$, were calculated from

$$F_o = \left[\frac{I_{corr}\, A^*}{Lp}\right]^{\frac{1}{2}}$$

$$\sigma(F) = \frac{\sigma(I)_{corr}\, A^*}{2LpF_o}$$

where $I_{corr} = I \cdot A_S$, $\sigma(I)_{corr} = \sigma(I) \cdot A_S$ and Lp is the Lorentz-polarization factor which may be calculated by

$$Lp = \frac{1 + \cos^2 2\theta}{2 \sin 2\theta}$$

This expression was used in the structure determination of potassium thyminate trihydrate, cis-1,2-dac $PtCl_2$, cis-1,2-dac $PtBr_2$ and hydroxo-cis-diammine (1-methylcytosine-N^3) platinum(II) nitrate dihydrate.

It was then realized that the Lorentz-polarization correction, as calculated above, did not include a polarization term for the diffraction occurring from the graphite-monochromator. For a crystal monochromator with the monochromator·2θ angle denoted by Ψ, the Lp factor reads as follows:

$$Lp = \frac{1}{\sin 2\theta}\left[f\left(\frac{1 + \cos^2\Psi \cos^2 2\theta}{1 + \cos^2\Psi}\right) + (1 - f)\left(\frac{\cos\Psi \cos^2 2\theta}{1 + \cos\Psi}\right)\right]$$

where f is a number between 0 and 1; this takes into account the fact that the graphite crystal may be considered partly ideally mosaic and partly perfect. The f value used was 0.5, as recommended by the manufacturer. This Lorentz-polarization term was used in the structure determination of the remainder of the complexes.

The final correction applied was that for secondary extinction. In the structure determination of potassium thyminate trihydrate, cis-1,2-dac $PtCl_2$ and cis-1,2-dac $PtBr_2$ the method of Larson [146] was followed: values were calculated for each reflection according to the following equation:

$$\beta = \left[\frac{1 + \cos^2\Psi \cos^4 2\theta}{\sin 2\theta\ (1 + \cos^2\Psi \cos^2 2\theta)}\right]$$

where Ψ is the monochromator 2θ angle. Least squares calculations in the program CUDLS (see below) were carried out by minimizing the quantity $\Sigma w(F_o - F_c^*)^2$, with

$$F_c^* = kF_c(1 + g\beta F_c^2)^{-\frac{1}{2}}$$

where k is a scale factor and g is the secondary extinction parameter. For the remainder of the structure determinations, the value of x was refined in the least squares refinement program SHELX [151], where x is an empirical isotropic extinction parameter, changing F_c to

$$F_c^* = F_c\left(\frac{1 - 0.0001 \cdot x \cdot F_c^2}{\sin\ \theta}\right)$$

2.2.2.3 Calculation of structure factors

Unscaled calculated structure factors were obtained from:

$$F_c(hkl) = \sum_{j=1}^{N} f_j \exp[\, 2\pi i(hx_j + ky_j + lz_j)] \exp[-T_j]$$

where f_j is the atomic scattering factor of the j^{th} atom of the unit cell situated at x_j, y_j, z_j along the a, b, c axes. Scattering factors were from Cromer and Waber [147]; corrections for anomalous dispersion [148] were applied for all the atoms except carbon, nitrogen and oxygen atoms in the structure determination of potassium thyminate trihydrate, cis-1,2-dac $PtCl_2$ and cis-1,2-dac $PtBr_2$. The temperature factor T_j describes the thermal motion of the j^{th} atom and is written as:

$$T_{j\ iso} = 2\pi^2 U\left(\frac{2 \sin \theta}{\lambda}\right)^2$$

where U is related to the root mean square amplitude of the atomic vibration. As written above, the equation implies that the atomic motion is equal in all directions in space. In general however, the thermal motion of atoms is not spherically symmetrical and an improved description of the motion can be obtained with the introduction of anisotropic temperature factors:

$$T_{j\ aniso} = 2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*).$$

2.2.3 Structure solution

For the potassium thyminate trihydrate structure, the phase problem was solved by direct methods [133] using the strategy available

in the SHELX program [151] and using 54 reflections with $|E| > 1.35$ and 14 sets of starting phases. A subsequent E-map with the most reliable set of phases yielded all the non-hydrogen atoms. A series of full-matrix least squares refinements, minimizing $\Sigma w(|F_o| - |F_c|)^2$, where w is a weight (see below), followed by three-dimensional difference syntheses revealed all the non-hydrogen atoms. The positions of the hydrogen atoms were refined but the temperature factors were fixed at a value 20% larger than the temperature factor of the atom to which they were attached.

Cis-1,2-dac $PtCl_2$ has 3 independent platinum atoms per asymmetric unit. The phase problem was solved by direct methods (see above) using 50 reflections with $|E| > 1.68$ and 14 sets of starting phases. A subsequent E-map with the most reliable phases yielded one platinum atom. A series of full-matrix least squares refinements followed by three-dimensional difference synthesis revealed all the non-hydrogen atoms.

For all the other structures, the positions of the platinum atoms were found from three-dimensional Patterson syntheses. Full-matrix least squares refinements followed by three-dimensional difference syntheses revealed all the non-hydrogen atoms.

For complexes containing platinum atoms, where hydrogen atoms were found, the positional parameters of the hydrogen atoms did not refine well; the positional parameters were fixed at the values obtained from difference maps from which all other atoms had been removed and for which increased weight was given to the low-angle reflections.

Anisotropic temperature factors were used for platinum, sulfur, chlorine and bromine atoms. Other atoms in the structures were also assigned anisotropic temperature factors when warranted by significance tests.[149] The anisotropic temperature factors are listed in the appendices attached to the end of the thesis.

Refinements using full-matrix least squares were terminated when the maximum shift/error was less than 0.3. For the structure determination of potassium thyminate trihydrate, cis-1,2-dac $PtCl_2$ and cis-1,2-dac $PtBr_2$, the least-squares refinement program CUDLS (see below) was used. In this program, reflections for which $I < \sigma(I)$ were removed; reflections were considered to be observed when $I > 3.0\sigma(I)$. Reflections with $\sigma(I) \leq I \leq 3.0\sigma(I)$ were considered unobserved and were given no weight in the structure determination unless $F_c > F_o$. For the least-squares calculations in the SHELX program [151], reflections for which $I \leq 0$ were rejected; all other reflections were used in the refinement procedure.

The figures of merit used were the following commonly used crystallographic residuals:

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

$$R_2 \text{ or } R_w = [\Sigma w(|F_o|-|F_c|)^2/\Sigma wF_o^2]^{\frac{1}{2}}$$

The weighting parameter used was the following:

$$w = (\sigma_{counting}^2 + (gF_o)^2)^{-1}$$

where $\sigma_{counting}$ is the error associated with the counting statistics

for a particular reflection and g takes into account the instrument instability. The value of g was determined from the estimated standard deviation of the standard reflections collected throughout data collection for potassium thyminate trihydrate, cis-1,2-dac $PtCl_2$ and cis-1,2-dac $PtBr_2$. For all the other structures, the value of g was chosen from the analysis of variance available in the SHELX program.[151] The observed structure factors are separated into ten intervals of increasing $(\bar{F}_o/F_{max})^{\frac{1}{2}}$, each containing roughly the same number of reflections, N, where $\bar{F}_o$ is the mean observed structure factor in the interval and F_{max} is the highest observed structure factor. The expression

$$V = 100\left[\frac{M\Sigma w(F_o-F_c)^2}{N\Sigma w}\right]^{\frac{1}{2}}$$

where M is the total number of structure factors, is calculated for each interval. The best g value is that which yields the smallest variation in V as a function of $(\bar{F}_o/F_{max})^{\frac{1}{2}}$.

The error in an observation of unit weight was calculated by fitting $(F_o-F_c)^2$ to $(\sigma(F)^2 + |g|F^2)$.

The moduli of F_o and F_c for the structures reported in this work are listed in reference 265.

2.2.4 Computer programs

The PRELIM procedure file was used to transfer the data collected from diffractometer output tapes to computer files in a suitable format for further work.

The empirical absorption correction was carried out using the PSI program, provided by the diffractometer manufacturer and modified locally for the CDC computer by Z. Tun and J. F. Britten.

Lorentz-polarization and cylindrical or spherical absorption corrections were carried out using the DATCOS, DATDRN packages from the X-RAY76 system.[150] The program SHELX[151] was used for direct method calculations in all cases and structure refinement in all structures with the exception of potassium thyminate trihydrate where the full-matrix least squares program CUDLS (written locally by J. S. Stephens) and the Fourier program SYMFOU (written locally by J. S. Rutherford) were used throughout the structure solution. CUDLS and SYMFOU were also used in the final three-dimensional difference synthesis for cis-1,2-dac $PtCl_2$ and cis-1,2-dac $PtBr_2$.

Least squares planes, dihedral planes and torsional angles were calculated by the programs PALS (written locally by P. G. Ashmore) or NRC-22.[152]

Diagrams were prepared using the ORTEP(II) program.[153]

All calculations were carried out on a CDC 6400 or a CYBER 170/730 computer.

2.3 INFRARED SPECTROSCOPY AND NMR SPECTROSCOPY

The infrared spectra of cis-1,2-dac $PtCl_2$ were obtained on a Perkin-Elmer Model 283 spectrometer. The samples were prepared as mulls in nujol and hexachloro-1,3-butadiene. The Nmr spectra were obtained on an 80 MHz Bruker WP-80 Fourier Transform spectrometer.

CHAPTER THREE

STRUCTURAL DETERMINATION OF BROMO AND CHLORO PLATINUM COMPLEXES OF cis-1,2-DIAMINOCYCLOHEXANE

3.1 INTRODUCTION

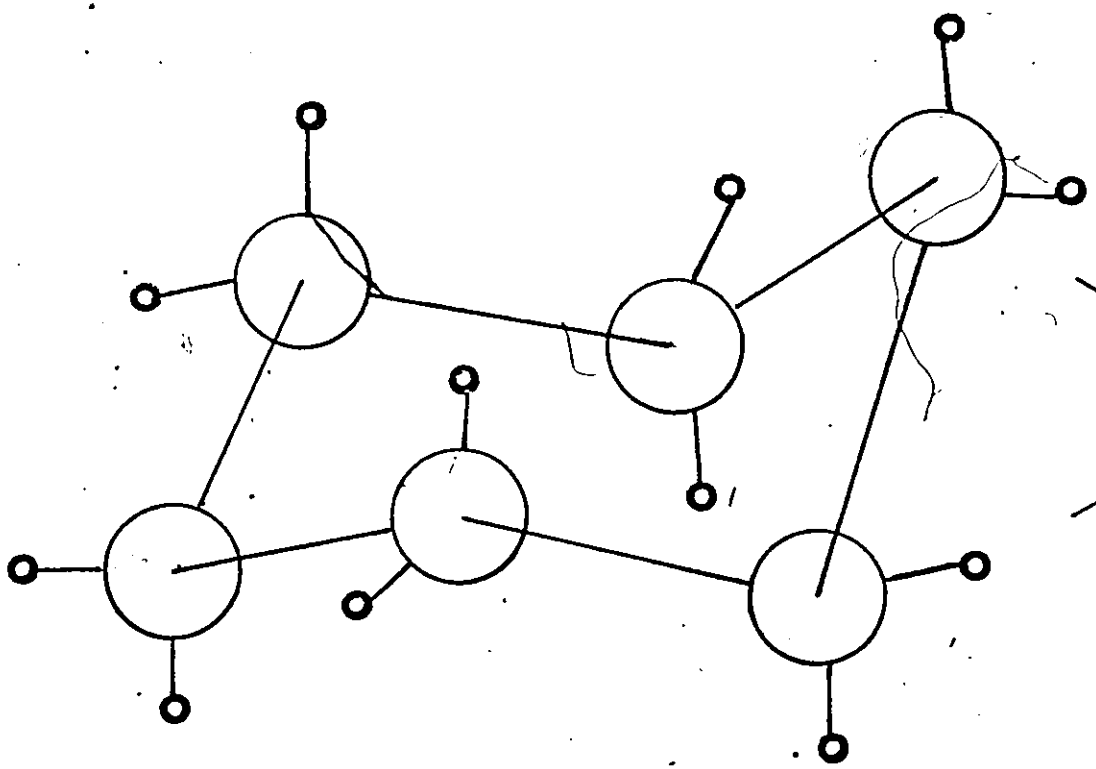
Early studies using 1,2-diaminocyclohexane (1,2-dac) platinum complexes indicated that these second-generation drugs were only as active as cis-DDP against certain tumours [17,20,21,154] and very toxic in male F344 rats.[155] Most of the research done with 1,2-dac platinum complexes however, has shown that they are potential second-generation drugs deemed worthy to enter clinical trials (see section 1.3.3).

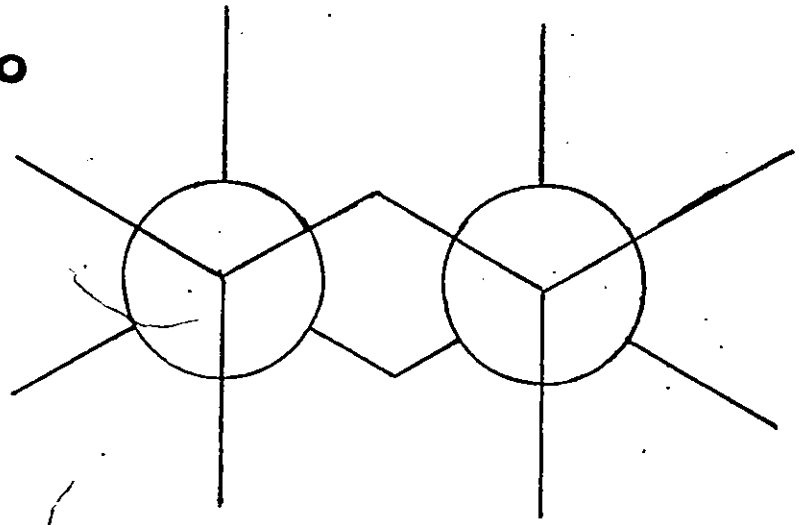
The cyclohexane ring is a puckered six-membered ring which can exist in a number of different conformations, the most stable being the chair conformation shown in Figure 17. Nearly every derivative of cyclohexane also exists in the chair conformation.[156] This has been found in the structural studies of complexes containing the 1,2-diaminocyclohexane ligand.[157-160]

The 1,2-dac ligand in the chair conformation can exist in three isomeric forms: cis and the two trans configurations, RR and SS. The cis isomer has one amino group in an equatorial position and the other in an axial position; this can lead to chelation on the platinum atom (Figure 18). One of the carbon atoms attached to an amino group has the R configuration while the other has the S configuration; thus cis-1,2-dac is not optically active.

Figure 17

Chair conformation of cyclohexane

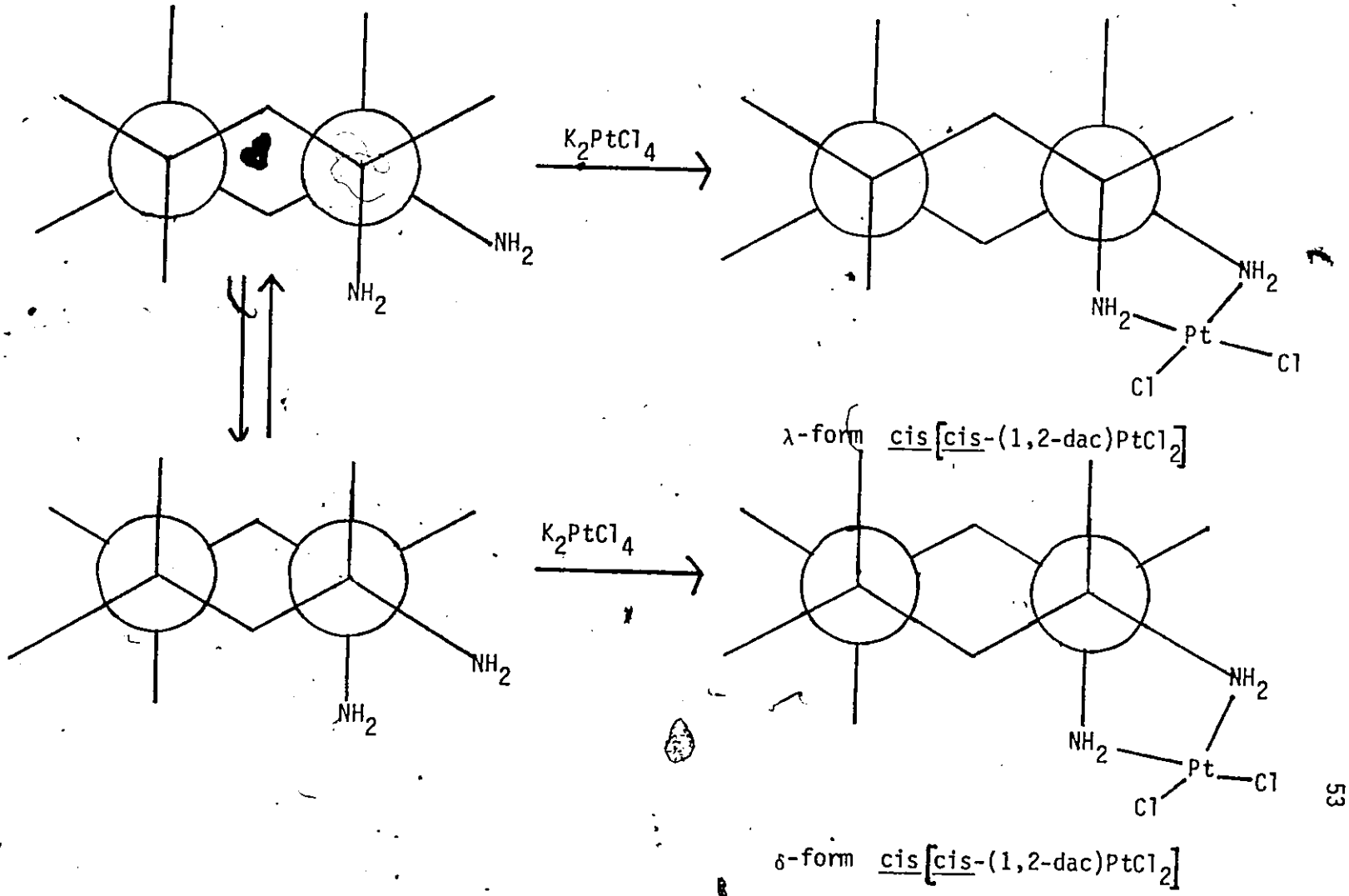




Newman projection

Figure 18

Conformations of cis-1,2-dac



Trans-1,2-dac can exist as two enantiomers, RR and SS. These are non-superimposable mirror images and the optical isomers can be separated. For each enantiomer two conformations are possible: the anti conformation with both amino groups in axial positions and the gauche conformation with both amino groups in equatorial positions. To form a chelate to platinum, both amino groups must be in equatorial positions (gauche conformation) (Figure 19).

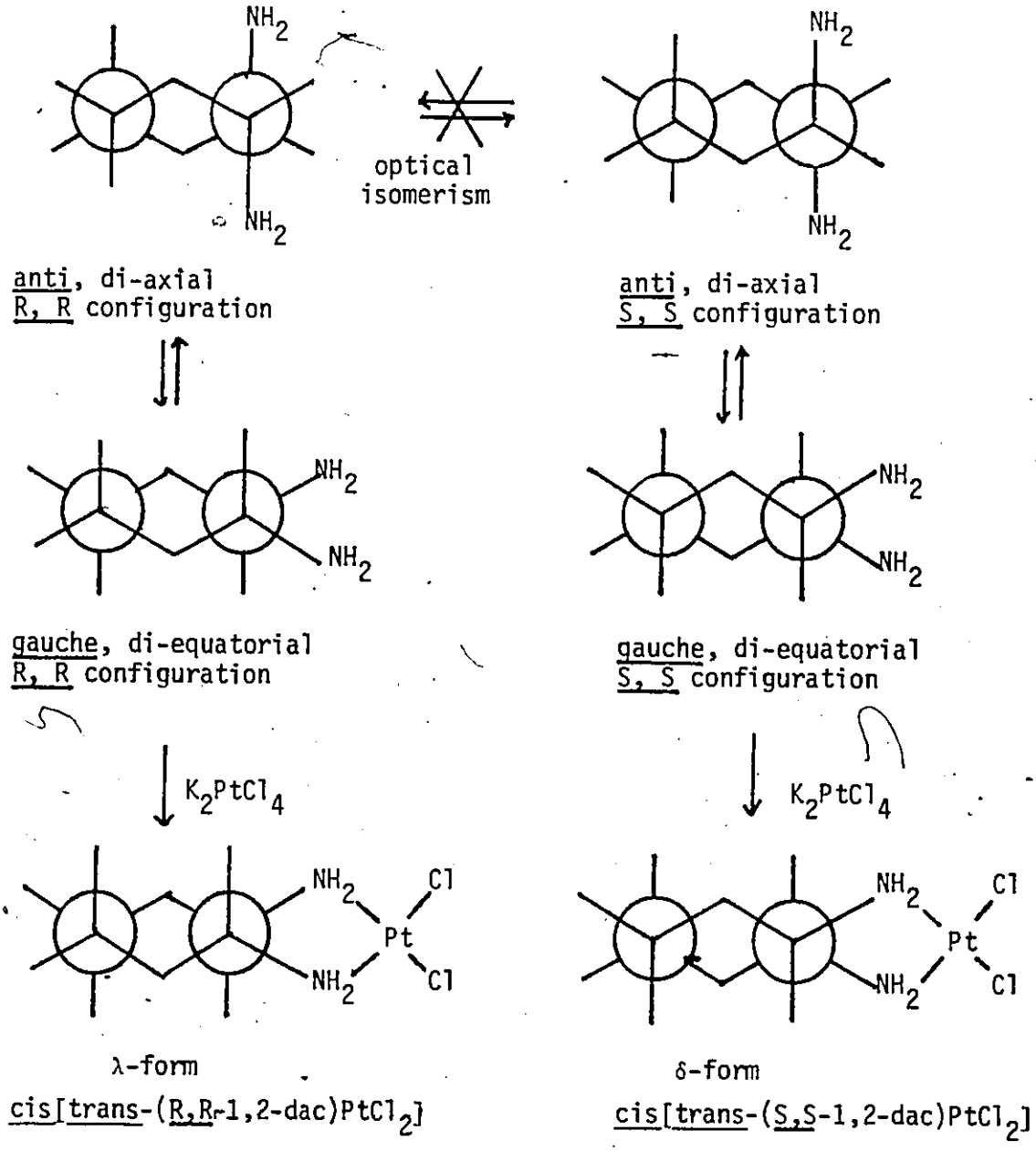
The absolute configuration of the optical isomers has been determined:[157] the levorotatory ligand, trans-(-)-1,2-dac, has the RR configuration; trans-(+)-1,2-dac has the SS configuration.

Chelation of the 1,2-dac ligand to a platinum atom introduces an asymmetry such that the NCCN system can exist in the δ or λ form (Figure 20). The orientation of the amino groups of the RR isomer is such that chelation to platinum always yields the λ form while chelation of the SS isomer gives the δ form (refer to Figure 19). For cis-1,2-dac, one conformation yields the δ form while the other yields the λ form (refer to Figure 18); because both conformers should exist in equal amounts, one should obtain a mixture of the δ and λ forms upon chelation of the cis-ligand to the platinum atom.

Most animal studies done with platinum complexes containing the separated isomers of 1,2-dac have shown that the complexes with the trans-(-)-1,2-dac ligand were the most active, regardless of the

Figure 19

Conformations and optical isomers of trans-1,2-dac

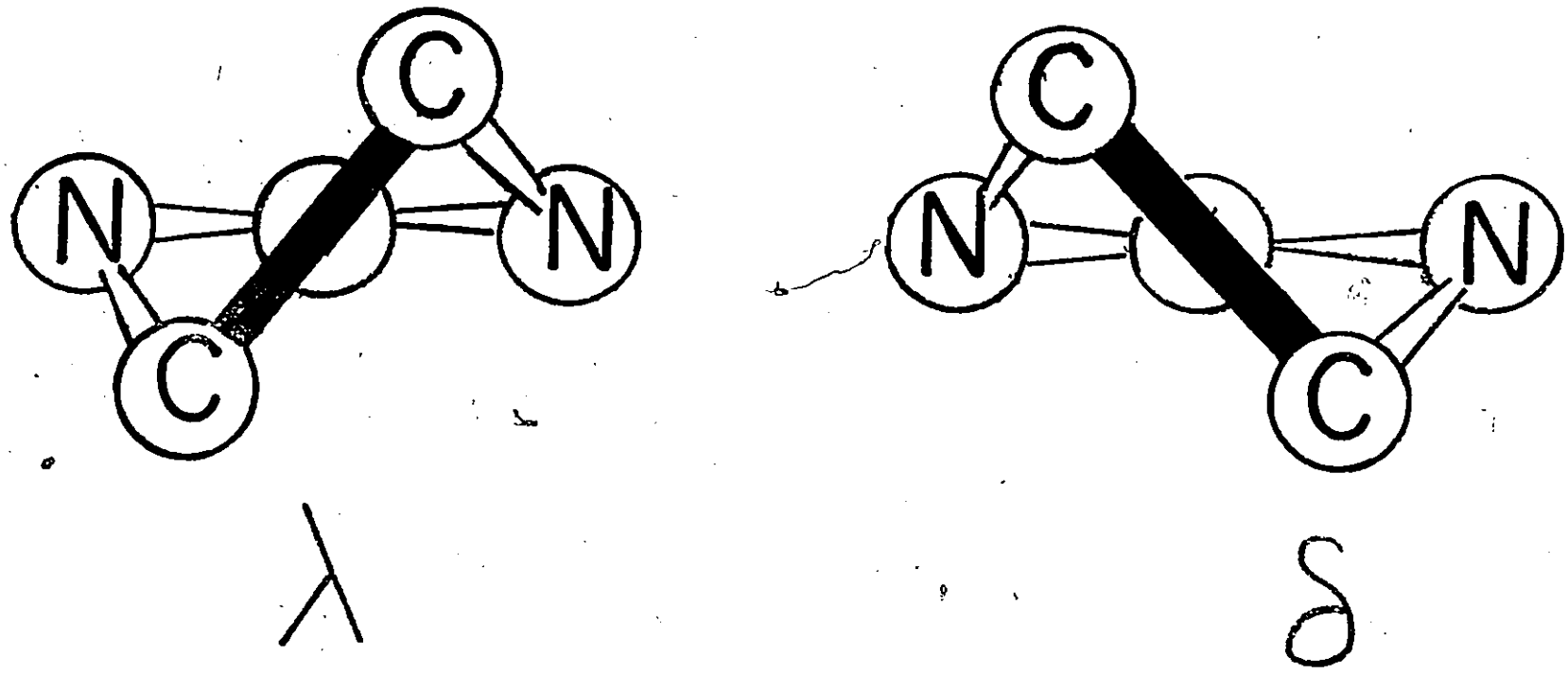


cis[trans-(R,R-1,2-dac)$PtCl_2$]

cis[trans-(S,S-1,2-dac)$PtCl_2$]

Figure 20

Asymmetry introduced upon chelation of 1,2-dac to platinum



leaving group or the tumour system being tested.[47-49,161-164] These results have prompted researchers to replace platinum complexes of isomeric mixtures of 1,2-dac by trans-(-)-1,2-dac platinum (II) for clinical trials.[48]

The structures described in this chapter involve platinum complexes of the cis-isomer of the 1,2-dac ligand with chloride and bromide leaving groups, cis-1,2-dac $PtBr_2$ and [cis-1,2-dac $PtCl_2$]$_3 \cdot H_2O$. At the time of their structure solution, these complexes were the first examples of structures of the 1,2-dac ligand with platinum. Since then, a structure involving the trans-(-)-1,2-dac ligand on platinum has been studied and will be discussed later in the chapter.

3.2 EXPERIMENTS

3.2.1 Separation of 1,2-dac into its cis and trans isomers

Commercial 1,2-diaminocyclohexane (25 g) from ICN Pharmaceuticals was used as the starting compound. The procedure of Saito and Kidani [165] was followed exactly to give [Ni(cis-1,2-dac)$_2$Cl$_2$] (yield = 13.49 g) and [Ni(trans-1,2-dac)$_2$Cl$_2$]$\cdot 2H_2O$ (yield = 13.3 g). The products were identified by infrared spectroscopy. Treatment of the nickel complexes with sulfuric acid gave cis-1,2-dac$\cdot H_2SO_4$ (yield = 10.32 g, 67%) and trans-1,2-dac$\cdot H_2SO_4$ (yield = 8.05 g, 73%).

3.2.2 Preparation of [Pt(cis-1,2-dac)Cl$_2$]$_3 \cdot H_2O$

This was prepared by a modification of the procedure of Ito, Fujita, and Saito [166] in which cis-1,2-dac$\cdot H_2SO_4$ (0.56 g) was

used instead of cis-1,2-dac and the reaction time was 36 h. An alternative method was used for subsequent preparations where cis-1,2-dac·H_2SO_4 and K_2PtCl_4 were mixed and the pH of the solution was raised with K_2CO_3 until the yellow [cis-1,2-dac $PtCl_2]_3$ H_2O precipitated. The mixture was stirred for a few hours, the solid was removed by filtration and the procedure repeated until completion of the reaction. In all cases, the solid was recrystallized by dissolution in dimethylformamide followed by the addition of 0.1M HCl, dropwise, until the solution just turned cloudy. The mixture was cooled in a refrigerator (273 K) for 3 d. Yellow crystals formed as thin plates. They were separated by filtration and air dried (calc. for $C_{18}H_{44}Cl_6N_6OPt_3$: C, 18.7, H, 3.8, N, 7.3%; found: C, 19.4, H, 3.9, N, 7.2%) .

3.2.3 Preparation of [Pt(cis-1,2-dac)Br_2]

[Pt(cis-1,2-dac)$Cl_2]_3 \cdot H_2O$ (0.107 g) was reacted, as a suspension in water, with two molar equivalents (0.090 g) of silver nitrate. The bulk of the silver chloride precipitate was removed by centrifugation; residual traces were removed by filtration. The filtrate was reacted with potassium bromide (0.04 g) . A yellow precipitate of [Pt(cis-1,2-dac)Br_2] was separated by filtration and recrystallized by precipitation from an acetone solution by vapour diffusion of water. Yellow crystals were obtained after two weeks (calc. for $C_6H_{14}Br_2N_2Pt$: C, 15.4, H, 3.0, N, 6.0%; found: C, 15.1, H, 2.8, N, 5.7%) .

3.3 RESULTS AND DISCUSSION

The crystal data and details of the refinement for both [cis-1,2-dac $PtCl_2]_3 \cdot H_2O$ and [cis-1,2-dac $PtBr_2$] are shown in Table 4. The final positional parameters and the isotropic or equivalent temperature factors (U_{iso} or U_{eq}) are given in Table 5 and Table 6 for the bromo and chloro complexes respectively. The molecular structures of the chloro and bromo complexes are very similar. In both, the 1,2-dac ligand adopts the chair conformation.

Figure 21 shows the structure of the bromo complex and the atom numbering, which are the same in the chloro complex. The chloro complex has three molecules in the asymmetric unit compared to one for the bromide; the difference is attributed to the extra water molecule in the chloro complex. Interatomic distances and angles for the bromide and three chloride molecules are given in Table 7 and dihedral angles between various planes in the molecules are given in Table 8. The two Pt-Br distances are significantly different, but there are no obvious reasons for the difference. The Pt-Cl distances (2.284(7) - 2.310(6)Å) are not significantly different in each molecule of the chloride and the average distance (2.293Å) is shorter than the average Pt-Br value (2.434Å) by about the difference between the Cl and Br covalent and ionic radii of 0.16 Å. The Pt-N distances (2.01(2) - 2.06(2)Å) are not significantly different in the four molecules. Equivalent C-N and C-C distances within the rings do not differ significantly within the sets and are in agreement with other

Table 4

Crystal data

Compound	$[Pt(C_6H_{14}N_2)Cl_2]_3 \cdot H_2O$	$[Pt(C_6H_{14}N_2)Br_2]$
F. W.	1158.3	469.0
Crystal shape, size(cm)	Thin plate; 0.006 X 0.003 X 0.04	Rectangular block 0.005 X 0.005 X 0.04
Space group	C2/c	C2/c
Unit cell parameters		
a(Å)	24.31(2)	15.212(4)
b(Å)	12.439(5)	11.612(5)
c(Å)	20.981(9)	13.268(5)
β(°)	110.59(6)	121.17(2)
Volume($Å^3$)	5938(6)	2006(1)
Z	8	8
ρ_{calc} (g cm^{-3})	2.59	3.11
ρ_{obs} (g cm^{-3})	2.56(2)	3.12(1)
Linear absorption coefficient (cm^{-1})	153.9	231.0
Absorption correction factor, A*, limits	4.17, 4.50	5.65, 6.43
Maximum 2θ(°)	55	55
Standard reflections and	0, 6, 2; 2, 0, 8	-2, -2, 5; 2, -2, 1
e. s. d. (%)	1.34; 1.68	1.24; 1.20
Temperature(°C)	22	22
No. of independent reflections	6048	2515

.....cont.

Table 4 (cont.)

No. with:		
$I > 3\sigma(I)$	3022	1677
$3\sigma(I) > I > \sigma(I)$; $F_c > F_o$	863[+]	368
$3\sigma(I) > I > \sigma(I)$; $F_c < F_o$	1289[+]	278
$I < \sigma(I)$, rejected	874[+]	192
R_1[a] observed[*](all)	0.059(0.077)	0.041(0.055)
R_2[a] observed (all)	0.072(0.076)	0.056(0.058)
Final shift/error Max. (Ave.)	0.01(0.0007)	0.03(0.004)
g (secondary extinction)	1.11×10^{-8}	2.93×10^{-8}
Final difference map		
Highest peak ($e \cdot Å^{-3}$)	1.52	1.02
Lowest valley($e \cdot Å^{-3}$)	-1.68	-0.57
Weighting, w	$(\sigma_F^2 + (0.03\ F_o)^2)^{-1}$	$(\sigma_F^2 + (0.03\ F_o)^2)^{-1}$
Error in observation of unit weight	1.200	1.249

[a] Definitions of R_1 and R_2 are given in Chapter 2, p.48

[+] Most of the unobserved and weak reflections were above $2\theta = 35°$

[*] Observed reflections are those for which $I > 3\sigma(I)$. Other reflections used in the refinement procedure were those for which $\sigma(I) \leq I \leq 3.0\sigma(I)$ and $F_c > F_o$.

Table 5

Positional parameters and isotropic temperature factors ($X10^4$) for cis-dibromo(cis-1,2-diaminocyclohexane)platinum(II)

Atom	x	y	z	U_{eq}* or U_{iso}
Pt	1820.8(3)	1307.4(4)	62.7(4)	212(2)*
Br(2)	3351(1)	175(1)	1311(1)	377(8)*
Br(1)	1707(1)	795(1)	-1784(1)	328(7)*
N(1)	555(7)	2364(9)	-791(9)	320(20)
N(2)	1815(7)	1821(9)	1540(8)	310(20)
C(1)	490(9)	3078(10)	100(10)	310(20)
C(2)	817(9)	2378(10)	1210(10)	280(20)
C(3)	30(10)	1492(10)	1044(10)	320(30)
C(4)	-1028(10)	2054(11)	631(11)	380(30)
C(5)	-1395(10)	2677(11)	-543(11)	390(30)
C(6)	-597(10)	3596(11)	-404(11)	370(30)

*$U_{eq} = 1/3(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$

Table 6

Positional parameters and isotropic temperature factors ($X10^3$) for tris[cis-dichloro(cis-1,2-diaminocyclohexane)platinum(II)]hydrate

Atom	x	y	z	U_{eq}* or U_{iso}
Pt(1)	442.30(4)	339.59(7)	280.87(5)	23.5(6)*
Pt(1A)	266.74(4)	202.18(7)	292.25(5)	22.9(5)*
Pt(1B)	69.81(4)	339.04(7)	251.75(5)	22.0(5)*
Cl(2)	488.9(3)	469.2(6)	358.7(4)	41(5)*
Cl(1)	480.0(3)	201.5(5)	355.4(3)	34(4)*
Cl(2A)	183.4(3)	139.2(5)	209.7(3)	40(4)*
Cl(1A)	321.1(3)	63.6(5)	274.2(3)	37(4)*
Cl(2B)	96.4(3)	468.7(5)	335.9(3)	33(4)*
Cl(1B)	100.4(3)	204.0(5)	331.1(3)	34(4)*
N(1)	400.7(9)	237(2)	204(1)	38(5)
N(2)	403(1)	454(2)	208(1)	40(5)
N(1A)	338.5(8)	266(2)	366(1)	28(5)
N(2A)	224(1)	331(2)	310(1)	42(5)
N(1B)	46.8(7)	235(2)	173(1)	24(4)
N(2B)	43.6(8)	448(2)	176(1)	31(5)
C(1)	377(1)	294(2)	141(1)	35(6)
C(2)	356(1)	402(2)	154(1)	25(5)
C(3)	300(1)	398(2)	169(1)	38(6)
C(4)	250(2)	341(3)	111(2)	67(9)
C(5)	273(1)	227(3)	102(2)	57(8)
C(6)	327(1)	230(2)	85(1)	43(7)
C(1A)	324(1)	385(2)	369(1)	27(5)
C(2A)	262(1)	391(2)	370(1)	34(6)
C(3A)	256(1)	347(2)	435(1)	39(6)
C(4A)	296(1)	412(2)	496(1)	52(7)
C(5A)	363(1)	397(2)	501(1)	49(7)
C(6A)	367(1)	436(2)	433(1)	42(7)
C(1B)	10(1)	290(2)	109(1)	34(6)
C(2B)	34(1)	402(2)	108(1)	30(6)
C(3B)	93(1)	403(2)	95(1)	37(6)
C(4B)	84(1)	344(3)	28(1)	49(7)
C(5B)	64(1)	226(3)	31(2)	62(9)
C(6B)	7(1)	226(2)	43(1)	44(7)
O	136(1)	391(2)	504(1)	94(8)

*$U_{eq} = 1/3(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$

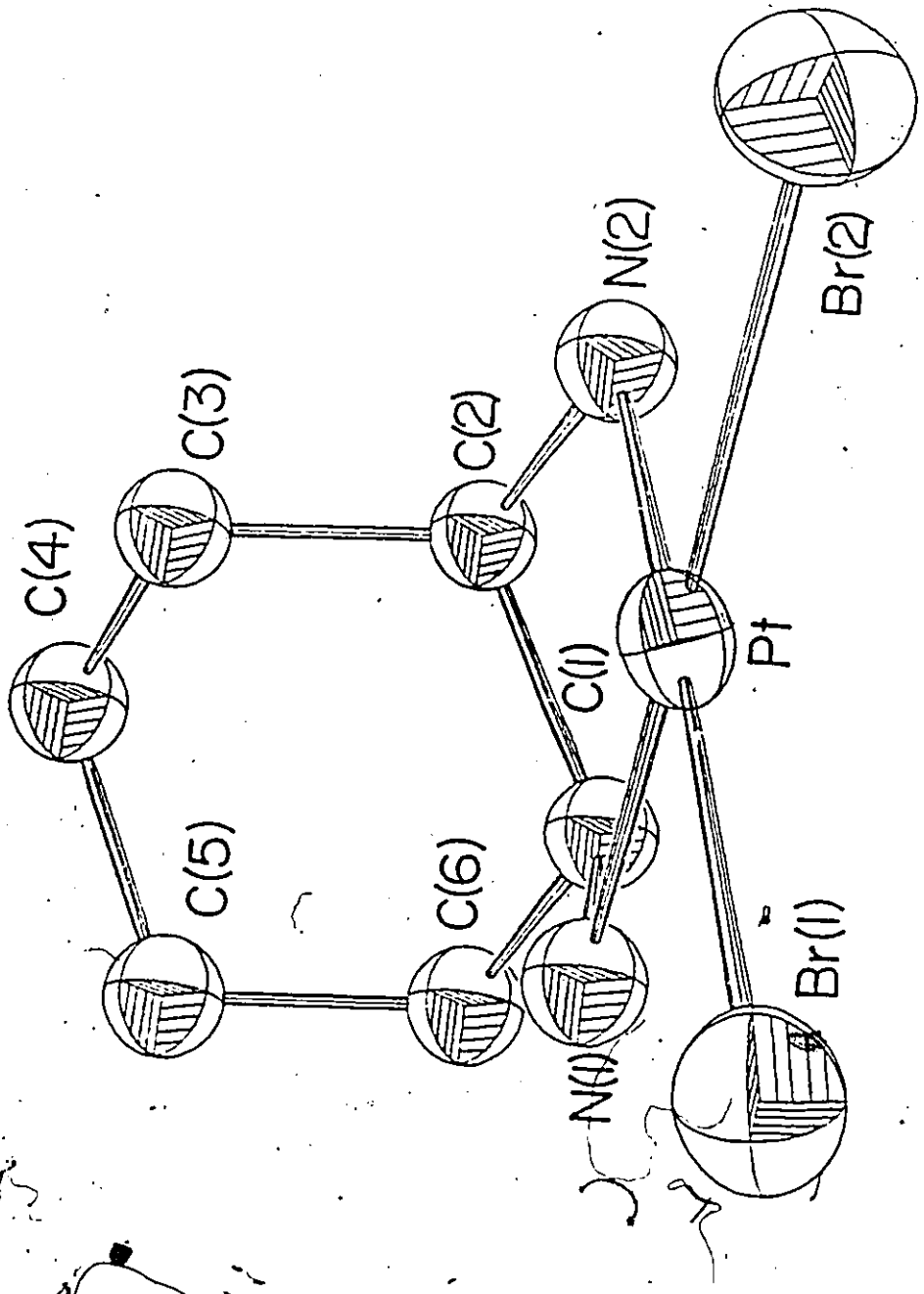


Figure 21

The molecule cis-1,2-dac $PtBr_2$ showing atom numbering

Table 7

Selected interatomic distances (Å) and angles(°)

Atoms	Distance			
	Br	Cl	Cl(A)	Cl(B)
Pt-X(1)	2.439(2)	2.286(6)	2.284(7)	2.296(6)
Pt-X(2)	2.429(1)	2.291(6)	2.291(6)	2.310(6)
Pt-N(1)	2.06(1)	2.03(2)	2.05(2)	2.02(2)
Pt-N(2)	2.05(1)	2.06(2)	2.02(2)	2.01(2)
N(1)-C(1)	1.49(2)	1.43(3)	1.53(3)	1.48(3)
N(2)-C(2)	1.49(2)	1.45(3)	1.47(3)	1.48(3)
C(1)-C(2)	1.52(2)	1.51(4)	1.52(4)	1.52(4)
C(2)-C(3)	1.51(2)	1.49(4)	1.52(4)	1.56(4)
C(3)-C(4)	1.55(2)	1.55(4)	1.54(4)	1.52(4)
C(4)-C(5)	1.54(2)	1.57(5)	1.60(4)	1.55(5)
C(5)-C(6)	1.55(2)	1.47(5)	1.55(4)	1.49(5)
C(6)-C(1)	1.55(2)	1.58(3)	1.53(3)	1.58(4)
Pt-Pt'	3.511(1)	3.479(1)	-	3.368(1)
		Angle		
X(1)-Pt-X(2)	95.61(6)	93.6(2)	91.5(2)	91.4(2)
X(1)-Pt-N(2)	175.4(3)	174.8(6)	175.9(6)	174.9(6)
X(1)-Pt-N(1)	91.9(3)	92.1(6)	91.8(6)	93.1(5)
X(2)-Pt-N(2)	89.0(3)	91.5(6)	92.2(5)	93.3(6)
X(2)-Pt-N(1)	172.4(3)	173.8(7)	176.7(6)	175.2(6)
N(1)-Pt-N(2)	83.5(4)	82.9(8)	84.6(8)	82.1(7)
Pt-N(1)-C(1)	108.9(6)	110(2)	105(1)	110(1)
Pt-N(2)-C(2)	110.6(7)	108(1)	111(1)	113(1)
N(1)-C(1)-C(2)	110(1)	109(2)	107(2)	108(2)
N(2)-C(2)-C(1)	107(1)	108(2)	107(2)	106(2)
C(1)-C(2)-C(3)	112.7(8)	114(2)	114(2)	114(2)
C(2)-C(3)-C(4)	111(1)	112(2)	109(2)	109(2)
C(3)-C(4)-C(5)	109(1)	107(2)	110(3)	111(3)
C(4)-C(5)-C(6)	110.6(9)	113(3)	107(2)	109(3)
C(5)-C(6)-C(1)	112(1)	111(2)	115(2)	113(2)
C(6)-C(1)-C(2)	112(1)	111(2)	111(2)	110(2)
N(1)-C(1)-C(6)	111.6(9)	113(2)	110(2)	112(2)
N(2)-C(2)-C(3)	111.0(9)	113(2)	111(2)	109(2)

Table 8

Interplanar angles and deviations from the best least squares plane

Dihedral angles (°)*	Br	Cl	Cl(A)	Cl(B)
N(1)C(1)C(2)N(2)	49(1)	52(3)	55(3)	48(3)
N(1)C(1)C(2)C(3)	73(1)	74(3)	68(3)	72(3)
N(2)C(1)C(2)C(3)	58(1)	54(3)	58(3)	60(3)
C(1)C(2)C(3)C(4)	57(1)	56(3)	59(3)	56(3)
C(2)C(3)C(4)C(5)	60(1)	56(3)	63(4)	59(4)
C(3)C(4)C(5)C(6)	58(1)	59(4)	59(4)	61(4)
C(4)C(5)C(6)C(1)	55(1)	57(4)	54(3)	56(3)
C(5)C(6)C(1)C(2)	51(1)	52(3)	51(3)	52(3)
C(6)C(1)C(2)C(3)	52(1)	52(3)	52(3)	51(3)
C(6)C(1)C(2)N(1)	55(1)	54(3)	60(3)	57(3)
C(6)C(1)C(2)N(2)	6(1)	2(3)	6(3)	9(3)
PtN(1)C(1)C(2)	37(1)	36(3)	46(2)	40(2)
PtN(2)C(2)C(1)	38(1)	41(2)	36(2)	35(2)
PtN(1)N(2)-PtX(1)X(2)	1.5(4)	2.9(8)	2.1(8)	2.3(7)

Deviation from plane (Å)				
Pt**	-0.015(1)	-0.011(1)	-0.024(1)	0.030(1)
X(1)	-0.011(1)	-0.032(8)	0.013(6)	0.000(8)
X(2)	0.011(1)	0.032(8)	-0.013(6)	0.000(8)
N(1)	0.02(1)	0.04(2)	-0.02(2)	0.00(2)
N(2)	-0.02(1)	-0.04(2)	0.02(2)	0.00(2)
C(1)**	0.32(1)	0.27(3)	0.55(2)	0.36(3)
C(2)**	-0.35(1)	-0.43(2)	-0.17(2)	-0.30(3)

*For the four atom labels the dihedral angle is between the planes defined by the first three atoms and the last three atoms. Thus for ABCD, the dihedral angle is between the planes ABC and BCD.

**The atoms given no weight in the refinement of the best plane; other atoms given unit weights.

structures containing the 1,2-dac moiety.[157-160,167-169] Interplanar angles show minor differences within the sets of the four molecules studied here; the differences are probably caused by the exigencies of crystal packing.

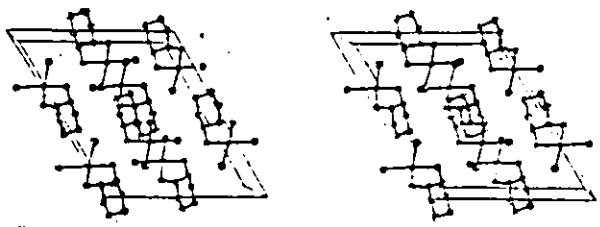
The packing of the bromo complex is illustrated in Figure 22. The structure consists of layers parallel to the ab plane at z = 0 and ½. Within each layer the molecules are arranged as centrosymmetrically related δλ pairs, with the square planes of the ligand atoms hydrogen bonded through $N(1)^{a}\cdots Br(2)$ and $N(2)^{a}\cdots Br(1)$ interactions*, giving a Pt···Pt' distance of 3.511(1) Å. In the a direction the dimer unit is in contact with its translationally equivalent unit through the cyclohexane rings. These dimer units are staggered with respect to their C-centred analogues so that in the b direction at x = 0 and ½ in each layer the dimer units are arranged in the layers like bricks in a wall. There is a stack of cyclohexane rings along b at x = 0 and ½. The forces between the dimer units within the layer are van der Waals as are the forces between layers in the c direction.

The structure of the chloro complex is shown in Figure 23. It may be considered as comprising very complex chains along the a direction centred at x = ¼, y = ¼ and symmetry-equivalent positions. These chains consist of two sets of pairs of molecules held square plane to square plane within the pair by hydrogen bonds through $Cl(1)\cdots N(1)^{b}$, $Cl(2)\cdots N(2)^{b}$ and $Cl(1B)\cdots N(1B)^{e}$, $Cl(2B)\cdots N(2B)^{e}$

*Atoms with superscripts are related to those in Tables 5 and 6 by (a) ½-x, ½-y, -z; (b) 1-x, y, ½-z; (c) ½-x, y-½, ½-z; (d) ½-x, ½+y, ½-z; (e) -x, y, ½-z; (f) ½-x, ½-y, 1-z.

Figure 22

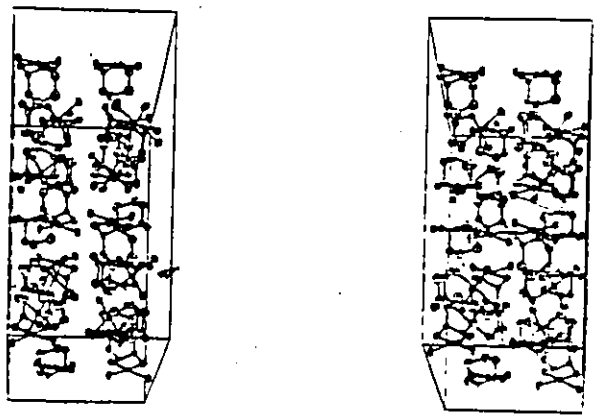
The contents of the unit cell of cis-1,2-dac $PtBr_2$



a* and c are parallel to the side and the bottom of the page respectively and the view is down b

Figure 23

The contents of the unit cell of cis-1,2-dac $PtCl_2$



a and b are parallel to the side and bottom of the page respectively and the view is down c*

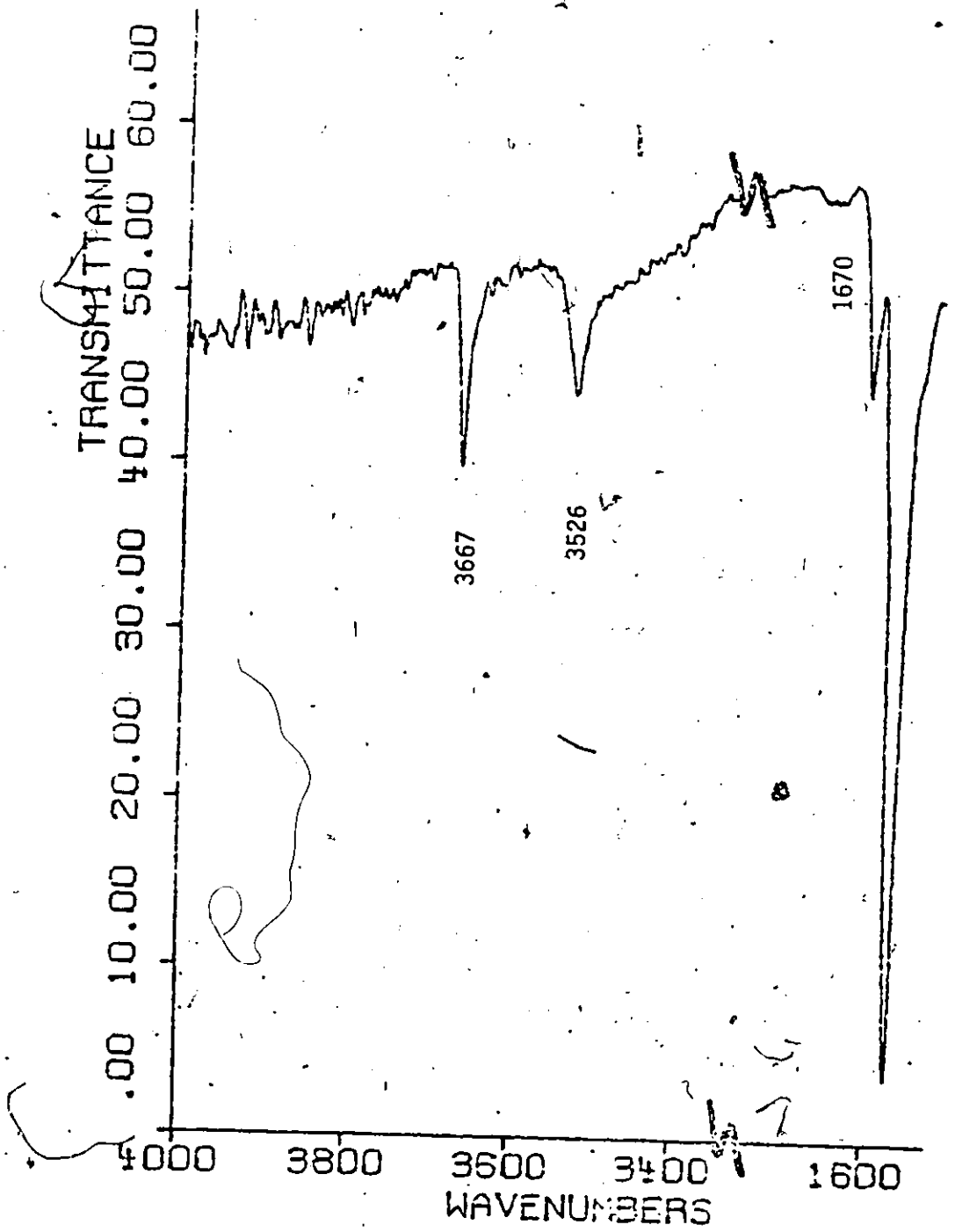
giving Pt···Pt distances of 3.479(1) and 3.368(1) Å. The conformation of the molecules is such that each pair exists in either the δδ or λλ form. The pairs are interspersed by the third molecule, which is not arranged in pairs, so that one has an arrangement pair(1)-monomer-pair(2)-monomer-etc. The monomer is bound to pair (2) by the hydrogen bond Cl(2A)···N(1B). Within a given complex chain all the monomer molecules have the same conformation while the two pairs have opposite conformations. Thus, in the left-hand upper(looking down c*) chain the arrangement is δδ[Pt-(1B)]-δ-λλ[Pt(1)]-δ- and the right-hand upper chain is λλ[Pt(1B)]-δ-δδ[Pt(1)]-δ-. The λ conformation of the monomer is observed in the lower chains.

Contact between the chains in the c direction at roughly z = 0, ½ is only between hydrocarbon units and Cl atoms and the interaction is van der Waals. The water molecule lies close to the z = 0,½ plane but does not provide a major cross-link between the chains. It is only relatively weakly hydrogen bonded to Cl(2B), 3.44(3) Å and N(1A), 3.25(3) Å, and probably is only present in a space-filling function. This is confirmed by the infrared spectrum which shows very sharp bands at 3667, 3526 and 1670 cm^{-1} (Figure 24) close to those observed in free and liquid water and higher in energy than those observed for water molecules involved in normal hydrogen bonding.[170]

Along b there is a fairly extensive network of hydrogen bonds between adjacent chains through $Cl(1)\cdots N(2B)^{c}$ 3.23(2), $Cl(2)\cdots N(1B)^{d}$ 3.43(2), $Cl(1A)\cdots N(2B)^{d}$ 3.40(2), $Cl(2B)\cdots N(1)^{d}$ 3.44(2), $Cl(1A)\cdots N(2A)^{c}$ 3.37(2), $Cl(1B)\cdots N(2)^{c}$ 3.21(2) Å.

Figure 24

Infrared spectrum of cis-1,2-dac $PtCl_2$ showing the bands caused by the lattice water molecule



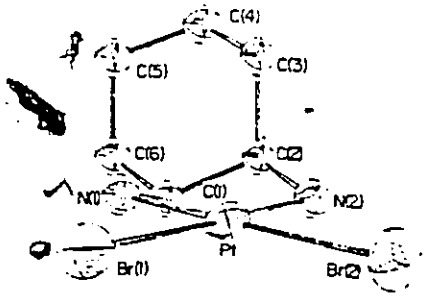
Generally, in structures of cis-diaminedihaloplatinum(II) compounds the molecules are arranged in square-plane-square-plane pairs, with a Pt···Pt distance of about 3.4 - 3.5 Å [138,139,141] (see section 1.6.5)) and this is observed in both compounds. The existence of the third molecule as a monomeric unit is unusual and we assume this is to maximize hydrogen-bonding interactions.

Our attempts at obtaining diffraction data on single crystals of trans-1,2-dac $PtCl_2$ did not succeed. A number of crystallization procedures using different solvents always yielded microcrystalline material. Small crystals were obtained by evaporating a DMF solution of the sample but these decomposed rapidly when removed from the solution. A crystal was sealed in a capillary tube with a drop of mother liquor but the loss of DMF from the lattice still occurred. The crystal structure of a platinum complex containing the trans-(-)-1,2-dac ligand has since been solved: $[(\text{trans-(-)-1,2-dac})_2PtCl]Cl_2$.[157] This will be used to compare the platinum complexes with the different isomers of 1,2-dac.

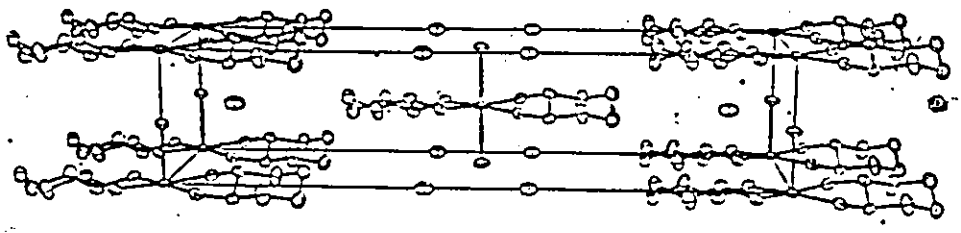
The molecules containing cis- and trans-1,2-dac differ in the orientation of the cyclohexane ring with respect to the platinum coordination plane (Figure 25). Kidani and his co-workers [161] have argued that the different orientation of the ligand plane with the platinum-containing plane may affect the fit of the platinum complexes in DNA; this may lead to a significant difference in the anti-tumour activity of the complexes. In the trans-(-)-1,2-dac platinum complex, the cyclohexane ring is almost co-planar with the

Figure 25

The orientation of the 1,2-dac ring with respect to the platinum coordination plane



a) in cis-1,2-dac $PtBr_2$



b) in $[(\text{trans-(-)-1,2-dac})_2PtCl]Cl_2$ (reference 157)

Notice the planarity of the molecules in comparison to cis-1,2-dac $PtBr_2$

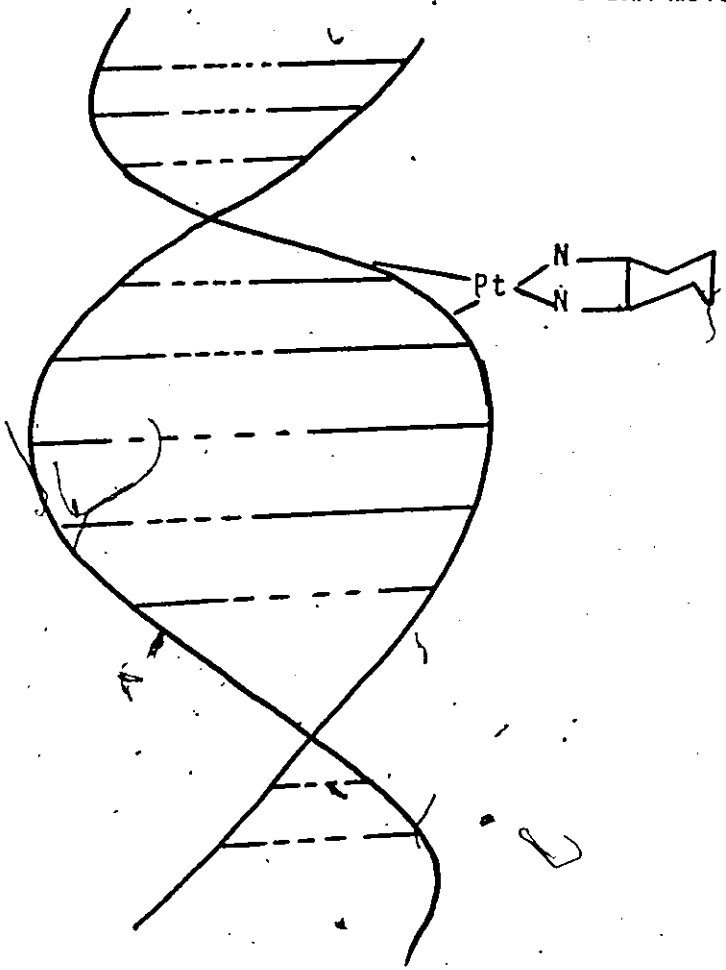
platinum coordination plane; the drug can approach the DNA molecule along its major grooves to interact with the bases. On the other hand, cis-1,2-dac platinum complexes, with their cyclohexane ring perpendicular to the platinum coordination plane, would be sterically hindered and would not interact with DNA (Figure 26).[164] This argument does not seem valid however since it has been found that the configuration of 1,2-diaminocyclohexane had no significant effect on the reactivity of sulfato 1,2-dac or dichloro 1,2-dac platinum complexes with DNA.[171]

Combination chemotherapy results indicate that the platinum drugs containing 1,2-dac may act by a mechanism different from that of cis-DDP: certain chemotherapeutic agents act synergistically with trans-(-)-1,2-dac platinum malonate but not with cis-DDP;[50] cisplatin acts synergistically with 1,2-dac platinum complexes.[33,50] Finally, 1,2-dac complexes are active against tumour lines which are resistant to cisplatin.[35,38-41,50]

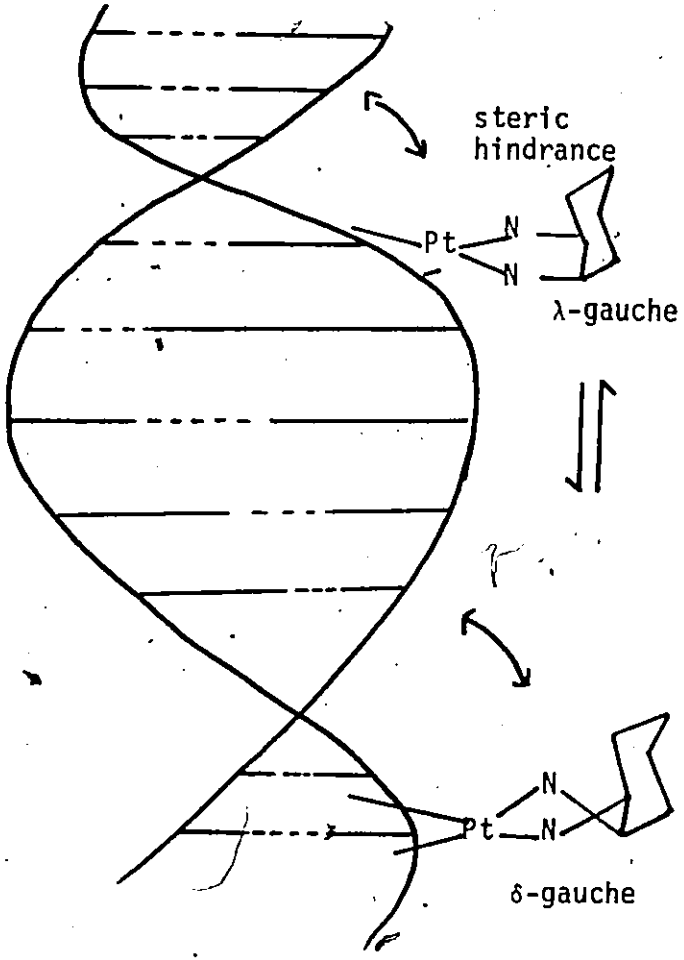
The mechanism of action of the 1,2-dac platinum drugs is not known. A recent study [172] proposes that the mechanism of action of the 1,2-dac complexes is fundamentally different and probably excludes the occurence of intrastrand crosslinks between adjacent guanine residues. Much more research must be done to elucidate the nature of the mechanism of action and the reason for the differing activities of complexes of the separated 1,2-dac isomers.

Figure 26

The relation of conformation to DNA molecules of platinum(II) complexes



trans-1-1,2-dac



cis-1,2-dac

CHAPTER FOUR

SOLVOLYSIS PRODUCTS OF *cis*-PtA_2X_2 COMPLEXES

4.1 INTRODUCTION

The solvolysis of a platinum complex is the intermediate step in the overall mechanism of action of these anti-cancer agents; hydrolysis products form before the reaction with the biological target can take place (refer to Figure 2, p. 6).

A more detailed look at the hydrolysis of platinum(II) complexes *in vitro* indicates that an aqueous solution of a platinum drug may consist of a mixture of products. In aqueous media, water is present in the highest concentration; yet, water is also a good leaving group and hydrolysis products can be suppressed in the presence of a better nucleophile in sufficiently high concentration[13]. Lim and Martin [173] have determined the relative concentrations of different species present in aqueous solutions of various compositions; the information was reviewed recently [174] and only the main points will be outlined here. In solutions where the chloride ion concentration is 103mM, equivalent to that in blood plasma, the ratio of different species of en PtX_2 complexes has been calculated to be: $(H_2O)_2$: $(OH)_2$: $(H_2O)(OH)$: $(H_2O)(Cl)$: $(OH)(Cl)$: Cl_2= 0.00134 : 0.033 : 0.053 : 1 : 1 : 37.3. In solutions containing 4mM chloride ion, equivalent to the concentration present in the cell, the ratio changes to 0.0345 : 0.86 :

1.38 : 1 : 1 : 1.45. In the plasma, only traces of complexes should contain the good water leaving group and the platinum(II) complexes should remain relatively inert. Inside the cell however, there are appreciable mole fractions of complexes with the labile water ligand and these will be more reactive toward the biological target.

The hydroxide species are formed from the corresponding aquo complexes, depending on the pH of the solution. Furthermore, when the platinum complex concentration is greater than 0.2mM and when the solutions are allowed to stand, hydroxo-bridged dimers or trimers are formed. The hydroxo-bridged complexes do not have titratable groups remaining and have been obtained at widely varying pH's [175], indicating that these complexes are very stable. The presence and structure of hydroxo-bridged dimers and trimers are now well-established.[175-178] Although there is no reason to believe that platinum complex concentrations as high as 0.2mM will be present in the cell, the formation of hydroxo-bridged species may occur during the preparation of complexes with leaving ligands other than the chloride ion (see section 4.2.1).

The platinum-containing species present in aqueous solutions depend on the chloride ion concentration, other possible ligand concentrations, the pH of the solution, the platinum complex concentration and the reaction time of the mixture.

4.2 HYDROXO COMPLEXES OF PLATINUM(II)

4.2.1 Hydroxo-bridged platinum(II) complexes

4.2.1.1 Introduction

The interest shown in the hydrolysis products of platinum(II) complexes led to interesting discoveries. For example, it was originally believed that cis-dinitratodiammine platinum(II) was toxic; the toxicity originally ascribed to the drug is actually caused by the formation of dimeric and trimeric hydroxo-bridged platinum complexes.[145] The preparation of complexes of platinum(II) with leaving ligands other than Cl^-, Br^- or I^- involves the reaction of the dichloro complex with silver nitrate to form the "aquo" species. The aquo complex is then reacted with a solution containing the appropriate anion.[17, 21] The presence of the platinum complexes in high concentration (> 6mM) in an aqueous medium probably leads to the formation of the hydroxo-bridged complexes. A water soluble complex of 1,2-diaminocyclohexaneplatinum(II), described as (1,2-dac)Pt(OH_2)(SO_4), has been found to be more active as an anti-tumour drug and to have approximately the same toxicity as the corresponding dichloro complex.[179] The formation of hydroxo-bridged species may occur in the preparation of the 1,2-dac platinum(II) complex or in the administration of the drug in an aqueous medium because the sulfate anion is a good leaving group. Gill and Rosenberg [180] have reported that the hydroxo-bridged dimer and trimer of (1,2-dac)platinum(II) are active anti-cancer agents and that they are less toxic than the dinitrato(1,2-dac)platinum(II) monomer. Thus the activity of the (1,2-dac)Pt(OH_2)(SO_4) complex may be the combination

of the activities of many compounds in a mixture.

Both cases mentioned above indicate that more careful analyses of platinum complexes are necessary to decide which drugs are the most active or least toxic when the presence of a mixture of compounds is suspected.

The cytotoxic and anti-cancer properties of the monomer, dimer and trimer species of 1,2-dac platinum(II) are quite different from the results obtained with the corresponding diammine platinum complexes.[180] The kinetics of formation of the 1,2-dac platinum hydroxo-bridged complexes have been studied [180] yet no structures have ever been reported. For these reasons, we investigated the structure of [cyclo-tri-μ-hydroxo-tris-(trans-1,2-diaminocyclohexane platinum(II)] nitrate hydrate (trans-(1,2-dac)trimer).

4.2.1.2 Experiments

The sample of trans-(1,2-dac) trimer was sent by Dr. D. S. Gill in Dr. Rosenberg's laboratory. The sample was a white powder which was recrystallized from an aqueous solution of pH 6.4. The solution was placed in the refrigerator and the solvent was evaporated slowly for 7d. at 5°C. The crystals obtained were colourless and lost water from the lattice when taken out of solution.

A large crystal was used for alignment photographs; after a few days, powder lines appeared on the film, indicating that the crystal was decomposing. The remainder of the crystals were kept at 0°C; even at this temperature, the crystals lost water molecules

present in the lattice.

Attempts to get more crystals always yielded large colourless crystals which could not be filtered out of solution without loss of crystallinity. A crystal was sealed in a capillary tube with a drop of mother liquor. This crystal was placed on a Syntex $P2_1$ diffractometer assembled for low temperature work. The same cell was found as that previously obtained from precession photographs. The three interaxial angles were close to 90° and a check of equivalent reflections in the monoclinic system based of 2/m and the orthorhombic system based on mmm indicated that the crystal belonged to the monoclinic system with $\beta = 90.48°$. The crystal data for the trans-(1,2-dac)trimer are shown in Table 9.

Although the crystal was sealed in a capillary tube and the data were collected at low temperature, there were many low-intensity reflections, probably caused by the large thermal motion of the loosely held water molecules. Thus the structure is not an accurate one and only the main features of the cation will be considered. Attempts are still being made to get better crystals so that a more accurate structure can be obtained.

The refinement of the structure was terminated when the maximum shift/error in the positional and thermal parameters of the atoms in the cation was less than 0.3. Some of the atoms of the anions and the oxygen atoms of the water molecules did not refine; they were fixed at the positions obtained from the Fourier difference map.

No absorption correction was performed on this crystal: upon

Table 9

Crystal data for cyclo-tri-μ-hydroxo-tris-[(trans-1,2-diaminocyclohexane)platinum(II)]nitrate hydrate

Compound	$[Pt(C_6H_{14}N_2)(OH)]_3(NO_3)_3 \cdot xH_2O$
F.W.	1236.97*
Space group	$P2_1/c$
Unit cell parameters	
a(Å)	12.912(3)
b(Å)	21.849(5)
c(Å)	12.763(5)
β(°)	90.48(3)
Volume ($Å^3$)	3601(2)
Z	4
$\rho_{calc}(g \cdot cm^{-3})$	2.28*
$\rho_{obs}(g \cdot cm^{-3})$	2.29(1)
Linear absorption coefficient, cm^{-1}	41.86*
Maximum 2θ(°)	45
Standard reflections and e.s.d.(%)	1, 7, 1; 1, 1, 4 2.31; 2.96
Temperature (°C)	-52
No. of independent reflections	5127
No. with $I > 0$	3808
No. with $I < 0$, rejected	1319
R_1^a, R_2^a	0.1611, 0.0827

.....cont.

Table 9 (cont.)

Final shift/error Max.(Ave.)	0.278(0.055)
X (secondary extinction)	-0.00001
Final difference map	
Highest peak($e \cdot \mathring{A}^{-3}$)	2.77
Lowest valley($e \cdot \mathring{A}^{-3}$)	-3.17
Weighting	$w = (\sigma^2)^{-1}$
Error in observation of unit weight	0.8332

[a]Definitions for R_1 and R_2 are given in Chapter 2, p. 48

*Based on tetrahydrate

warming the crystal to room temperature for the ψ-scan data collection, the crystal decomposed sufficiently to cause doubts in the accuracy of the intensity measurements. For the same reason, an accurate size determination of the crystal could not be performed. In addition, the density determination is not an accurate one.

4.2.1.3 Results and discussion

The positional parameters and the temperature factors for the atoms in the cation are listed in Table 10 and the interatomic distances and angles are given in Table 11. For clarity, the trimeric cation has been separated into 3 molecules, each molecule containing a 1,2-diaminocyclohexane ring and a platinum atom. The molecular structure of the cation and the labelling of the atoms are shown in Figure 27.

The Pt-O and Pt-N distances are normal for these types of complexes. As was mentioned in Chapter 3, chelation of the 1,2-dac ligand to platinum introduces an asymmetry (δ or λ). The cation shown in Figure 27 has the configuration $\lambda\lambda\delta$ around Pt(1), Pt(2) and Pt(3) respectively. Since the space group $P2_1/c$ is centric, there are two molecules in the unit cell with the $\lambda\lambda\delta$ configuration and two with the $\delta\delta\lambda$ configuration. This is expected since the starting ligand is a racemic mixture of trans (+) and trans (-)-1,2-dac; upon complexation, half of the ligands will give a λ complex while the other half will yield the δ complex.

The 1,2-diaminocyclohexane ring exists in the chair conformation, as has been seen in all previous structures of the ligand investi-

Table 10

Positional parameters and isotropic temperature factors ($X10^3$) for the atoms of the cyclo-tri-μ-hydroxo-tris-[(trans-1,2-dac)platinum(II)] cation

Atom	x	y	z	U_{eq}* or U_{iso}
Pt(1)	360.0(1)	-85.33(8)	105.7(2)	58(1)*
Pt(2)	298.8(1)	13.46(9)	-92.5(2)	62(1)*
Pt(3)	355.0(1)	66.75(8)	154.4(2)	61(1)*
O(12)	394(2)	-61(1)	-48(2)	45(7)
O(13)	444(2)	-15(1)	159(2)	49(7)
O(23)	403(2)	62(1)	-4(2)	84(10)
N(11)	268(2)	-159(1)	52(2)	44(9)
N(12)	328(3)	-117(1)	258(3)	68(11)
N(21)	209(2)	82(1)	-138(3)	61(10)
N(22)	202(2)	-36(1)	-192(2)	57(10)
N(31)	334(2)	72(1)	313(2)	52(9)
N(32)	270(2)	142(1)	145(2)	51(9)
C(11)	252(5)	-201(3)	137(5)	131(22)
C(12)	230(5)	-164(3)	241(5)	126(21)
C(13)	213(4)	-209(2)	330(4)	80(15)
C(14)	126(4)	-253(2)	309(4)	92(16)
C(15)	142(3)	-287(2)	219(3)	56(12)
C(16)	168(3)	-248(2)	118(3)	73(14)
C(21)	153(5)	64(3)	-234(5)	138(23)
C(22)	119(4)	6(3)	-215(4)	104(17)
C(23)	62(4)	-28(2)	-318(4)	90(16)
C(24)	-38(4)	16(3)	-357(5)	127(21)
C(25)	-14(5)	70(3)	-356(5)	144(23)
C(26)	58(4)	98(2)	-268(4)	88(16)
C(31)	236(3)	113(2)	321(3)	53(12)
C(32)	256(4)	168(2)	257(4)	103(18)
C(33)	145(5)	213(2)	261(5)	126(21)
C(34)	153(4)	229(2)	379(4)	95(17)
C(35)	127(4)	180(3)	446(4)	116(19)
C(36)	224(4)	134(2)	451(4)	91(16)

*$U_{eq}=1/3(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$

Table 11

Interatomic distances and angles in the cyclo-tri-μ-hydroxo-tris-[(trans-1,2-dac)platinum(II)] cation

Atoms	Molecule 1	Molecule 2	Molecule 3
		Distance(Å)	
Pt(1)-O(12)	2.08(2)	-	-
Pt(1)-O(13)	2.00(2)	-	-
Pt(2)-O(12)	2.12(2)	-	-
Pt(2)-O(23)	2.05(3)	-	-
Pt(3)-O(13)	2.12(2)	-	-
Pt(3)-O(23)	2.12(3)	-	-
Pt-N(1)	2.11(3)	1.97(3)	2.05(3)
Pt-N(2)	2.11(3)	2.08(3)	1.99(3)
N(1)-C(1)	1.44(7)	1.47(7)	1.56(5)
N(2)-C(2)	1.64(7)	1.45(6)	1.55(6)
C(1)-C(2)	1.59(9)	1.36(9)	1.48(6)
C(2)-C(3)	1.53(7)	1.68(7)	1.73(8)
C(3)-C(4)	1.49(7)	1.67(8)	1.55(8)
C(4)-C(5)	1.40(6)	1.23(9)	1.42(7)
C(5)-C(6)	1.59(6)	1.57(8)	1.61(7)
C(6)-C(1)	1.50(8)	1.51(8)	1.72(6)
		Angle(°)	
O(12)-Pt(1)-O(13)	90.4(9)	-	-
O(13)-Pt(3)-O(23)	80(1)	-	-
O(12)-Pt(2)-O(23)	83(1)	-	-
O(12)-Pt(1)-N(11)	91(1)	-	-
O(12)-Pt(1)-N(12)	176(1)	-	-
O(13)-Pt(1)-N(11)	178.5(9)	-	-
O(13)-Pt(1)-N(12)	93(1)	-	-
O(12)-Pt(2)-N(21)	178(1)	-	-
O(12)-Pt(2)-N(22)	96(1)	-	-
O(23)-Pt(2)-N(21)	99(1)	-	-
O(23)-Pt(2)-N(22)	176(1)	-	-
O(13)-Pt(3)-N(31)	95(1)	-	-
O(13)-Pt(3)-N(32)	178(1)	-	-
O(23)-Pt(3)-N(31)	179(1)	-	-
O(23)-Pt(3)-N(32)	99(1)	-	-
N(1)-Pt-N(2)	86(1)	82(1)	86(1)
Pt-N(1)-C(1)	110(3)	109(3)	102(2)
Pt-N(2)-C(2)	104(3)	103(3)	109(3)
N(2)-C(2)-C(1)	107(4)	113(4)	104(4)
N(1)-C(1)-C(2)	109(5)	105(5)	106(3)
N(1)-C(1)-C(6)	116(5)	120(5)	107(3)

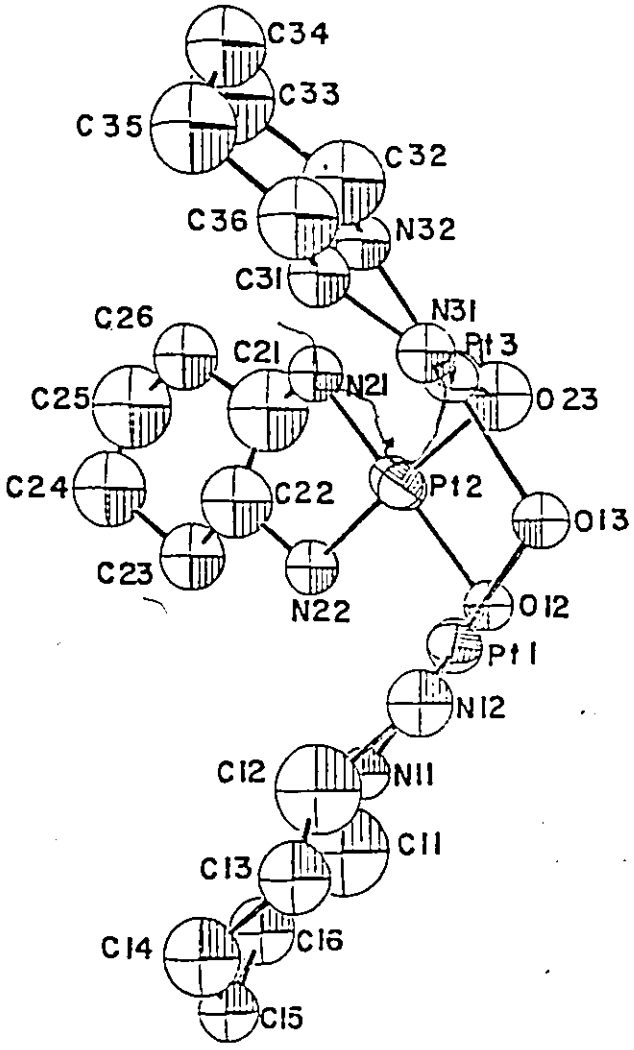
.....cont.

Table 11(cont.)

Atoms	Molecule 1	Molecule 2	Molecule 3
C(2)-C(1)-C(6)	111(5)	104(5)	109(3)
N(2)-C(2)-C(3)	115(4)	101(4)	110(4)
C(1)-C(2)-C(3)	109(4)	114(5)	107(4)
C(2)-C(3)-C(4)	113(4)	108(4)	97(4)
C(3)-C(4)-C(5)	112(4)	111(5)	113(4)
C(4)-C(5)-C(6)	114(4)	122(6)	108(4)
C(5)-C(6)-C(1)	114(4)	119(4)	102(3)
Pt(1)-O(12)-Pt(2)	109(1)		
Pt(1)-O(13)-Pt(3)	110(1)		
Pt(2)-O(23)-Pt(3)	111(1)		

Figure 27

The molecular cation
cyclo-tri-μ-hydroxo-tris-[(trans-1,2-diaminocyclohexane)platinum(II)]



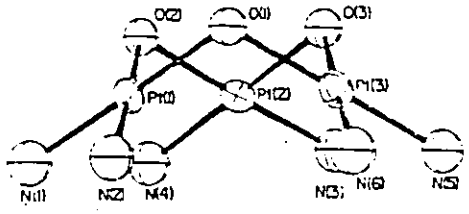
gated by X-ray diffraction.

It was of interest to investigate the geometry of the platinum, nitrogen and oxygen planes in view of the previous studies of structures of trimeric cis-diammine hydroxo-bridged platinum(II) complexes: in one case,[178] the cation has roughly C_{3v} symmetry with all the hydroxide groups lying on the same side of the plane defined by the platinum atoms (Figure 28a); in the other case,[177] the cation has roughly C_2 symmetry, with one of the hydroxide bridges lying almost in the plane of the three platinum atoms and the other two hydroxo groups on either side of the oxygen - three platinum plane (Figure 28b). The cation studied here corresponds to an approximate C_{3v} symmetry when only the platinum, oxygen and nitrogen atoms are considered (Figure 29). The Pt-O-Pt angles in this structure (109 - 111(1)°) lie close to normal tetrahedral angles and agree well with those observed in the other hydroxo-bridged trimeric cation of C_{3v} symmetry. The Pt---Pt distances however are more in line with those observed in the cation of C_2 symmetry (C_{3v} symmetry[178]: Pt---Pt = 3.282(2) - 3.291(2)Å; C_2 symmetry[177]: Pt---Pt = 3.342(2) - 3.521(2)Å; this work: Pt---Pt = 3.381(2) - 3.431(3)Å). This is caused by the longer Pt-O bond distances in the cation studied here.

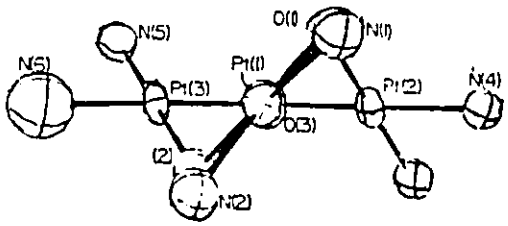
There appears to be no major differences in the structure of the trimer studied here and the structures of the trimers of diammine platinum(II). The differences in activity and toxicity between the trimeric species of cis-DDP and 1,2-dac $PtCl_2$ seems to corroborate the proposition that a different mechanism of action

Figure 28

Molecular structure of hydroxo-bridged platinum trimers



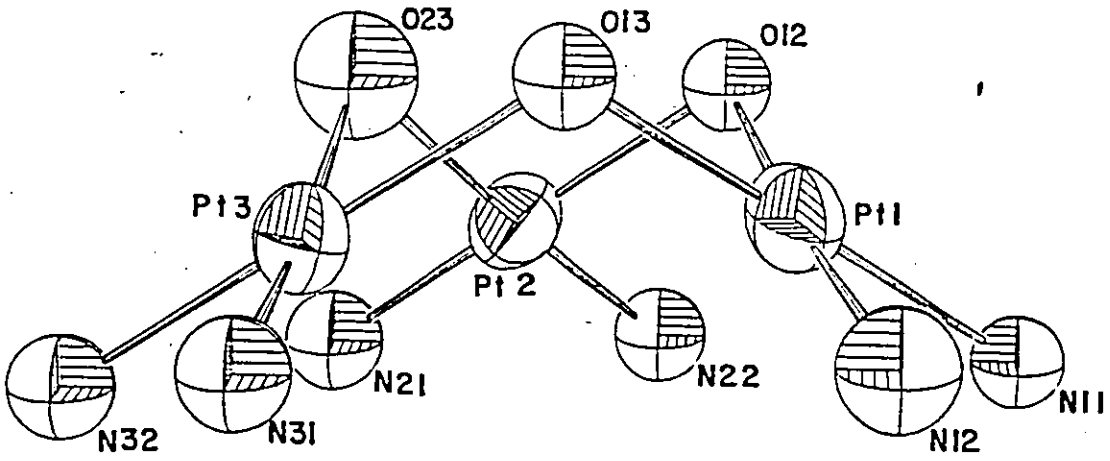
a) cation of bis[cyclo-tri-μ-hydroxo-tris(cis-diammineplatinum(II))] trisulfate hexahydrate, C_{3v} symmetry [178]



b) cation of cyclo-tri-μ-hydroxo-tris[cis-diammineplatinum(II)] nitrate, C_2 symmetry [177]

Figure 29.

C_{3v} symmetry of the Pt, O, N skeleton of
cyclo-tri-μ-hydroxo-tris-[(trans-1,2-diaminocyclohexane)platinum(II)]



occurs with 1,2-dac platinum complexes.[172]

4.2.2 Complexes of platinum(II) with terminal hydroxo ligands

4.2.2.1 Introduction

Platinum(II) complexes with terminal aquo and/or hydroxo groups are generally assumed to occur in aqueous solution.[173] Though the existence of hydroxo complexes in the solid state in some cases has been deduced by spectroscopic means, there have also been doubts as to whether other complexes claimed to contain OH ligands indeed were formulated correctly.[181] Any attempts at isolating platinum(II) complexes with terminal hydroxo ligands have failed [181] or have yielded the dimeric and trimeric complexes mentioned in the previous section. ^{195}Pt Nmr spectra of hydroxo-bridged dimers and trimers of trans-(1,2-dac) platinum(II) also demonstrated that they are important species in solution.[180]

In contrast to platinum(II), platinum(IV) is known to readily form stable Pt-OH bonds (bridging and terminal) and there are crystal structures of such complexes available.[182-184] The complex studied here, [cis-$(NH_3)_2$Pt(1-MeC)(OH)]$NO_3 \cdot 2H_2O$, where 1-MeC is 1-methylcytosine, has been obtained in a crystalline form; the fact that this complex was not isolated as the exclusive product from the solution clearly shows that there must be a delicate balance of conditions leading to the crystallization of the complex (c.f. experimental section, 4.2.2.2). There are, in our opinion, two main reasons for the formation of the complex: first, the specific hydrogen-bonding properties that

stabilize the hydroxo ligand in the complex and second, the poor nucleophilicity of O(2) of 1-methylcytosine toward platinum(II) in aqueous solution. With silver, for example, N(3), O(2) bridging occurs[185] and bidentate N(3), O(2) binding is also observed in complexes of cadmium(II),[186] mercury(II) and copper(II).[187-189] Many more examples of varying degrees of O(2) involvement in metal binding are known.[190-192]

4.2.2.2 Experiments

Dr. B. Lippert prepared the sample of hydroxo-cis-diammine(1-methylcytosine-N^3)platinum(II) nitrate dihydrate, [cis$(NH_3)_2$Pt(OH)(1-MeC)]$NO_3 \cdot 2H_2O$. Titration of freshly prepared [cis-Pt$(NH_3)_2$(1-MeC)(H_2O)]$(NO_3)_2$ [193] with 1 equivalent of NaOH under N_2 (1 mmol, 15 ml volume), subsequent concentration at low temperature to about 0.7 ml volume and cooling at 3°C (2days) gave 220 mg of thin, colourless columns of composition [Pt$(NH_3)_2$(1-MeC)(OH)]NO_3. Further cooling of the filtrate (2 days) gave 90 mg of [cis Pt$(NH_3)_2$ (1-MeC)(OH)]$NO_3 \cdot 2H_2O$ as tiny colourless cubes. Occasionally, but not reproducibly, a third crystalline compound was isolated in low yield; from the IR spectrum it is suspected that this compound contains bridging (N^3, N^4)-1-methylcytosinato ligands similar to the recently described 1-MeC-H dimer,[100] where 1-MeC-H is N(4) deprotonated 1-methylcytosine. (Dr. B. Lippert, personal communication)

The crystal data for hydroxo-cis-diammine (1-methylcytosine-N^3) platinum(II) nitrate dihydrate are shown in Table 12.

Table 12

Crystal data for hydroxo-cis-diammine-(1-methylcytosine-N^3) platinum(II) nitrate dihydrate

Compound	$[Pt(NH_3)_2(OH)(C_5H_7N_3O)]NO_3 \cdot 2H_2O$
F.W.	469.33
Crystal shape, size(cm)	Cylinder; r=0.010, l=0.037
Space group	$P2_1/c$
Unit cell parameters	
a(Å)	12.207(4)
b(Å)	6.203(1)
c(Å)	18.853(5)
β(°)	109.64(2)
Volume ($Å^3$)	1344.5(6)
Z	4
ρ_{calc} (g cm^{-3})	2.32
ρ_{obs} (g cm^{-3})	2.29(1)
Linear absorption coefficient, cm^{-1}	110.2
Absorption correction factor, A*, limits	5.26, -5.90
Maximum 2θ(°)	55
Standard reflections	1, 2, 7; 5,0, 4
e.s.d. (%)	1.30; 1.38
Temperature (°C)	-65
No. of independent reflections	3100
No. with I>0	2844
I<0, rejected	256
R_1^a, R_2^a for all reflections, I>0	0.0657, 0.0688

.....cont.

Table 12 (cont.)

Final shift/error Max.(Ave.)	0.157(0.023)
X (secondary extinction)	0.00026
Final difference map	
highest peak ($e \cdot \mathring{A}^{-3}$); location	2.5; 0.14, 0.01, 0.42
lowest valley ($e \cdot \mathring{A}^{-3}$); location	-2.2; 0.22, 0.12, 0.44
Weighting	$w=(\sigma^2 + 0.0016\ F_o^2)^{-1}$
Error in observation of unit weight	1.315

[a]Definitions for R_1 and R_2 are given in Chapter 2, p. 48

4.2.2.3 Results and discussion

The positional parameters and temperature factors of the atoms are listed in Table 13 and selected interatomic distances and angles are given in Table 14. The molecular cation is illustrated in Figure 30. The cation studied here is very similar to that of a corresponding aquo complex of cis-diammine platinum(II)(1-methylcytosine-N^3);[193] there are no significant differences in equivalent bond lengths and angles.

As in all complexes of platinum bonded to N(3) of 1-methylcytosine reported previously,[84,93-96,99,193,194] the dihedral angle between the platinum coordination plane and the pyrimidine plane is large (79.8(5)°).

The Pt-O distance (2.027(9)Å) is comparable to the Pt-N distances, to the Pt-O distances seen in hydroxo-bridged complexes reported previously,[175-178] (see also section 4.2.1.3 of this work) (range = 1.99(3) - 2.13(3)Å) and to the Pt-O distance in cis-diammine aquo(1-methylcytosine-N)platinum(II) dinitrate hydrate;[193] it is insignificantly longer than the Pt-O values of 2.00(1)Å in $Pt(NH_3)_2Cl_2(OH)_2$.[184] Thus the Pt-O bond lengths seen in the complexes with terminal aquo[193] and terminal hydroxo groups give no indication of weakness of the Pt-O bond which has been suggested by the rapid rate of reaction of square planar d^8 complexes. We suggest therefore that the rapid rate of reaction of OH and OH_2 groups on platinum is associated with a marked weakening of the Pt-O bond in the five-coordinate state. Such a weakening has been observed previously

Table 13

Atomic positional coordinates and temperature factors ($X10^3$) for [cis-$(NH_3)_2Pt(OH)(1\text{-MeC})](NO_3)\cdot 2H_2O$

Atom	x	y	z	U_{iso} or U_{eq}*
Pt	148.80(4)	98.68(7)	452.35(2)	14.4(2)*
O(3)	207.7(7)	-53(1)	376.9(5)	23(2)
N(5)	86.9(8)	239(2)	528.0(5)	22(2)
N(6)	19.5(8)	231(2)	364.6(5)	21(2)
N(3)	283.1(8)	-35(2)	536.3(5)	18(2)
C(2)	263.2(9)	-225(2)	571.1(6)	16(2)
O(2)	164.3(7)	-293(2)	556.2(5)	26(4)*
N(1)	356.8(8)	-319(2)	623.9(5)	19(2)
C(1)	332(1)	-503(2)	665.9(8)	33(3)
C(6)	465.0(9)	-240(2)	643.2(6)	18(2)
C(5)	487(1)	-57(2)	610.7(7)	24(3)
C(4)	392(1)	50(2)	555.7(6)	19(2)
N(4)	509.7(9)	232(2)	525.1(6)	25(2)
O(7)	355.8(8)	612(1)	427.4(5)	27(2)
O(8)	36.9(9)	-344(2)	303.7(5)	36(2)
N(7)	250(1)	417(2)	244.8(6)	32(2)
O(71)	259.3(8)	315(2)	302.4(5)	32(5)*
O(72)	320(1)	549(2)	241.4(9)	69(9)*
O(73)	157.8(9)	382(2)	186.7(6)	55(6)*

* $U_{eq} = 1/3(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$

Table 14

Interatomic distances (Å) and angles (°) for [cis-$(NH_3)_2Pt(OH)(1\text{-MeC})](NO_3)\cdot 2H_2O$[a]

Atoms	Distance	Atoms	Angle
Pt-N(3)	2.035(8)	N(3)-Pt-N(5)	91.2(4)
Pt-N(6)	2.036(8)	N(3)-Pt-O(3)	88.5(4)
N(1)-C(2)	1.37(1)	N(5)-Pt-O(3)	177.7(4)
N(3)-C(4)	1.36(2)	N(3)-Pt-N(6)	177.0(5)
C(5)-C(6)	1.36(2)	N(5)-Pt-N(6)	91.7(4)
N(1)-C(1)	1.48(2)	N(6)-Pt-O(3)	88.7(4)
C(4)-N(4)	1.32(2)	Pt-N(3)-C(2)	118.9(7)
N(7)-O(72)	1.21(2)	C(6)-N(1)-C(2)	123(1)
Pt-N(5)	2.02(1)	C(2)-N(3)-C(4)	120.4(8)
Pt-O(3)	2.027(9)	C(4)-C(5)-C(6)	118(1)
C(2)-N(3)	1.41(2)	C(6)-N(1)-C(1)	119.9(9)
C(4)-C(5)	1.44(2)	N(1)-C(2)-O(2)	123(1)
C(6)-N(1)	1.34(2)	N(3)-C(4)-N(4)	120.3(9)
C(2)-O(2)	1.22(1)	O(71)-N(7)-O(72)	122(1)
N(7)-O(71)	1.23(2)	O(72)-N(7)-O(73)	120(1)
N(7)-O(73)	1.30(1)	Pt-N(3)-C(4)	120.6(8)
		N(1)-C(2)-N(3)	117.6(9)
		N(3)-C(4)-C(5)	120(1)
		C(5)-C(6)-N(1)	121(1)
		C(1)-N(1)-C(2)	117(1)
		O(2)-C(2)-N(3)	119.8(9)
		N(4)-C(4)-C(5)	120(1)
		O(71)-N(7)-O(73)	118(1)

.....cont.

Table 14 (cont.)

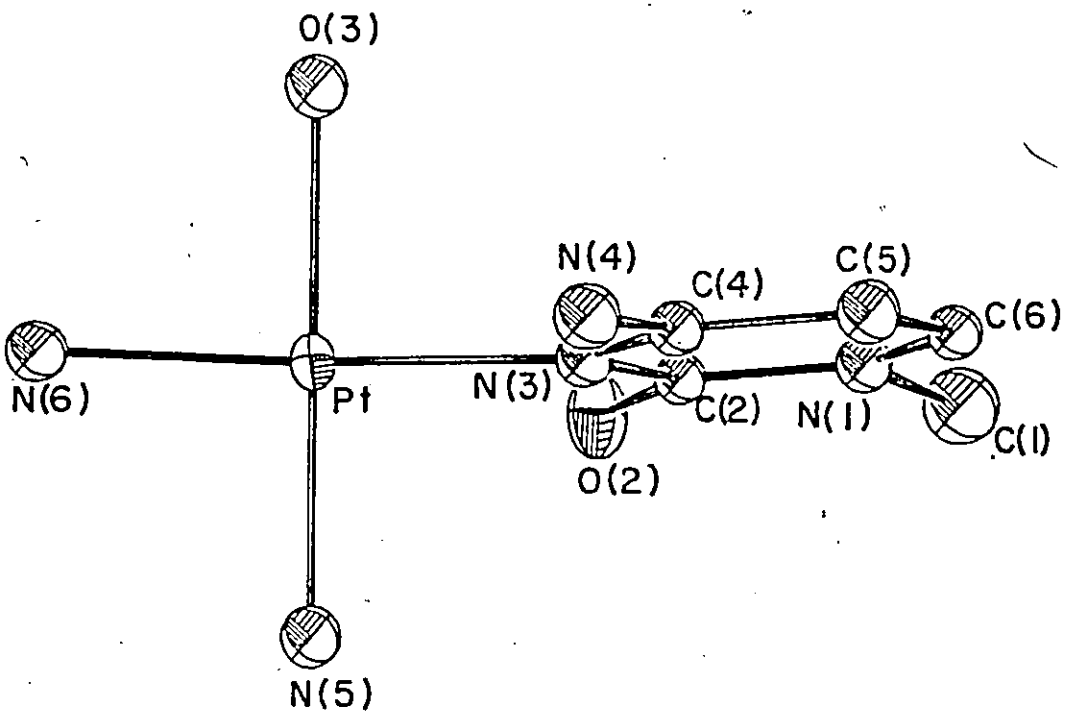
Hydrogen bonding

Atoms	Distance	Atoms	Distance
O(3)-(71)	2.86(1)	N(6)-O(8)^{vi}	3.05(1)
O(3)-H(31)	0.9(1)	N(6)-O(73)^{vi}	2.98(2)
H(31)-O(71)	1.9(1)	N(6)-H(61)	0.7(1)
O(3)-O(8)	2.75(1)	H(61)-O(8)^{vi}	2.3(1)
O(8)-H(81)	1.0(1)	N(6)-O(8)^{v}	2.91(1)
O(3)-H(81)^{iii}	2.3(1)	O(7)-O(71)	2.91(1)
O(3)-O(7)^{iii}	2.71(1)	O(7)-H(71)	1.2(1)
O(7)-H(72)	1.1(1)	H(71)-O(71)	2.5(1)
O(3)-H(72)^{iii}	1.7(1)	O(8)-O(73)^{vii}	2.82(2)
N(5)-O(2)^{ii}	2.96(1)	O(8)-H(82)	1.0(1)
N(5)-H(51)	0.7(1)	H(82)-O(73)^{vii}	1.8(1)
H(51)-O(2)^{ii}	2.5(1)	N(4)-O(7)	2.93(1)
N(5)-O(73)^{iv}	2.92(1)	N(4)-O(7)^{i}	2.87(1)
N(5)-O(2)^{v}	3.05(1)		

[a]Atoms are related to those in Table 13 by the following transformations: (i) 1-x, 1-y,1-z; (ii) -x, -y, 1-z; (iii) x, y-1, z; (iv) x, ½-y, ½+z; (v) x, 1+y, z; (vi) -x, ½+y, ½-z; (vii) -x, y-½, ½-z.

Figure 30

The molecular cation hydroxo-cis-diammine(1-methylcytosine-N^3)platinum(II)



in rhodium(I) complexes where the Rh-O distances to an acetylacetonate ion increased from 2.025(5)Å and 2.037(5)Å in the square planar complex [195] to 2.217(9)Å and 2.235(8)Å in the five-coordinate complex.[144]

Since the Pt-O bond in a terminal hydroxo or aquo platinum(II) complex is not inherently weak, it was interesting to investigate why it is so difficult to isolate these complexes; it is well known that aquo species occur in solution.[196] It has been postulated previously that in order to form aquo and terminal hydroxo complexes of platinum(II) certain hydrogen bonding requirements would have to be fulfilled.[197] The postulate is based on Brown's acid-base model [198] which assumes that the valence V_i of each atom in a solid is shared between the bonds it forms so that

$$V_i = \sum_j S_{ij} \qquad (4.1)$$

where S_{ij} is the valence for the bond between atoms i and j. S_{ij} can be calculated from the experimental bond length between atoms i and j by the following equation:

$$S_{ij} = (r_{ij}/r_o)^{-n} \qquad (4.2)$$

where r_o and n are fitted parameters. Once the bonding interactions to each atom have been taken into account one can define a residual bond valence as a measure of the acid (S_A) or base strength (S_B) depending on whether the group is an electron acceptor or donor. These residual valences will be satisfied through interactions with other ions or molecules; thus, in addition to the normal bonding interactions, one must also consider weak interactions to satisfy the valence on each atom. Brown [198] postulated that bonds will

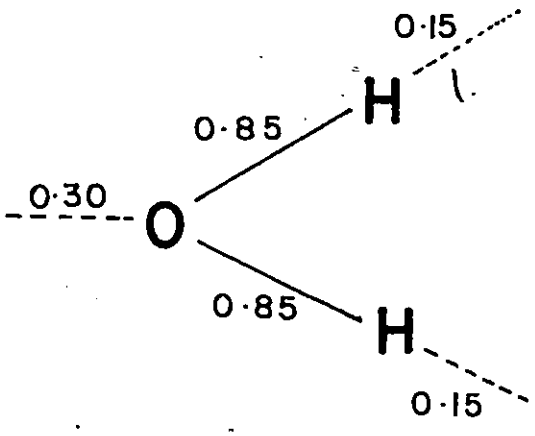
normally form only when the Lewis-acid strength of the electron acceptor is close to the Lewis-base strength of the electron donor i.e. $S_A = S_B$.

If one considers water (Figure 31a) with an O-H bond valence of 0.85, the oxygen atom has a base strength of 0.30 and the hydrogen atoms have an acid strength of 0.15. In this way, the valences add up to 2 and 1 on the oxygen atom and each of the protons, respectively. Similarly for the hydroxide ion, the oxygen atom has a base strength of 1.05 and the proton has an acid strength of 0.05, making the hydroxide group a very strong base (Figure 31b).

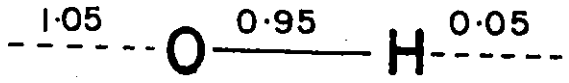
If one binds either of these ligands to platinum(II), the Pt-O bond will have a valence of 0.5. Neither the aquo or the hydroxo group has a residual valence of 0.5 and some rearrangements must occur (Figure 32). The overall result for the aquo ligand is an increase in its acid strength after coordinating to the platinum atom (Figure 32a). In aqueous solution, water acts as an excellent hydrogen bond acceptor and the excess bond valence on the coordinated water can be satisfied through hydrogen bonds. In the structure of the platinum(II) complex with a terminal aquo group, two very strong hydrogen bonds to two acceptor water molecules are formed.[193] In the case of the hydroxo ligand (Figure 32b), the formation of a bond to platinum leads to a negative bond valence at the hydrogen atom, which is not possible. The division of the residual valence on the oxygen atom into two shows how the formation of a hydroxo-bridged complex is very favourable; thus, it is not surprising that the

Figure 31

Residual valences in a water molecule and hydroxide anion in a lattice *



(a) water molecule

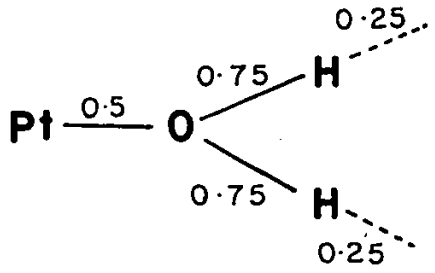


(b) hydroxide ion

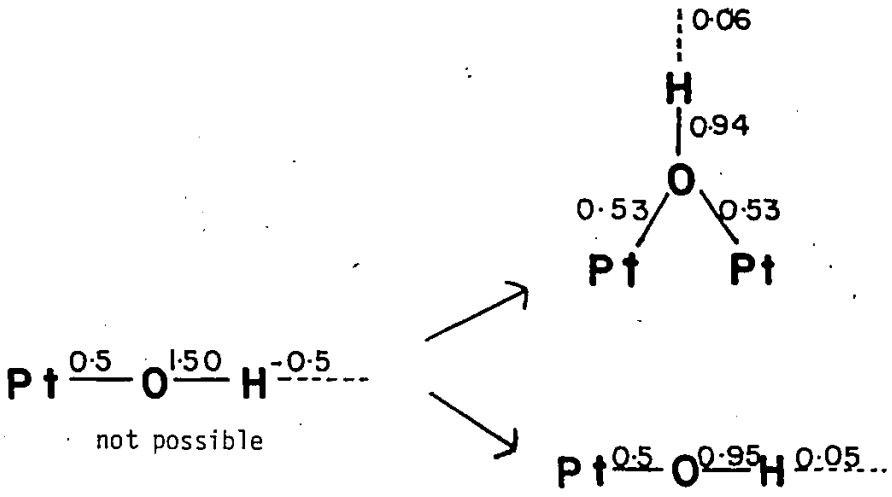
*Values for the valence of the O-H bonds are from reference 197.

Figure 32

Rearrangement of bond valences of aquo and hydroxo ligands after bond formation to platinum(II)



(a) rearrangement of the bond valences leads to an increase in the acid strength of the aquo ligand



(b) rearrangement of the bond valences in the hydroxo ligand can lead to the formation of hydroxo-bridged complexes or to the formation of strong donor hydrogen bonds to the oxygen atom of the hydroxo ligand to satisfy the residual valence

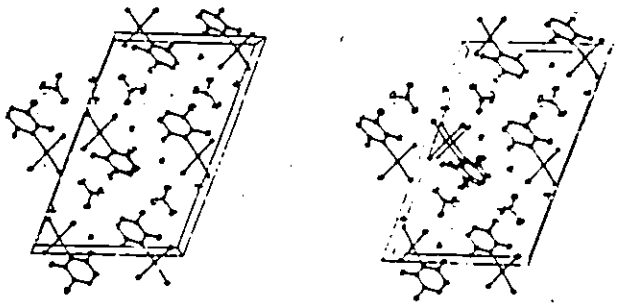
hydroxide ion forms bridges between two platinum atoms so readily. Alternatively, the acceptance of hydrogen bonds from other hydrogen donors will stabilize the hydroxide ion. This is observed here with two strong hydrogen bonds to water molecules in the lattice (O(3)---O(7)^{iii} = 2.71(1)Å and O(3)---O(8) = 2.75(1)Å). The positions of the hydrogen atoms attached to these oxygen atoms were located and the hydrogen atoms are in the expected positions. Thus, the presence of lattice water molecules is essential to the stability of the complex.

Another reason for the formation of this terminal hydroxo platinum(II) complex is the poor nucleophilicity of the O(2) position of the 1-methylcytosine ligand towards platinum(II). Unlike other metal complexes of 1-methylcytosine where there is an interaction between the exocyclic O(2) atom and the metal centre, there has never been any evidence for such an interaction when platinum is the metal ion. This is reflected in the difference between the M-N3-C4 and the M-N3-C2 angles (Δ value).[187] When there is a metal to O(2) interaction, the Δ value is large (12.6(2)-24°).[185,187] In platinum complexes the Δ values tend to be lower (Δ = 0.6(9)°-9.8(8)°). In this complex, the Δ value is 1.7(9)°.

The packing of the unit cell is shown in Figure 33. The cations are arranged in layers centered in the planes z = 0, z = ½. The anions lie in separating layers at z = ¼, 3/4. Within a layer the cations are stacked up along the b direction and canted so that there is some cytosine ring overlap; the rings are overlapped like tiles

Figure 33

The unit cell of
hydroxo-*cis*-diammine(1-methylcytosine-N^3)platinum(II) nitrate dihydrate



a and *c** are parallel to the bottom and side of the page, respectively and the view is down *b*.

on a roof. This stack of cations is hydrogen-bonded together through O(3)---O(7)^{iii}, O(7)---N(4), N(5)---O(2)^{ii}, N(6)---O(8)^{v} and N(6)^{iii}---O(8). At the x=½ plane, cations in adjacent stacks are hydrogen bonded through N(4)---O(7)^{i}, N(4)^{i} ---O(7) giving a four centered system of two N(4) and two O(7) in a diamond shape. This type of hydrogen bonding has been seen previously,[96] although the oxygen atoms were from nitrate groups. At x=0, the hydrogen bonding between cation stacks is through N(5)---O(2)^{ii}. Hydrogen bonding to the nitrate ion provides binding in the c direction, besides the ionic interactions, through O(3)---O(71), O(7)---O(71) and N(5)---O(73)^{iv}, N(6)---O(73)^{vi}, and some binding in the a direction through the extra. O(8)---O(73)^{vii} hydrogen bonds. The large thermal motion of O(72) clearly arises because it is not involved in hydrogen bonding.

4.3 SOLVOLYSIS OF cis-DDP WITH DIMETHYLSULFOXIDE

4.3.1 Introduction

Hydrolysis products of cis-DDP with terminal aquo groups occur in solution [173,196] yet with the exception of the complex mentioned in Section 4.2 no samples of the complexes have been obtained in the solid state. The difficulty in isolating these products has led us to try dimethylsulfoxide as a solvent system.

Dimethylsulfoxide (DMSO) is an interesting ligand because it can exhibit linkage isomerism: in general, sulfoxides bind to the hard first-row transition metals via the oxygen atom but via the sulfur atom to the softer metals.[199] In sterically hindered complexes, DMSO may

bind through oxygen to relieve the steric strain as observed in a square-planar palladium(II) complex with two DMSO ligands binding through the sulfur atom and the other two ligands attached through their oxygen atom.[200] In platinum complexes with no steric strain, sulfoxide ligands always bind through the sulfur atom.[92,95,98,201-209] Most of these structures involve complexes of the type $[PtCl_2(L)(R)]$ where L is an amine or DMSO and R is a dialkylsulfoxide. These have been studied mainly because DMSO has been used as a solvent in the tests for the anti-tumour activity of some platinum complexes and partly because cis-$(DMSO)_2PtCl_2$ has common features with cis-DDP, both complexes having two chloride ligands and two neutral ligands in cis-positions.

Because of the relative ease in isolating platinum complexes with DMSO as a ligand, we decided to study the structure of the cation formed in the first step of the solvolysis of cis-DDP in dimethylsulfoxide. It was isolated as the nitrate salt, [cis-$(NH_3)_2$ Pt(DMSO)Cl]NO_3.

4.3.2 Experiments

This complex was prepared by Dr. B. Lippert.

cis-DDP(5 mmol) was dissolved in 5 ml of DMSO. $AgNO_3$ (5 mmol), dissolved in 5 ml of DMSO, was added slowly (0.5-1.0 hr). The silver chloride was removed by filtration and 10 ml of concentrated acetic acid were added to the yellowish solution, followed by 5 ml of CCl_4. The mixture was stoppered and placed in the refigerator. After one week to two months and addition of more CCl_4 (25 ml, finally 50 ml) several crops of [cis-$(NH_3)_2Pt(DMSO)Cl]NO_3$ were obtained. Analysis for

$PtC_2H_{12}ClN_3O_4S$; calc: C, 5.93; H, 2.99; N, 10.38; O, 15.81; Pt, 48.2 %; found: C, 6.32; H, 3.00; N, 10.35; O, 15.89; Pt, 47.4 %.

The crystals were sent in a sealed vial and had a wet appearance. Attempts to grind the crystals into a cylindrical shape gave very broad diffraction spots. Similar results were obtained when crystals were cut: the crystals were very soft and seemed made up of thin plates stacked together. These plates slipped past one another when attempts were made at cutting the crystal. Finally, a crystal of truncated pyramidal shape was chosen and was sealed in a capillary tube. Precession photographs indicated the orthorhombic system with the systematic absences for the space group Cmcm, $Cmc2_1$ or Ama2(C2cm).

The intensities of h, k, $\pm$l reflections were measured for a C-centered cell. A comparison of the h, k, l and h, k, -l reflections showed that they were significantly different. This would usually indicate that the crystal belongs to the mm2 orthorhombic system and that the space group is $Cmc2_1$ rather than Cmcm. However, absorption may affect the intensities of equivalent reflections; the solution of the structure was attempted in Cmcm but the model was not good. The C2cm possibility was also attempted but again, the model was not good.

Attempts to correct for the strong absorption problem were not successful. The crystal has a large linear absorption coefficient (μ = 146.1 cm^{-1}), and the size variation is also quite large from one face to another (see Table 15). Very few reflections above 2θ = 35° were strong enough to give a good absorption correction curve using the ψ-scan method. The correction was attempted nonetheless

and the index of agreement between equivalent reflections in mm2 became worse when using absorption corrected data. Furthermore, the solution of the structure gave a better model when structure factors not corrected for absorption were used. The measurement of the crystal faces was not possible mainly because the faces were not very sharp and partly because of the further deterioration of the faces as the crystal was pushed inside the capillary tube.

The density of the crystal was obtained in a chloroform/bromoform mixture (ρ_{obs} = 2.56 $g \cdot cm^{-3}$). This value, coupled with the volume of the unit cell and the molecular weight of the complex gave a Z value of 3.97. Thus, the platinum atom must lie on the mirror plane in $Cmc2_1$. This agrees with the results of the three-dimensional Patterson synthesis. All the atoms in the platinum molecule are located on the mirror plane at x = 0 with the exception of the carbon atom of the DMSO ligand. Similarly, only one oxygen atom of the nitrate ion lies away from the mirror plane at x = $\frac{1}{2}$.

Because of the softness of the crystal, the reflections were broad. This in turn caused much difficulty in the centering procedure used to determine the unit cell parameters. Two of the interaxial angles were significantly different from 90° and the possibility of the crystal belonging to other crystal systems was investigated; the only possible space group is Cc. The solution of the structure in Cc gives the same packing of molecules in the unit cell. The constraints of the crystallographic mirror plane have been removed yet none of the atoms move away from their position in $Cmc2_1$ to any

significant extent; the carbon atoms of the DMSO ligand and the oxygen atoms of the nitrate ion, which were related by the mirror planes in $Cmc2_1$ show the same relation in Cc. For these reasons, the structure was solved in the more symmetric space group.

The final difference Fourier synthesis still shows a number of large peaks ($\sim 5\ e \cdot A^{-3}$) close to the platinum atom. This is probably caused by the neglect of absorption mentioned earlier. This effect may also be enhanced by the fact that the best weighting scheme for the structure has a large g^2 value (0.004) which gives less weight to the stronger reflections. (see equation for weighting scheme, Chapter 2)

4.3.3 Results and discussion

The crystal data for [chloro-cis-diammine-(dimethylsulfoxide-S)platinum(II)]nitrate are given in Table 15. The platinum complex and the nitrate anion are shown with their labelled atoms in Figure 34. The atomic parameters and the temperature factors are listed in Table 16 and the bond lengths and angles are given in Table 17.

As expected for platinum complexes with a dimethylsulfoxide ligand, the DMSO molecule binds to platinum through the sulfur atom. The bond lengths and angles in the cation are normal for these types of complexes.[92,95,98,201-209] The geometry of the DMSO ligand is in fair agreement with that in free DMSO.[210,211] The cation is planar as required by its position on the crystallographic mirror plane; the only atom lying away from the mirror plane is the carbon atom of

Table 15

Crystal data for
[chloro-cis-diammine(dimethylsulfoxide-S)platinum(II)]nitrate

Compound	$[(NH_3)_2PtCl(OS(CH_3)_2)]NO_3$
F.W.	404.74
Crystal shape, size (cm)	Truncated pyramid, 0.013 X 0.027 X 0.030
Space group	$Cmc2_1$
Unit cell parameters	
a(Å)	6.609(2)
b(Å)	9.384(3)
c(Å)	16.782(4)
Volume ($Å^3$)	1040.7(5)
Z	4
ρ_{calc} ($g \cdot cm^{-3}$)	2.58
ρ_{obs} ($g \cdot cm^{-3}$)	2.56(1)
Linear absorption coefficient, cm^{-1}	146.1
Maximum 2θ(°)	55
Standard reflections and e.s.d. (%)	1.21; 1.20 0, 2, 7; 1, -3, -4
Temperature (°C)	22
No. of independent reflections	1355
No. with $I > 0$	1294
No. with $I < 0$, rejected	61
R_1[a], R_2[a]	0.0816, 0.0972

.....cont.

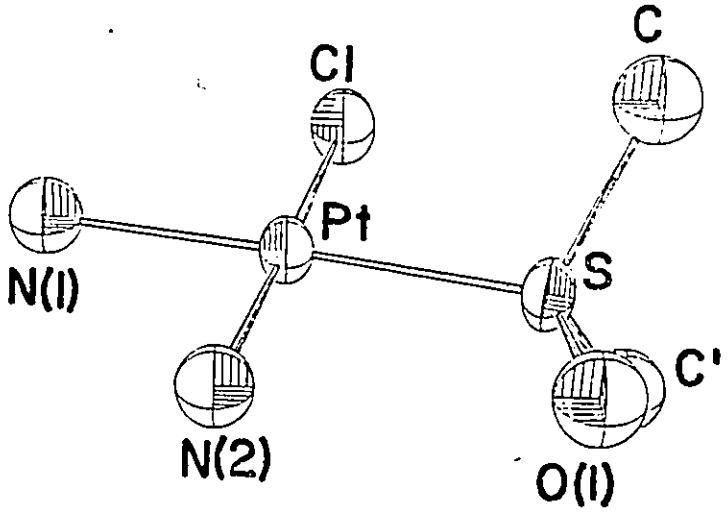
Table 15 (cont.)

Final shift/error, Max.(Ave.)	0.051(0.008)
χ (secondary extinction)	0.00059
Weighting	$w = (\sigma^2 + 0.004\ F_o^2)^{-1}$
Error in observation of unit weight	1.0480

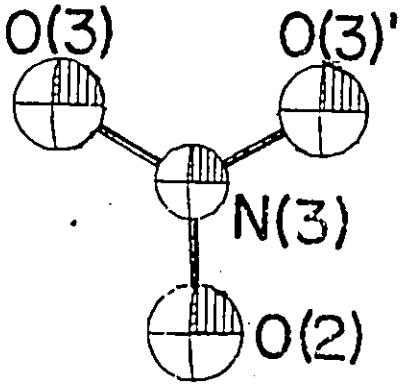
[a]Definitions of R_1 and R_2 are given in Chapter 2, p. 48

Figure 34

The cation chloro-cis-diammine(dimethylsulfoxide-S)platinum(II) (a) and the nitrate anion (b)



(a) The cation cis-$(NH_3)_2Pt(Cl)(DMSO)^+$. All atoms lie on the crystallographic mirror plane with the exception of C and C'.



(b) The nitrate anion. O(3) and O(3)' are related by the crystallographic mirror plane through N(3) and O(2).

Table 16

Atomic parameters and isotropic or equivalent temperature factors ($X10^3$) for [chloro-cis-diammine(dimethylsulfoxide-S)platinum(II)]nitrate

Atom	x	y	z	U_{iso} or U_{eq}*
Pt	0	170.98(8)	0	29.8(9)*
Cl	0	410.7(9)	-29.8(5)	44(6)*
S	0	107.8(8)	-127.5(4)	35(6)*
N(1)	0	222(3)	123(2)	41(5)
N(2)	0	-42(3)	31(2)	38(5)
C	206(5)	185(3)	-177(2)	51(6)
O(1)	0	-47(3)	-142(2)	51(6)
N(3)	500	86(3)	160(2)	36(5)
O(2)	500	214(3)	138(2)	62(7)
O(3)	662(3)	24(2)	165(1)	55(4)

*$U_{eq} = 1/3(U_{11} + U_{12} + U_{13})$

Table 17

Bond lengths (Å) and bond angles (°) in [cis-$(NH_3)_2Pt(DMSO)Cl]NO_3$

Atoms	Distances
Pt-N(1)	2.11(3)
Pt-N(2)	2.07(3)
Pt-Cl	2.304(8)
Pt-S	2.220(6)
S-O(1)	1.47(3)
S-C	1.75(3)
N(3)-O(2)	1.25(4)
N(3)-O(3)	1.23(2)

Atoms	Angles
N(1)-Pt-N(2)	89(1)
N(1)-Pt-Cl	89.5(8)
N(1)-Pt-S	177.5(8)
N(2)-Pt-Cl	178.0(8)
N(2)-Pt-S	89.1(8)
Cl-Pt-S	93.0(3)
Pt-S-O(1)	115(1)
C-S-O(1)	110(1)
C-S-C'	102(1)
Pt-S-C	110(1)
O(2)-N(3)-O(3)	119(1)
O(3)-N(3)-O(3)'	122(2)

Possible hydrogen bonds and other interactions

Atoms	Distance	Atoms	Distance
$Cl(2)\cdots N(2)^{i}$	3.486(9)	N(1)-O(1)	2.99(3)
$Cl(2)-N(2)^{ii}$	3.486(9)	$N(1)-O(1)^{iii}$	2.99(3)
$O(1)-C^{iv}$	3.23(3)	$O(1)-C^{v}$	3.23(3)
$O(3)-C^{vi}$	3.42		

Atoms are related to the positions given in Table 16 by the following symmetry operations: (i) x-½, ½+y, z; (ii) ½+x, ½+y, z; (iii) -x+1, y, z; (iv) x-½, y-½, z; (v) ½-x, y-½, z; (vi) -x+1, -y, z+½.

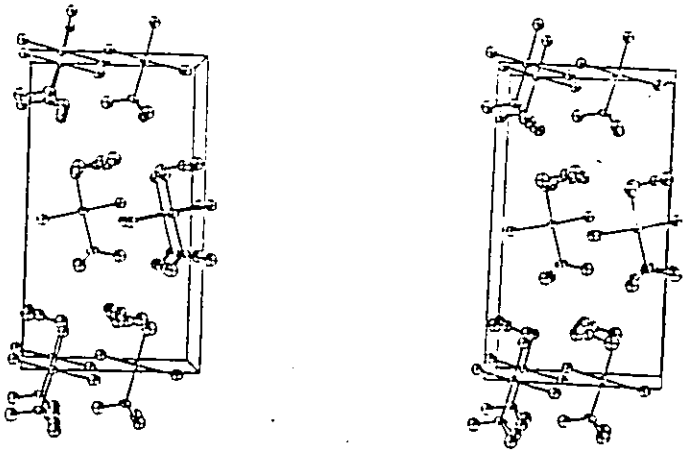
the DMSO ligand. The geometry of the nitrate anion is also in agreement with previously published structures (see for example references 176 and 177).

The packing of the molecules in the unit cell is shown in Figure 35. The crystal consists of layers of molecules in the ab plane: the platinum complexes stand in the plane at z = 0 and z = ½ while the nitrate anions lie in the plane at approximately z = ¼ and z = 3/4. The nitrate anions lie much closer to one layer of platinum complexes than they do to another related by the 2-fold screw axis along c; thus, in the c direction there are distinct layers of molecules; these are skewed with respect to one another. The shortest contact between the layers occurs between an oxygen atom of the nitrate anion and a carbon atom of the DMSO ligand(O(3)---C = 3.42(3)Å). The large separation is presumably caused by the bulkiness of the DMSO groups.

The cations in a layer are arranged in long interlocking chains along a. There are two long contacts between the chains which involve molecules related by the centering operation. The first contact involves N(2) of one molecule and the chloride ligand of two cations in the second chain (N(2)---Cl = 3.486(9)Å); the second interaction occurs between the DMSO ligands of molecules in separate chains (O(1)---C = 3.23(3)Å). The nitrate anions fit between two platinum molecules in the same chain. There is a hydrogen bond between two oxygen atoms of the nitrate anion and the amine ligand of two cations related by a unit translation along a (N(1)---O(1) = 2.99(3)Å). The intermolecular interactions are summarized in Table 17.

Figure 35

The contents of the unit cell of [cis-$(NH_3)_2Pt(Cl)(DMSO)]NO_3$



c and b are parallel to the side and bottom of the page, respectively and the view is down a.

4.4 PURIFICATION OF cis-$Pt(NH_3)_2Cl_2$ WITH DMF

The notable clinical success of cis-DDP [3] has led to a great interest in the chemistry of this compound. Because of its significance as an anti-tumour agent, the purity of cis-DDP is of utmost importance. This aspect has been addressed previously [212,213] and it has been shown that crystallization or reprecipitation of cis-DDP from N, N-dimethylformamide (DMF) or N, N-dimethylacetamide dramatically improves the quality of the product. Furthermore, the crystallization procedure does not convert the cis isomer of the product to the trans isomer; isomerization has been observed in recrystallization procedures of cis-platinum(II) complexes.[214]

It is also possible to isolate solvates of cis-DDP and cis cis-$(NH_3)_2PtI_2$ with formamide and substituted formamides (N-methylformamide, DMF and N, N- diethylformamide) and the IR spectra of crystalline adducts have been recorded (personal communication from Dr. B. Lippert). Only the cis-DDP·DMF product shows major changes as compared to the two components cis-DDP and DMF. These changes are attributed to hydrogen bonding interactions between the NH_3 groups and DMF. It was with this information in mind that the structure of cis-$(NH_3)_2PtCl_2$·DMF was investigated.

The cis-DDP·DMF complex was prepared by Raudaschl and her co-workers.[213] Crystals of the complex are rectangular blocks which slowly decompose by loss of DMF from the lattice. The systematic absences observed in precession photographs corresponded to those of the orthorhombic system, space group Pcca. According to the molecular

weight calculation and measurement of the unit cell volume, the density was calculated as 2.53 $g \cdot cm^{-3}$ for Z = 4 and 5.06 $g \cdot cm^{-3}$ for Z = 8. Attempts at measuring the density failed: the crystal, which originally floated in bromoform, slowly sank to the bottom of the test tube. The appearance of the yellow solid under a microscope was that of a cloudy solid of unchanged shape. Removal of the crystal from the bromoform solution yielded a yellow powder. We attribute this behaviour to the rapid loss of DMF from the lattice upon immersion of the crystal in bromoform. The fact that the crystal floated in bromoform originally leads us to believe that Z = 4 (ρ = 2.53 $g \cdot cm^{-3}$, $\rho_{bromoform}$ = 2.8899 $g \cdot cm^{-3}$). Once the DMF is lost from the lattice, we are left with cis-DDP which has a density of 3.86 $g \cdot cm^{-3}$ [138] and the crystal sinks. Our belief that Z = 4 was also reinforced by the fact that for all reflections, those with l = 2n were of much higher intensity than those with l = 2n + 1, indicating that the platinum atom lies on a two-fold rotation axis, special position d or e in the International Tables, at ¼, 0, z or ¼, ½, z.

The platinum atom position was verified by a three-dimensional Patterson synthesis followed by a full-matrix least-squares refinement, minimizing $\Sigma w(|F_o| - |F_c|)^2$, and followed by a three-dimensional difference synthesis which revealed the ligands of the cis-DDP molecule. Some of the atoms of the DMF molecule could not be found however and it appeared as though the packing of the DMF molecule may belong to another space group. A systematic search determined that the packing was that of the space group $Pca2_1$. The structure was then solved in $Pca2_1$.

The crystal data for cis-dichlorodiammineplatinum(II)-N, N-dimethylformamide are given in Table 18. The atomic parameters and temperature factors are listed in Table 19. The labelling of the atoms of the platinum complex and the DMF molecule is shown in Figures 36a and 36b respectively and the bond lengths and angles are listed in Table 20.

The geometry around the platinum atom is square-planar with the platinum atom sitting out of the plane defined by the four ligands by 0.015(1)Å. The Pt-N and Pt-Cl bond lengths are normal for these types of complexes.

The DMF molecule is planar with the nitrogen atom being farthest out of the mean plane of the molecule at 0.04(1)Å. The DMF molecule is disordered, as indicated by the large thermal parameters of its atoms compared to the thermal parameters of the atoms of the cis-DDP molecule. This effect has been observed in many structures containing lattice DMF molecules.[215-218] The disorder often results in bond lengths and angles which vary from the normal values.[217,218] This is observed in this structure with C(3)-N(3), 1.56(5)Å and C(2)-N(3), 1.33(5)Å. Any attempts made at resolving the disorder led to solutions which were implausible.

The cis-DDP molecules pack in the same way in either Pcca or $Pca2_1$. In Pcca, the DMF molecules are disordered about the two-fold rotation axis along y at z = ¼. This simply adds to the disorder of the solvent molecules; the thermal parameters on the atoms of the DMF molecule were still much larger than those of the atoms of the

Table 18

Crystal data for cis-DDP·DMF

Compound	[cis-$Pt(NH_3)_2Cl_2$]·$(CH_3)_2NCHO$
F.W.	373.15
Crystal shape, size(cm)	Rectangular block, 0.025 X 0.021 X 0.018
Space group	$Pca2_1$ *
Unit cell parameters	
a(Å)	11.372(2)
b(Å)	7.723(2)
c(Å)	11.165(3)
$\alpha = \beta = \gamma = 90°$	
Volume ($Å^3$)	980.5(4)
Z	4
$\rho_{calc}(g.cm^{-3})$	2.53
Linear absorption coefficient, cm^{-1}	155.38
Absorption correction factor, A*, limits	11.908, 9.258
Maximum 2θ(°)	55
Standard reflections and e.s.d. (%)	2, 1, 2 ; 4, 4, 0 1.48; 1.75
Temperature (°C)	22
No. of independent reflections	2542
No. with $I > 0$	2085
No. with $I < 0$, rejected	457
$R_1{}^a$, $R_2{}^a$	0.0637, 0.0388

.....cont.

Table 18 (cont.)

Final shift/error, Max.(Ave.)	0.015 (0.004)
X (secondary extinction)	0.00077
Final difference map	
highest peak ($e \cdot \mathring{A}^{-3}$); location	2.5; 0.14, 0.01, 0.42
lowest valley ($e \cdot \mathring{A}^{-3}$); location	-2.2; 0.22, 0.12, 0.44
Weighting	$w = (\sigma^2)^{-1}$
Error in observation of unit weight	0.8465
PSI Scan	
2θ Max/Min	54.67°, 5.26°
χ Max/Min	93.03°, 86.97°
No. reflections used	10
PSI increment/range	10°, 0-350°
Min correction factor	0.410

[a]Definitions of R_1 and R_2 are given in Chapter 2, p. 48

*The transformation matrix used to interchange the axes in going from Pcca to $Pca2_1$ is given by:

$$\begin{bmatrix} 0 & 0 & -1 \\ 0 & 1 & 0 \\ 1 & 0 & 0 \end{bmatrix}$$

The unit cell parameters given in this table are those obtained after the transformation.

Table 19

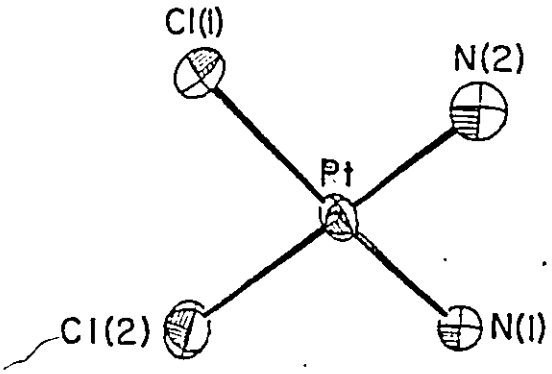
Atomic parameters and isotropic or equivalent temperature factors ($X10^3$) for cis-DDP·DMF

Atom	x	y	z	U_{iso} or U_{eq}*
Pt	-11.66	-9.15	0	25.7(2)*
Cl(1)	128.5(6)	-158.7(9)	109.2(7)	41(4)*
Cl(2)	129.4(6)	146.0(8)	-102.6(8)	42(4)*
N(1)	-138(2)	123(2)	-85(2)	25(4)
N(2)	-137(2)	-154(2)	92(2)	38(5)
O(1)	394(1)	491(2)	956(1)	74(4)
C(1)	492(2)	457(2)	914(2)	62(5)
N(3)	504(1)	391(2)	801(1)	49(4)
C(2)	612(4)	357(5)	760(3)	70(4)
C(3)	389(4)	336(5)	736(3)	70(4)

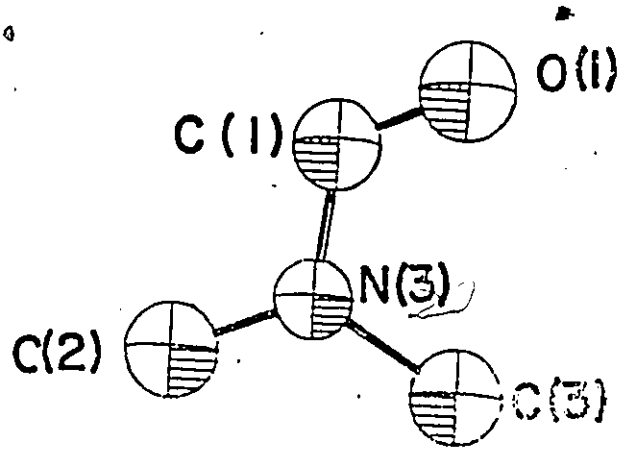
*$U_{eq} = 1/3(U_{11} + U_{22} + U_{33})$

Figure 36

The molecules in cis-DDP·DMF



(a) cis-dichlorodiammineplatinum(II)



(b) dimethylformamide

Table 20

Bond lengths (Å) and bond angles (°) for
[cis-$(NH_3)_2PtCl_2$]C_3H_7NO

Atoms	Distance	Atoms	Angles
Pt-N(1)	2.00(2)	N(1)-Pt-N(2)	91.0(7)
Pt-Cl(2)	2.306(7)	N(2)-Pt-Cl(1)	86.8(6)
N(3)-C(2)	1.33(5)	O(1)-C(1)-N(3)	122(2)
Pt-N(2)	2.08(2)	C(2)-N(3)-C(3)	124(2)
O(1)-C(1)	1.24(2)	N(1)-Pt-Cl(1)	176.4(5)
N(3)-C(3)	1.56(5)	N(2)-Pt-Cl(2)	178.7(6)
Pt-Cl(1)	2.315(7)	C(1)-N(3)-C(2)	120(2)
C(1)-N(3)	1.36(2)	N(1)-Pt-Cl(2)	89.9(5)
		Cl(1)-Pt-Cl(2)	92.4(3)
		C(1)-N(3)-C(3)	116(2)

Possible hydrogen bonds

$O(1)\text{-}N(2)^{i}$	3.03(3)
$O(1)\text{-}N(2)^{ii}$	3.04(2)
$N(1)\text{-}Cl(1)^{iii}$	3.43(2)
$N(2)\text{-}Cl(2)^{iv}$	3.42(2)
$N(1)\text{-}Cl(2)^{v}$	3.37(2)
$N(2)\text{-}Cl(2)^{v}$	3.43(2)

Atom positions are related to those given in Table 16 by the following symmetry operations: i) ½+x, -y+1, z+1 ii) ½+x, -y, z+1 iii) -x, -y, z-½ iv) -x, -y, z+½ v) x-½, -y, z

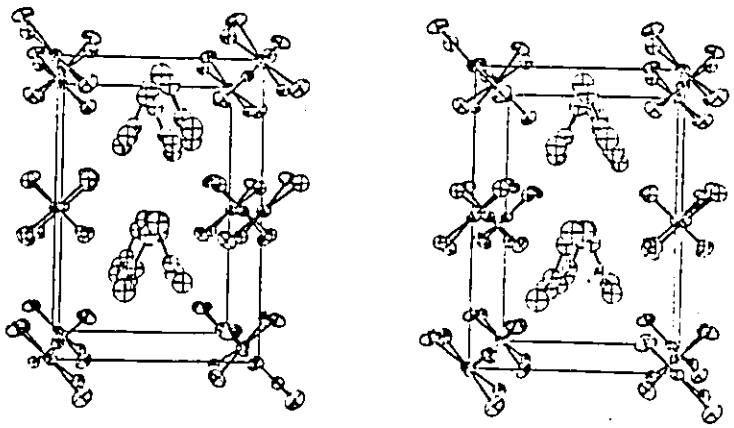
platinum complex.

The packing of the molecules in the unit cell is shown in Figure 37. The packing can be described as layers of cis-DDP molecules at y = 0 and layers of DMF molecules at y = ½. The interactions between the two layers occur through weak hydrogen bonds between the oxygen atom of the DMF molecule and N(2) of a cis-DDP complex and N(1) of a second platinum molecule, related to the first by a translation along b(refer to Table 20). These interactions are strong enough to affect the positions of the NH_3 modes in the solid state vibrational spectra (personal communication from Dr. B. Lippert) and to influence the loss of solvent from the lattice; in all other isolated adducts of cis-$(NH_3)_2PtX'_2$ with various formamides, the solvent loss was much more rapid and the vibrational spectra represent a good super-position of the spectra of cis-$(NH_3)_2PtX_2$ and the formamides, indicating that there is little interaction between the two molecules. The hydrogen bonding interactions between the cis-DDP and the DMF molecules are obviously not strong enough to prevent the large thermal motion of the atoms in the DMF molecule and particularly its oxygen atom.

Within the layers at y = 0, the interactions of the cis-DDP molecules along the c direction occur though long hydrogen bonds (N(1)---Cl(1) 3.43(2)Å and N(2)---Cl(2), 3.42(2)Å) between molecules related by the two-fold screw axis; this leads to a zig-zagging chain of cis-DDP complexes. In the a direction, the intermolecular interactions occur through long hydrogen bonds between N(2) and Cl(2) (3.43(2)Å) and Cl(2) and N(1) (3.37(2)Å) atoms of molecules related by

Figure 37

The contents of the unit cell of cis-DDP.DMF



The a and c axes are parallel to the side and bottom of the page respectively and the view is down b.

the c-glide. The chloride ligand on one molecule and the nitrogen atoms of a symmetry related molecule form loosely interlocked chains. The Cl---N hydrogen bond distances seen in this work are approximately the same as those observed in cis-DDP (3.30(4)Å and 3.34(4)Å).[138] Thus, the shift in the NH_3 modes seen in cis-DDP·DMF must be caused by the hydrogen bonding of the cis-DDP molecule to the DMF molecules present in the lattice.

In the DMF layer at y = ½, the interactions between DMF molecules are weak van der Waals' interactions; this again accounts for the disorder of the DMF moieties.

CHAPTER FIVE

INTERACTION OF PLATINUM COMPLEXES WITH DNA BASES

5.1 MODEL STUDIES OF PLATINUM-DNA COMPLEXES

Many methods and techniques are used to obtain structural details of nucleic acids. Melting temperatures of DNA can yield the content of guanine-cytosine base pairs while UV spectroscopy and circular dichroism give qualitative results on the extent of base overlap in the DNA helix; the conformation of the DNA molecule can be obtained from circular dichroism and X-ray diffraction patterns and the sequence of bases along the helix can be determined by enzymatic hydrolysis of DNA. Many of these techniques have been used to determine the nature of the interaction of platinum antitumour drugs with DNA. The results obtained will be discussed below.

With the advent of computers and graphics capabilities in many research centres, crystallographers can now identify molecular fragments in DNA. But in order to obtain information on the positional parameters of atoms and the interactions of these atoms with neighbouring fragments in a molecule, model complexes of DNA must be used. The complexity of the model systems ranges from one DNA base, nucleoside or nucleotide to polynucleotides of varying lengths. The site of interaction of platinum on DNA bases can be determined and variations

in the conformation of the model complex upon platinum binding can be studied. For solution work, much information has been obtained using nuclear magnetic resonance spectroscopy.[219]

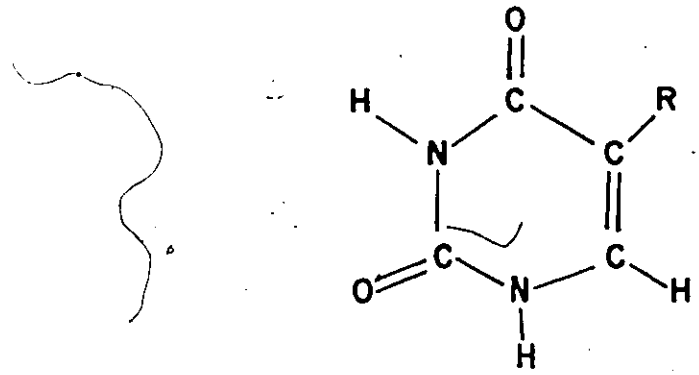
This chapter describes the work done with platinum complexes of different DNA bases and correlates the results to those obtained with other model systems and nucleic acids. Some of the work described here is a consequence of previous studies carried out on platinum complexes of the nucleic acids; other work follows up previous model complex structures which required further elucidation.

5.2 INTERACTION OF PLATINUM COMPLEXES WITH THYMINE OR URACIL LIGANDS

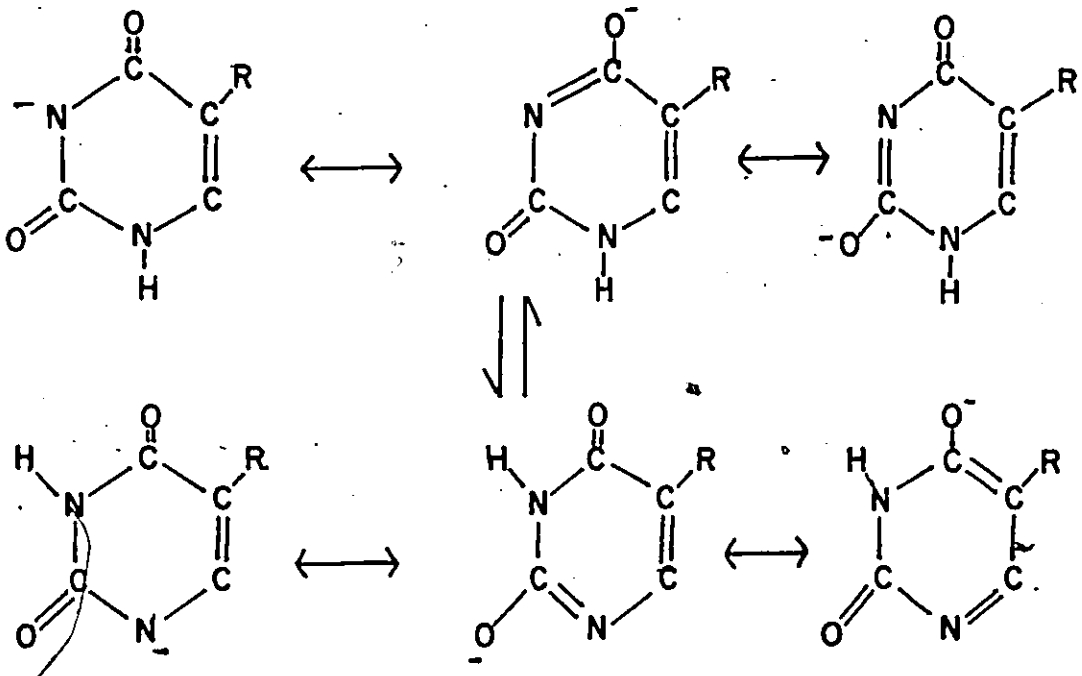
Thymine and uracil exist in solutions of neutral pH in their diketo forms (Figure 38a) and as such, do not react with platinum complexes. Reaction with platinum can take place with the monoanions of the DNA bases. The monoanions of thymine and uracil exist in solution in two tautomeric forms, namely the N(1) and N(3) deprotonated forms (Figure 38b).[220-224] The tautomer equilibrium is dependent on the solvent and it should be possible, in theory, to obtain metal complexes of the individual tautomers by choosing the right solvent.[221] Results have shown that it is not always possible to obtain the tautomer wanted.[223] Furthermore, only N(1) bonded thyminato complexes have been crystallographically characterized.[93,106,225,226] If N(1) is blocked as in the 1-methylthyminate or the 1-methyluracilate anions, coordination occurs through N(3)[101,127] or bridging is seen through N(3) and O(4) between two metal atoms (Figure 39).[101-105,228,229]

Figure 38

Possible forms of thymine and uracil in solution



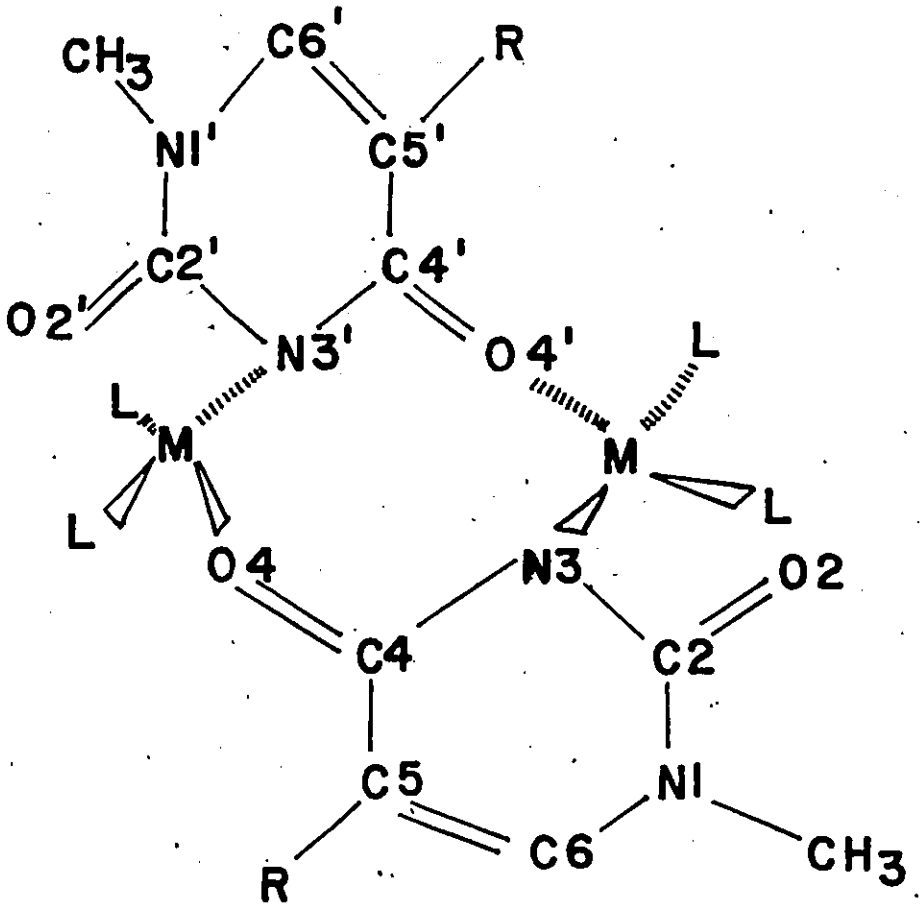
(a) diketo tautomer of thymine (R=CH_3) and uracil (R=H)



(b) monoanions of thymine and uracil

Figure 39

Bridging of two metal atoms by the uracil (R=H) or thymine ($R=CH_3$) anions



In one case where a DNA base bridges two platinum atoms, the C2-O2 and C4-O4 distances are significantly different. [105] In another structure, there is a tendency of the C-O distance to lengthen when the oxygen atom is attached to the metal (O4). [228]

No differences in the C2-O2 and C4-O4 bond lengths were observed when platinum was bonded only to N(3) or N(1) [101,106,225-227] and the two distances are not different in non-metallated thymine.[230] It was of interest to see whether any difference in C-O bond lengths exists in the free anion.

Thus we have examined, by single crystal X-ray diffraction, the structure of potassium thyminate trihydrate. The result of this study was unexpected in that the thyminate ligand existed in the N(1) deprotonated form in the solid state. From considerations concerning the polarity of the individual tautomers, one might have expected the more polar N(3) deprotonated form to dominate. [221] We suspect that factors of solubility and hydrogen bonding are of importance in deciding which tautomer was found in the potassium salt.

5.2.1 Preparation and crystal structure of potassium thyminate trihydrate

The compound was prepared by Dr. B. Lippert by reaction of equivalent amounts of thymine and KOH in a small amount of water. After filtration of the solution, evaporation to dryness and stirring for half an hour in excess dimethylformamide at 363K, the salt was filtered off and dried under vacuum. $K(C_5H_5N_2O_2)$; calc: C, 36.6; H, 3.1;

N, 17.1 %; found: C, 36.7; H, 3.2: N, 16.9 %. By recrystallizing the anhydrous salt from H_2O the trihydrate was obtained: $K(C_5H_5N_2O_2)\cdot 3H_2O$; calc: C, 27.4; H, 5.1; N, 12.9 %; found: C, 27.6; H, 5.2; N, 12.8 %. The colourless crystals were corner-truncated prisms.

The crystal data for potassium thyminate trihydrate are presented in Table 21. The final positional parameters are given in Table 22. The thyminate anion is illustrated in Figure 40 and bond lengths and bond angles are shown in Tables 23 and 24 together with corresponding data for thymine monohydrate*.[230] The C-O bond lengths in the thymine anion are not significantly different. In addition, although the mean values of the C-O distances are greater than in neutral thymine, the errors are such that there is no significance in the difference. Indeed, none of the corresponding pairs of bond lengths differ significantly in thymine and the thyminate anion. Nevertheless, some electronic rearrangement has taken place, since the internal angle at deprotonated N(1) has decreased significantly (8.8 σ) compared to the corresponding angle in thymine, while the adjacent internal angles at C(2) and C(6) have increased (5.0 σ and 7.4 σ respectively). This change of the internal angles upon protonation has been noticed previously.[233] The thyminate anion can be treated in terms of resonance structures in a manner similar to Gerdil.[230] The forms considered are shown in Figure 41. Calculations using a

*Although the structures of thymine and thymine p-benzoquinone have been determined,[231,232] they are not particularly accurate and we have used the more accurate work of Gerdil [230] for comparison.

Table 21

Crystal data for potassium thyminate trihydrate

Compound	$C_5H_{11}N_2O_5K$
F.W.	218.26
Crystal shape, size (cm)	Cylinder; r = 0.01, l = 0.03
Space group	$P2_1/c$
Unit cell parameters	
a(Å)	11.673(3)
b(Å)	6.572(2)
c(Å)	13.072(2)
β(°)	110.24(2)
Volume ($Å^3$)	941.1(4)
Z	4
$\rho_{calc}(g \cdot cm^{-3})$	1.54
$\rho_{obs}(g \cdot cm^{-3})$	1.55(1)
Linear absorption coefficient, cm^{-1}	5.55
Maximum 2θ(°)	55
Standard reflections and e.s.d.(%)	2, 1, 4; 1, -2, -2 1.8; 1.8
Temperature (°C)	22
No. of independent reflections	2468
No. with $I > 3\sigma(I)$	936
$3\sigma(I) > I > 0$	941
$I < 0$, rejected	591

.....cont.

Table 21 (cont.)

R_1[a], R_2[a]	0.059. 0.044
Final shift/error Max. (Ave.)	0.30
g(secondary extinction)	1.25×10^{-6}
Final difference map	
highest peak ($e \cdot \AA^{-3}$); location	0.33; 0.31, 0.35, 0.68
lowest valley ($e \cdot \AA^{-3}$); location	-0.36; 0.79, 0.40, 0.68
Weighting	$w = [\sigma^2 + (0.03F_o)^2]^{-1}$

[a]Definitions for R_1 and R_2 are given in Chapter 2, p.48

Table 22

Atomic parameters and equivalent temperature factors ($X10^3$) for potassium thyminate trihydrate

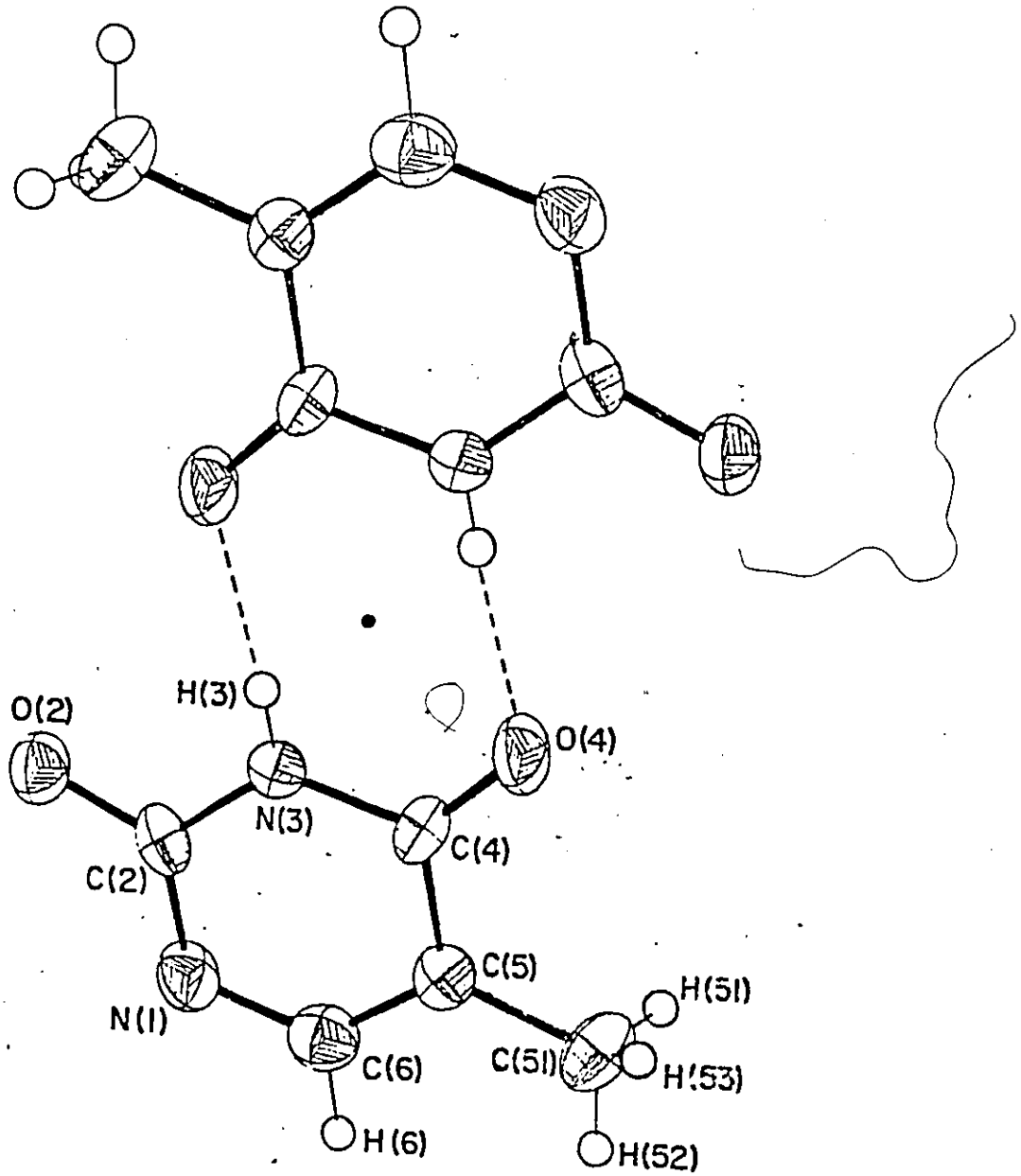
Atom	x	y	z	U_{eq} +
K	28.1(1)	263.5(2)	417.5(1)	42(2)
N(1)	321.9(4)	28.4(6)	296.4(3)	35(6)
C(2)	309.7(4)	207.9(8)	339.2(4)	29(6)
O(2)	208.7(3)	292.1(5)	324.9(3)	35(5)
N(3)	413.1(4)	307.6(6)	402.4(3)	27(5)
H(3)	407(6)	410(11)	429(5)	33*
C(4)	530.4(4)	240.2(8)	424.7(4)	28(6)
O(4)	617.0(3)	344.7(6)	484.7(3)	40(5)
C(5)	541.5(4)	50.5(8)	377.5(4)	29(6)
H(51)	696(7)	20(13)	348(6)	54*
H(52)	658(6)	-190(12)	369(6)	54*
H(53)	701(6)	-30(12)	459(6)	54*
C(6)	436.8(5)	-42.3(9)	318.0(4)	36(8)
H(6)	447(6)	-180(12)	283(6)	43*
O(1)	-148.3(3)	215.1(7)	208.5(3)	44(6)
H(101)	-215(7)	300(13)	198(6)	53*
H(201)	-185(7)	130(13)	183(6)	53*
O(3)	-21.6(4)	-158.2(7)	381.7(3)	51(6)
H(103)	-85(7)	-190(13)	330(6)	60*
H(203)	35(7)	-190(13)	362(6)	60*
O(5)	-175.4(4)	457.6(7)	435.3(3)	45(6)
H(105)	-238(6)	400(12)	453(6)	53*
H(205)	-214(6)	480(12)	370(6)	53*
C(51)	665.8(6)	-36(10)	395.9(5)	48(8)

$^{+}U_{eq} = 1/3(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$

* Hydrogen atom temperature factors were made 20% larger than the temperature factor of the atom to which they were attached and were not refined.

Figure 40

Atom numbering of the thyminate anion



There is hydrogen bonding between two anions related by the centre of symmetry at ½, ½, ½ to give a T-T pair.

Table 23

Bond distances (Å) within the thyminate anion

Atoms	Distance		
	This work	Thymine monohydrate[a]	Calculated
N(1)-C(2)	1.334(7)	1.355(9)	1.338
C(2)-O(2)	1.256(6)	1.234(7)	1.254
C(2)-N(3)	1.372(6)	1.361(8)	1.373
N(3)-H(3)	0.78(7)	0.81	-
N(3)-C(4)	1.371(6)	1.391(6)	1.373
C(4)-O(4)	1.249(5)	1.231(8)	1.251
C(4)-C(5)	1.417(7)	1.447(9)	1.427
C(5)-C(51)	1.497(8)	1.503(8)	-
C(51)-H(51)	0.90(9)	0.97	-
C(51)-H(52)	1.04(8)	0.88	-
C(51)-H(53)	0.79(7)	0.80	-
C(5)-C(6)	1.346(7)	1.349(9)	1.348
C(6)-H(6)	1.02(8)	0.86	-
C(6)-N(1)	1.355(7)	1.382(7)	1.341

[a]Values are from reference 230

Table 24

Interatomic angles (°) within the thyminate anion

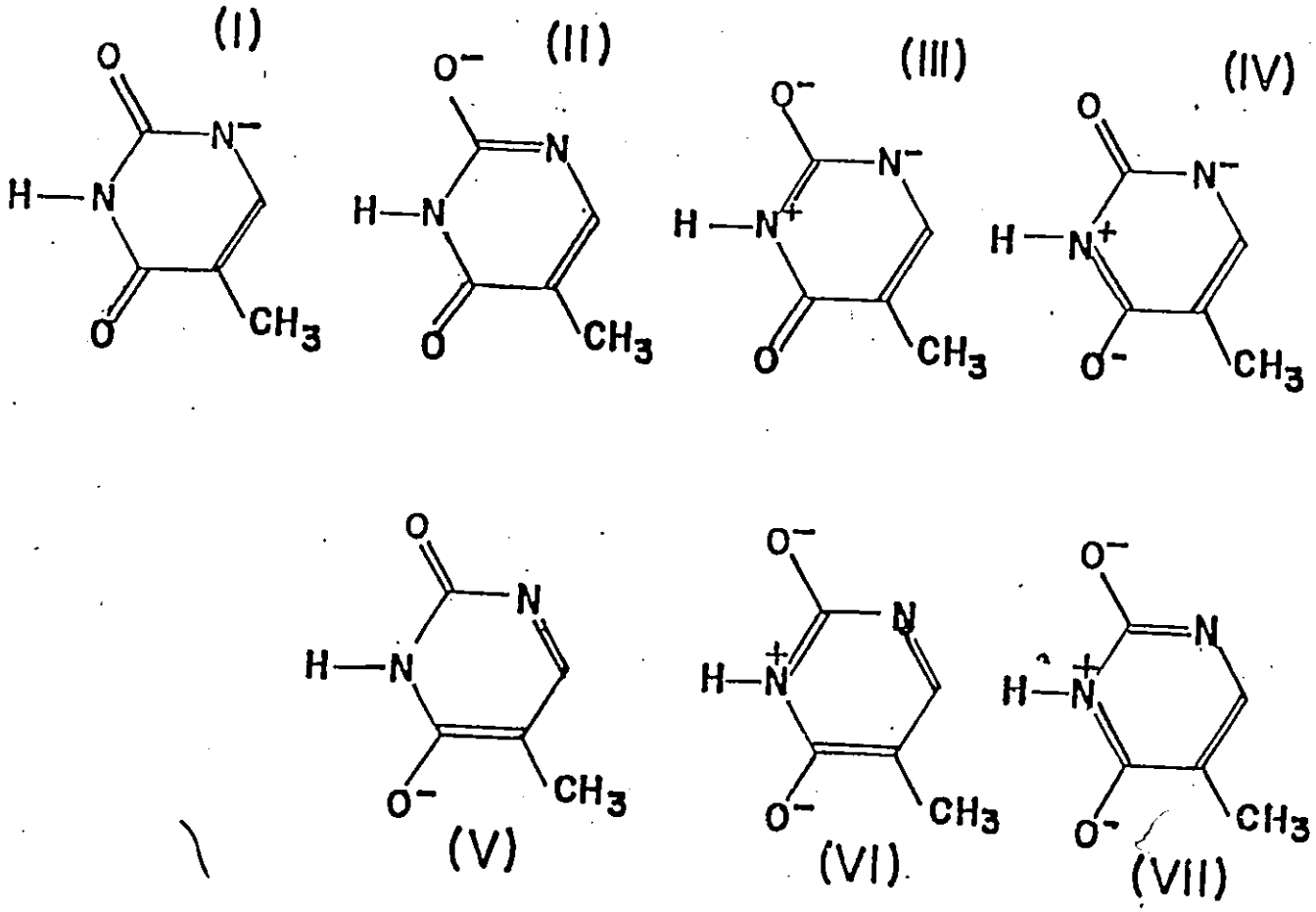
Atoms	Distance	
	This work	Thymine monohydrate[a]
N(1)-C(2)-O(2)	123.9(4)	122.7[b]
N(1)-C(2)-N(3)	118.4(4)	115.2
O(2)-C(2)-N(3)	117.7(5)	122.1
C(2)-N(3)-H(3)	119(5)	108
C(2)-N(3)-C(4)	125.5(4)	126.3
H(3)-N(3)-C(4)	115(4)	125
N(3)-C(4)-O(4)	119.2(5)	118.3
N(3)-C(4)-C(5)	155.3(4)	115.6
O(4)-C(4)-C(5)	125.5(4)	126.1
C(4)-C(5)-C(51)	119.5(4)	119.0
C(4)-C(5)-C(6)	116.6(5)	118.2
C(5)-C(51)-H(51)	110(5)	126
C(5)-C(51)-H(52)	110(4)	123
C(5)-C(51)-H(53)	106(6)	118
H(51)-C(51)-H(52)	98(7)	96
H(51)-C(51)-H(53)	122(7)	96
H(52)-C(51)-H(53)	111(6)	89
C(51)-C(5)-C(6)	123.9(5)	122.8
C(5)-C(6)-H(6)	115(4)	127
C(5)-C(6)-N(1)	127.0(5)	121.8
H(6)-C(6)-N(1)	117(4)	111
C(6)-N(1)-C(2)	117.2(4)	122.8

[a]Values are taken from reference 230

[b]Errors for angles not involving hydrogen are 0.3 to 0.5°. Other errors were not given.

Figure 41

Resonance structures of the thyminate anion



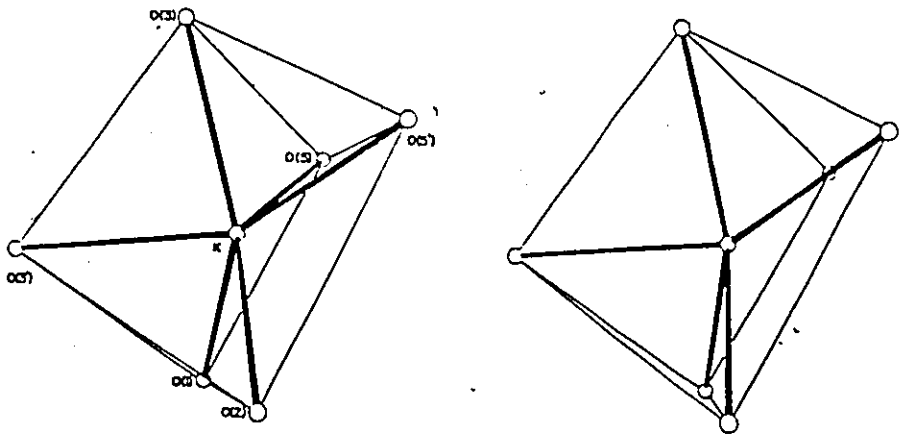
Pauling relationship [234] for bond lengths and bond orders and based on values of single and double bond lengths quoted by Gerdil [230] with resonance corrections of 0.03Å for C-C, 0.04Å for C-N and 0.05Å for C-O gave I, 14%; II, 25%; III, 11%; IV, 12%; V, 24%; VI, VII, 7%. The calculated bond lengths are shown in Table 23 and it can be seen that there is excellent agreement with experimental values. The net charges on the various atoms are (thymine in brackets[230]): N(1), 0.37^{-}(0.39^{+}); N(3), 0.37^{+}(0.35^{+}); O(2), 0.50^{-}(0.42^{-}); O(4), 0.50^{-}(0.32^{-}). The net effect of the removal of the proton from N(1) is to change it from a positive to a negative centre, but a significant amount of charge (0.24^{-}) has been delocalized onto the oxygen atoms in such a way as to give an equal charge to both.

The environment of the potassium ion is shown in Figure 42. The ion is surrounded by six oxygen atoms at roughly 2.8Å. The only other atoms closer than 3.5Å are the hydrogen atoms of the water molecules. The oxygen atoms form a very distorted trigonal prism around the potassium ion. The most noticeable distortions are the long triangular edges (O(2)-O(1), 3.94Å; O(5)-O(5)', 3.89Å; O(2)-O(3), 4.23Å). The O(2)-O(1) distance is longer than normal because of the hydrogen bonding of each of these atoms to an O(3) water molecule. Similarly the nearest approach of O(5) and O(5)' is constrained by hydrogen bonding to N(1) and O(4). The O(2)-O(3) distance is long because of the steric requirements of an adjacent O(3) group bonded to O(2) through an O(1) water molecule.

Hydrogen bonding is of prime importance in holding the thymine

Figure 42

The coordination of the potassium atom in potassium thyminate trihydrate



The oxygen atoms form a distorted trigonal prismatic arrangement. O(3)' is related to O(3) by the symmetry operation -x, -y, -z+1. O(5)' is related to O(5) by the symmetry operation -x, -y+1, -z+1.

bases together. As can be seen in Figure 40 the thyminate ions are held as "base pairs" through N(3)-H(3)---O(4) bonds. In addition, O(4) in any base pair is bonded through the water molecule H(501)-O(5)-H(502) to N(1) in an adjacent base pair related by the 2_1 operation. Similarly N(1) in a molecule is also bonded through H(101)-O(1)-H(102) to O(2) in a molecule related to the first by a unit translation along b; in addition, O(1) is bonded through H(302)-O(3)-H(301) to another O(2) atom in a molecule related to that containing the first O(2) atom by the 2_1 operation and an a translation. Oxygen and nitrogen atoms, except N(3) and O(4), can be considered as interacting with four other atoms, which form a very rough tetrahedron about the central atom; the interactions may be covalent, ionic or hydrogen bonded. They are:

Central Atom	Interacting atoms/ions
O(1)	H(101), H(102), H(302), K^+
O(3)	H(301), H(302), K^+, K'^+
O(5)	H(501), H(502), K^+, K'^+
N(1)	H(101), H(502), C(2), C(6)
O(2)	H(102), H(301), C(2), K^+
N(3)	H(3), C(2), C(4)
O(4)	H(3), H(501), C(4)

This is consistent with Brown's model of hydrogen bonding,[235] as are the hydrogen bond lengths and angles, shown in Table 25.

The packing of the unit cell is shown in Figure 43. The hydrogen bonded base pairs form the basis of the structure, being

Table 25

Hydrogen bonding distances (Å) and angles (°) (X-H----Y) in potassium thyminate trihydrate

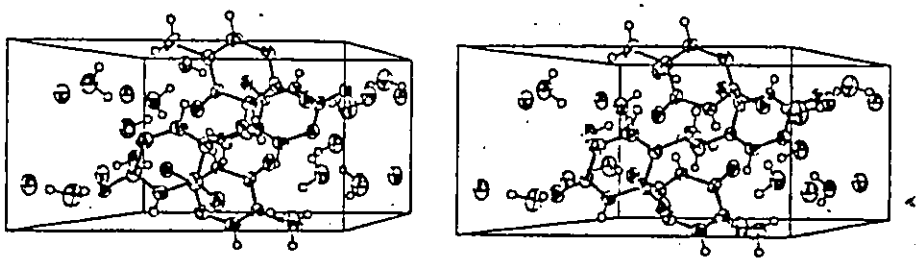
X-H----Y	Distance			Angle
	X-Y	X-H	H----Y	X-H----Y
N(3)-H(3)-O(4)	2.807(6)	0.78(7)	2.04(7)	171(8)
O(1)-H(101)-N(1)	2.874(6)	0.92(8)	1.99(8)	163(5)
O(1)-H(102)-O(2)	2.864(6)	0.73(8)	2.22(8)	148(7)
O(3)-H(301)-O(2)	2.845(5)	0.85(6)	2.04(7)	159(8)
O(3)-H(302)-O(1)	2.765(7)	0.81(10)	1.96(10)	169(7)
O(5)-H(501)-O(4)	2.815(6)	0.92(8)	1.92(8)	166(7)
O(5)-H(502)-N(1)	2.955(5)	0.83(7)	2.13(7)	177(9)

Other angles

Atoms	Angle	Atoms	Angle
H(101)-O(1)-H(102)	93(7)	H(301)-O(3)-H(302)	105(8)
H(501)-O(5)-H(502)	97(7)	C(2)-N(3)-H(3)	119(5)
C(4)-N(3)-H(3)	115(5)	C(2)-N(1)-H(502)	117(2)
C(6)-N(1)-H(502)	111(2)	C(2)-N(1)-H(101)	120(2)
C(6)-N(1)-H(101)	109(2)	H(101)-N(1)-H(502)	76(3)
C(2)-O(2)-H(301)	118(2)	C(2)-O(2)-H(102)	123(2)
H(102)-O(2)-H(301)	82(3)	H(3)-O(4)-H(501)	144(3)
H(101)-O(1)-H(302)	114(6)	H(102)-O(1)-H(302)	116(8)
C(4)-O(4)-H(3)	123(2)	C(4)-O(4)-H(501)	123(2)

Figure 43

The contents of the unit cell of potassium thyminate trihydrate



a and b are parallel to the top and side of the page respectively, and the view is down c*.

arranged in layers parallel to the bc plane, centred at $x = \frac{1}{2}$. A given pair of bases is tilted with respect to the b axis so that pairs of bases related by the b translation overlap like tiles on a roof. In the c direction the pairs of bases are related by the c glide so that each subsequent pair of bases is tilted in the opposite direction to adjacent pairs. Contact between adjacent pairs is primarily between the methyl group and H(6) on one base with the π-cloud and the C(4)-C(5) bond of a base in an adjacent pair. The hydrogen bonding network holding the base layer together orients the water molecules such that the oxygen atoms point towards the x = 0 plane. The packing in the a direction is then primarily an ion-dipole interaction between these external oxygen atoms of the base layer and the potassium ions which lie close to x = 0.

5.3 INTERACTION OF cis-DDP WITH MIXED PURINE-PYRIMIDINE NUCLEOBASES

Many mechanisms of action have been proposed to explain the activity of the platinum anti-cancer drugs.[129] All the evidence points to the DNA bases as the site of interaction of the platinum atom.[67,68] The structure of cis-(9-ethylguaninato-N^7)(1-methyluracilato-N^3)diammineplatinum(II) dihydrate discussed in this section represents a model for the interaction of cis-DDP with a guanidine and a uridine ligand in RNA or a guanidine and a thymidine ligand in DNA. Initially, it was believed that the reaction of platinum complexes with uridine or its derivatives did not occur to any significant extent;[68,236,237] it was later shown that the

reaction could take place under the right experimental conditions.[173,238] Although there is no reason to believe that a crosslink between a thymidine and a guanidine moiety in DNA is biologically important, our reasons for investigating the structure were threefold:
1) it is the first example of a purine-pyrimidine mixed-base platinum complex where the uracil anion is the pyrimidine ligand. All other structures of mixed-nucleobase complexes have involved cytosine.[84]
2) it was of interest to investigate the conformational features in the complex in view of the recent work of Orbell and his co-workers.[99]
3) the interaction of cis-platinum complexes with DNA leads to strong perturbations in the structure of the macromolecule (see below). The investigation of the spatial distribution of two DNA bases attached to cis positions of a platinum atom may lead to a better understanding of the nature of the platinum-DNA interaction.

The structure of cis$(NH_3)_2$Pt(9-Et-G-H)(1-MeU-H)·$2H_2O$, where 9-Et-G-H is the 9-ethylguanine anion deprotonated at N(1) and 1-MeU-H is the 1-methyluracil anion, is also another example of the relatively facile deprotonation of guanine at the N(1) position after binding of platinum to the N(7) position.[70-72] No biologically relevant hydrogen bonding is expected between the 9-ethylguanine anion and the uracil anion since the uracil anion is methylated at N(1) and is bound to platinum at N(3), thus eliminating the base mispairing possibility mentioned in a previous work[72] and shown in Figure 15, p. 35.

The crystal data for the structure of cis$(NH_3)_2$Pt(9-Et-G-H)

(1-MeU-H)·$2H_2O$ are shown in Table 26. The atomic parameters and temperature factors for the complex are listed in Table 27. The bond lengths and angles are listed in Table 28 and the labelled molecular structure is shown in Figure 44.

Bonding of the platinum atom occurs through the N(7) and N(3) positions of the 9-ethylguanine and 1-methyluracil anions respectively. These are the normal binding sites as seen in previously studied complexes of platinum [70-72,84,101] where there is no bridging by the 1-methyluracil anion to two metal ions. There is no indication of any interaction to the exocyclic oxygen atoms on either of the bases, the shortest oxygen to platinum distance being Pt---O(2A) = 3.08(2)Å.

The geometry around the platinum atom is square planar with the platinum atom sitting 0.0010(9)Å above the plane defined by the four coordinated nitrogen atoms. The platinum to nitrogen bond distances, ranging between 2.05(2)Å and 2.11(2)Å, are normal for these types of complexes.

The errors in bond lengths and angles within the ligand rings are relatively large. For the 9-ethylguanine anion, they do not differ from the values reported previously for coordinated 9-ethylguanine in its neutral or anionic form.[70-72,84] In the case of the 1-methyluracil anion, the bond lengths agree, within 3σ, with those reported for cis-bis(1-methyluracilato-N^3)diammine-platinum(II) tetrahydrate [101] but some of the angles vary by more than 3σ. This is attributed to the disorder of the 1-methyluracilate

Table 26

Crystal data for cis-(9-ethylguaninato-N^7)(1-methyluracilato-N^3)diammine platinum(II)dihydrate

Compound	$C_{12}H_{23}N_9O_5Pt$
F.W.	568.46
Crystal shape, size (cm)	Truncated pyramid; 0.013 X 0.023 X 0.026
Space group	C2/c
Unit cell parameters	
a(Å)	30.777(9)
b(Å)	12.907(2)
c(Å)	9.685(2)
β(°)	106.15(2)
Volume ($Å^3$)	3695(2)
Z	8
$\sigma_{calc}(g \cdot cm^{-3})$	2.04
Linear absorption coefficient, cm^{-1}	80.39
μR	0.88
Absorption correction factor, A*, limits	4.20, 4.02
Maximum 2θ(°)	45
Standard reflections and e.s.d. (%)	-3, 1, 2; 6, 2, 3 2.01; 2.72
Temperature (°C)	22
No. of independent reflections	2622
No. with $I > 0$	2143

.....cont.

Table 26 (cont.)

No. with $I < 0$, rejected	479
R_1[a], R_2[a]	0.1019, 0.0572
Final shift/error Max(Ave.)	0.190(0.018)
X(secondary extinction)	0.00007
Final difference map highest peak ($e \cdot Å^{-3}$); location	1.71; 0.14, 0.16, 0.27
lowest valley ($e \cdot Å^{-3}$); location	-2.2; 0.22, 0.12, 0.44
Weighting	$w = (\sigma^2)^{-1}$
Error in observation of unit weight	0.9397
PSI-Scan	
2θMax/Min	42.75/7.67
x Max/Min	283.72/256.28
No. reflections used	9
PSI Increment/Range	10°/0-350°
Min. correction factor	0.416

[a]Definitions for R_1 and R_2 are given in Chapter 2, p. 48

Table 27

Atomic parameters and isotropic or equivalent temperature factors ($X10^3$) for cis-$(NH_3)_2$Pt(9-Et-G-H)(1-MeU-H)·$2H_2O$

Atom	x	y	z	U_{iso} or U_{eq} *
Pt	121.02(3)	120.88(7)	171.0(1)	39.5(5)*
N(7)	99.4(6)	251(1)	254(2)	42(5)
N(4)	139.3(6)	-14(1)	78(2)	63(5)
N(5)	54.8(5)	66(1)	112(2)	38(4)
C(4)	61.9(6)	364(1)	353(2)	37(5)
C(5)	71.4(6)	257(1)	343(2)	28(5)
C(6)	49.2(8)	188(2)	410(2)	48(6)
O(6)	53.6(5)	88(1)	406(2)	56(4)
N(1)	20.7(6)	228(1)	483(2)	42(4)
N(3)	35.2(5)	406(1)	428(1)	41(4)
C(2)	14.6(7)	332(2)	483(2)	46(6)
N(2)	-15.4(5)	364(1)	554(2)	47(4)
C(8)	111.7(7)	346(1)	228(2)	40(5)
N(9)	89.2(6)	418(1)	291(2)	43(4)
C(9)	91.8(8)	531(2)	278(2)	47(6)
C(10)	130.1(8)	569(2)	217(2)	61(20)*
N(3A)	188.7(6)	173(1)	236(2)	54(5)
C(4A)	199.1(9)	245(2)	151(3)	68(7)
O(4A)	175.1(6)	286(1)	49(2)	66(5)
C(2A)	213.5(9)	112(2)	345(3)	78(8)
O(2A)	203.3(6)	46(1)	411(2)	94(6)
N(1A)	260.4(8)	157(2)	382(2)	101(8)
C(1A)	290(1)	100(3)	501(4)	148(13)
C(5A)	249(1)	285(2)	197(3)	88(9)
C(6A)	273(1)	235(2)	302(3)	81(8)
O(7)+	37(1)	146(3)	759(4)	99(14)
O(7)'+	57(2)	186(3)	794(4)	98(14)
O(8)+	147(2)	152(3)	832(4)	89(15)
O(8)'+	127(2)	171(4)	802(5)	101(18)

*$U_{eq} = 1/3(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$

+These atoms were given a site occupancy of one-half.

Table 28

Bond lengths (Å) and angles (°) in cis-$(NH_3)_2$Pt(9-Et-G-H)(1-MeU-H)·$2H_2O$

Atoms	Distance	Atoms	Distance	Atoms	Distance
Pt-N(7)	2.05(2)	Pt-N(4)	2.11(2)	Pt-N(5)	2.08(2)
Pt-N(3A)	2.11(2)	N(7)-C(8)	1.33(2)	N(7)-C(5)	1.38(3)
C(5)-C(4)	1.42(3)	C(5)-C(6)	1.39(3)	C(6)-O(6)	1.29(3)
C(6)-N(1)	1.37(3)	N(1)-C(2)	1.36(2)	C(2)-N(2)	1.36(3)
C(2)-N(3)	1.34(3)	N(3)-C(4)	1.35(3)	C(4)-N(9)	1.35(3)
N(9)-C(9)	1.46(2)	N(9)-C(8)	1.40(3)	C(9)-C(10)	1.54(4)
N(3A)-C(2A)	1.37(3)	C(2A)-O(2A)	1.16(3)	C(2A)-N(1A)	1.51(4)
N(1A)-C(1A)	1.45(4)	N(1A)-C(6A)	1.38(4)	C(5A)-C(6A)	1.26(4)
C(5A)-C(4A)	1.55(4)	C(4A)-O(4A)	1.19(3)	C(4A)-N(3A)	1.33(3)

Atoms	Angle	Atoms	Angle
N(7)-Pt-N(4)	176.6(6)	N(4)-Pt-N(5)	87.7(7)
N(7)-Pt-N(5)	89.1(6)	N(7)-Pt-N(3A)	91.4(7)
N(4)-Pt-N(3A)	91.7(7)	N(5)-Pt-N(3A)	178.5(6)
Pt-N(7)-C(8)	123(2)	Pt-N(7)-C(5)	128(1)
C(8)-N(7)-C(5)	109(2)	N(7)-C(5)-C(4)	106(2)
N(7)-C(5)-C(6)	137(2)	C(4)-C(5)-C(6)	117(2)
C(5)-C(6)-O(6)	124(2)	C(5)-C(6)-N(1)	118(2)
N(1)-C(6)-O(6)	119(2)	C(6)-N(1)-C(2)	119(2)
N(1)-C(2)-N(2)	114(2)	N(1)-C(2)-N(3)	129(2)
N(2)-C(2)-N(3)	117(2)	C(2)-N(3)-C(4)	111(2)
N(3)-C(4)-C(5)	127(2)	N(3)-C(4)-N(9)	125(2)
C(5)-C(4)-N(9)	108(2)	C(4)-N(9)-C(9)	128(2)
C(4)-N(9)-C(8)	107(2)	C(8)-N(9)-C(9)	125(2)
N(9)-C(9)-C(10)	115(2)	N(7)-C(8)-N(9)	109(2)
Pt-N(3A)-C(4A)	115(1)	Pt-N(3A)-C(2A)	110(2)
C(2A)-N(3A)-C(4A)	134(2)	N(3A)-C(2A)-O(2A)	132(3)
N(3A)-C(2A)-N(1A)	105(2)	O(2A)-C(2A)-N(1A)	123(2)
C(2A)-N(1A)-C(1A)	110(2)	C(2A)-N(1A)-C(6A)	123(2)
C(1A)-N(1A)-C(6A)	127(3)	N(1A)-C(6A)-C(5A)	130(3)
C(6A)-C(5A)-C(4A)	112(3)	C(5A)-C(4A)-N(3A)	116(2)
C(5A)-C(4A)-O(4A)	115(2)	O(4A)-C(4A)-N(3A)	129(2)

.....cont.

Table 28 (cont.)

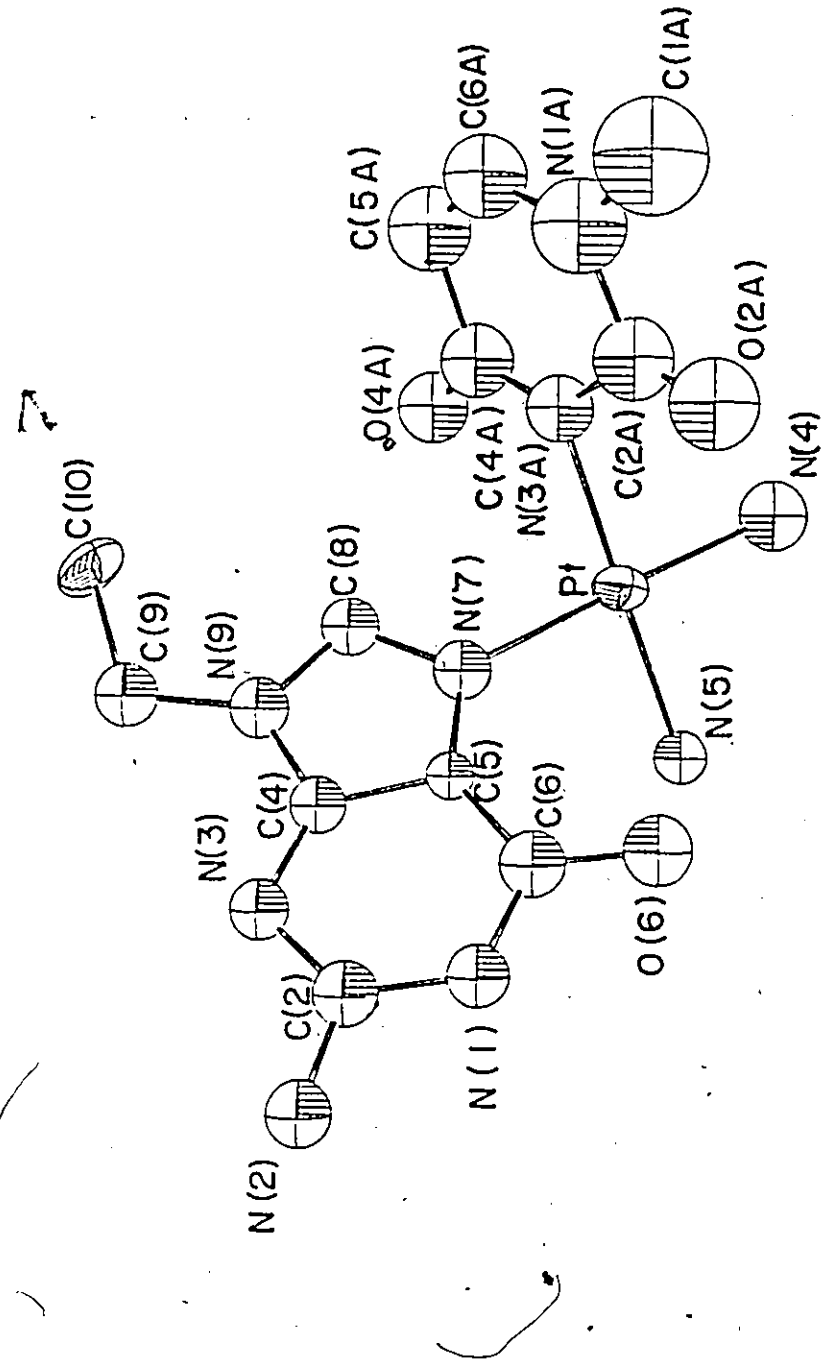
Possible hydrogen-bonded distance

System 1		System 2	
Atoms	Distance	Atoms	Distance
N(1)-O(7)	2.79(4)	O(7)'-O(8)	2.72(6)
N(6)-O(7)^{i}	3.20(4)	O(7)'-N(1)	2.96(4)
O(7)-O(7)'^{ii}	2.86(6)	O(7)'-N(2)^{ii}	3.19(5)
O(7)-O(8)'	2.68(6)	O(8)-O(4A)^{iii}	2.67(4)
N(8)-O(8)'	3.07(5)	O(8)-O(2A)^{i}	3.06(5)
O(8)'-O(4A)^{iii}	2.86(4)	O(7)'-O(7)^{ii}	2.86(6)

Atom positions are related to those given in Table 27 by the following symmetry operations: (i) x, -y, ½+z; (ii) -x, y, ½-z+1; (iii) x, y, z+1.

Figure 44

The molecular structure of cis-(9-ethylguaninato-N^7)(1-methyluracilato-N^3)diammineplatinum(II)



ligand. The disorder was detected because of the large thermal parameters on the atoms of the ring (refer to Table 27). All attempts made to resolve the disorder did not yield a better model of the observed data.

Both ligands are planar, with O(2A) sitting furthest out of the pyrimidine plane (0.08(2)Å) and N(2) being 0.09(2)Å out of the purine plane. The dihedral angle between the imidazole and the pyrimidine rings in the 9-ethylguanine anion is small (3(1)°).

The interaction of platinum complexes with DNA leads to strong perturbations of the DNA structure. These perturbations reveal themselves through the following effects: the reduction of the effective length of DNA,[134,239,240] the inhibition of intercalation of ethidium bromide in DNA,[241] the reduction of the viscosity of the macromolecule,[113,242,243] the decrease of the DNA melting temperature,[113] and the enhancement of the ellipticity of circular dichroism bands [134,135,140] and UV absorption bands.[134,242] It has been suggested that the local denaturation seen in the DNA structure after the incubation of the macromolecule with platinum complexes may be caused by the disruption of hydrogen bonding between base pairs;[244] this would generate local single-stranded regions.[239,240,242, 243,245] The single-stranded regions may be caused by the formation of intrastrand crosslinks [240] or may help in the formation of intrastrand crosslinks.[241]

The structure of cis-$(NH_3)_2Pt(9\text{-Et-G-H})(1\text{-MeU-H})\cdot 2H_2O$ can be considered as a model for the interaction of cis-DDP with

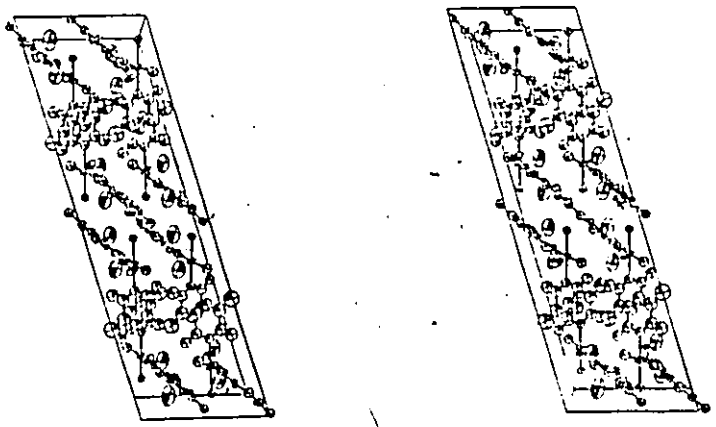
a guanidine and a uridine or thymidine residue adjacent to one another on the same strand of the DNA helix. In a structure of a B-DNA dodecamer, the largest magnitude of the angle between successive base-plane normals is 18.2°, with a mean angle between successive base-plane normals of 7.82°.[246] The angle between the two bases in the complex studied here has a magnitude of 72(2)°; this suggests that an intrastrand crosslink would cause strong local perturbations in the DNA structure. Large dihedral angles have been seen in all platinum complexes containing two DNA bases or analogous ligands in cis positions [70-72,76,79,84,86,89,93,96,97,99,101,247-249] (see also section 5.4).

The dihedral angles between the platinum coordination plane and the ligand planes are also very large (9-Et-G-H/PtN_4 = 132(1)°; 1-MeU-H/PtN_4 = 75(1)°). These angles were calculated according to the method of Orbell and his co-workers.[99] The magnitude of the angle between the 9-ethylguanine anion and the platinum coordination plane lies far from 90° and is consistent with the presence of an intramolecular hydrogen bond between the exocyclic O(6) and an ammine ligand (N(5)---O(6) = 2.86(2)Å) as seen in previous structural works.[70-72,84]

The packing of the molecules in the unit cell of cis-$(NH_3)_2Pt$(9-Et-G-H)(1-MeU-H)·$2H_2O$ is shown in Figure 45. The molecules pack to give layers of 1-methyluracilate anions in the bc plane at x = ¼ and x = 3/4. The only strong interaction of any atom in the pyrimidine ring occurs between an exocyclic oxygen atom

Figure 45

The contents of the unit cell of cis-$(NH_3)_2Pt(9\text{-Et-G-H})(1\text{-MeU-H})\cdot 2H_2O$



The a* and c axes are parallel to the side and the bottom of the page, respectively and the view is down b.

and a water molecule in the lattice (O(4A)---O(8) = 2.67(4)Å). The only other interaction is a weaker contact between O(2A) and O(8) (3.06(5)Å). The remainder of the interactions consist of van der Waals contacts between the rings of symmetry-related molecules. This explains the high thermal parameters of the atoms in the pyrimidine ring since the rings can flap about the line joining N(3A) to O(4A). At x = ¼, y = ¼, the rings are arranged in parallel layers along the c axis. At x = ¼, y = 3/4, there is another layer of parallel ligands. The two ligand layers are skewed with respect to one another. At x = 0 and x = ½, the cations are packed such that the 9-ethylguanine anions of two molecules related by the two-fold rotation axis along b are stacked 3.73(2)Å apart, maximizing π-π interactions. This distance is much larger than those seen for intermolecular base-base distances in complexes containing neutral 9-ethylguanine moieties (3.33(2)Å and 3.37(2)Å (see section 5.4)). The anions making up the stacked base pairs are hydrogen bonded to other 9-ethylguanine anions related by the c glide (N(3)---N(2) = 3.05(2)Å). The result of this packing gives a zig-zag chain of base pairs about the ac plane at y = 0 and y = 1. At y = ½, there are interactions between the two chains through hydrogen bonds, N(4)---O(6) = 2.86(2)Å and N(5)---O(6) = 2.81(2)Å. The remainder of the interactions at y = ½ occurs through hydrogen bonding to the lattice water molecules. It is interesting to note that there is no hydrogen bonding between two 9-ethylguanine anions through N(1)---N(2) seen in a previous work.[70] The water molecules in the lattice

do not conform to the local 2-fold symmetry along b at z = ¼. The distance between oxygen atoms related by this symmetry element was very short (O(7)---O(7)^{ii} = 2.26(6)Å). Giving a site occupation factor of 0.5 to O(7) meant that, for proper stoichiometry, another water molecule with a site occupation factor of 0.5 was present. This was found and labelled O(7)'. The O(7)---O(7)'^{ii} distance is 2.86(6)Å. The disorder in the O(7) position in turn caused the disorder in the O(8) position. Thus there are two possible hydrogen-bonded networks: one involves O(7), O(7)'^{ii}, O(8)', the other is made up of O(7)', O(7)^{ii} and O(8) (see Table 28 for hydrogen bonded-distances). For clarity, only one of the hydrogen-bonded chains is shown in Figure 45.

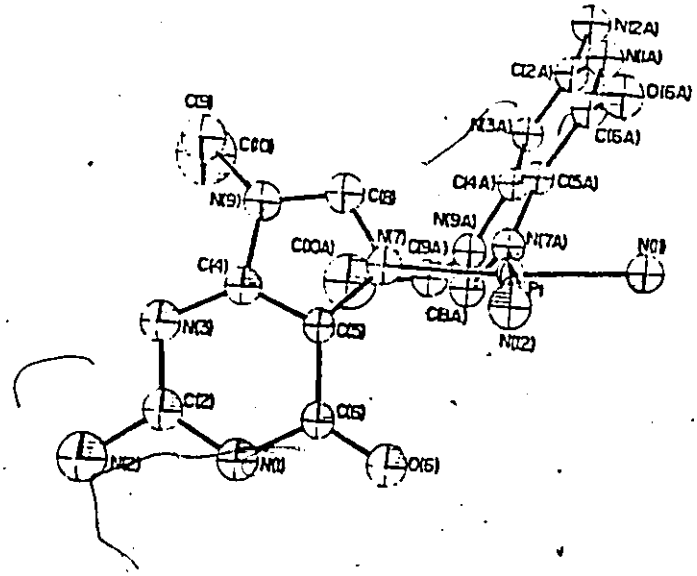
5.4 INTERACTION OF cis-PLATINUM COMPLEXES WITH TWO GUANINE BASES

The intrastrand crosslinking of two adjacent guanine bases is one of the most attractive hypotheses concerning the mode of action of anti-tumour platinum drugs. Because of the evidence pointing to a G-G intrastrand crosslink (section 1.6.2) and because of the distortions caused when platinum interacts with DNA, workers have opted for the binding of platinum to two guanine bases as one of the main causes for the local denaturation in DNA.[250-252] Examination of the interaction of cis-DDP with $(dC_4)(dG_4)$ using space filling models, reveals that the platinum complex can bind two adjacent guanine bases at N(7) if base pairing is disrupted. The models indicate that such binding could produce a two-fold shortening of DNA measured along the original axis as found by electron microscopy.[120]

Because of the suspected biological significance of intrastrand guanine-guanine crosslinking, a number of model compounds containing platinum(II) and two oxo-purine in cis positions have been prepared and studied crystallographically.[70,71,76,79,86,247,248,253-256] Two noteworthy features evolved from these studies: first, one can consider the O(6) position of 9-ethylguanine as the head of the ligand and the ethyl group as the tail; all crystallographically studied examples of cis-bis(oxopurine) complexes of platinum(II) reveal an approximate C_2 molecular symmetry; this gives a head to tail arrangement of the bases relative to the platinum coordination plane (Figure 46) where the O(6) atoms from the two guanine ligands lie on opposite sides of the platinum coordination plane. This geometry also holds for other examples of cis-bis(nucleobase) complexes of platinum(II)[96,97,99,101,249] but it is a rather unlikely arrangement of two bases crosslinked in native DNA. Only in solution has there been spectroscopic evidence for a head to head arrangement of two guanine bases in a GpG dinucleotide complex of cis platinum(II).[257] Second, the extent of base-base interaction, though variable to some degree, may be divided into two categories: in the first, with large dihedral angles (larger than 65°) between the nucleobase planes, substantial intercomplex base stacking is observed;[70,71,76,79,253] in the second, with smaller dihedral angles, e.g. 39.6° in a complex containing two phosphate methyl ester of guanosine monophosphate as ligands, only the intracomplex base-base interaction is significant.[86] The solution of the crystal structures of the compounds [cis-$(NH_3)_2Pt(9\text{-Et-G})_2]Cl_2 \cdot 3H_2O$, I, and

Figure 46

Head to tail arrangement of cis-bis(oxopurine)platinum(II) complexes



Structure from reference 70. Note how O(6) and O(6A) are on opposite sides of the platinum coordination plane.

[cis-$(NH_3)_2Pt(9\text{-Et-G})_2]_2Cl_3(HCO_3)\cdot 3H_2O$, II, has been undertaken to determine the arrangement of the two purine bases in the cis-$(NH_3)_2Pt(9\text{-Et-G})_2^{2+}$ cation, where 9-Et-G is the 9-ethylguanine ligand, and the extent of purine-purine interaction which is a measure for a local distortion of DNA in a guanine-guanine intrastrand crosslink.

[cis-$(NH_3)_2Pt(9\text{-Et-G})_2]Cl_2\cdot 3H_2O$, I, and [cis-$(NH_3)_2Pt(9\text{-Et-G})_2]Cl_{1.5}(HCO_3)_{.5}\cdot 1.5H_2O$, II, were obtained by Dr. B. Lippert and G. Raudaschl in the following way: I was prepared by the reaction of cis-DDP[213] with 1.5 mmole of 9-ethylguanine suspended in 15 ml H_2O and kept at 40°C for 4 days. A white precipitate (110 mg) of unreacted 9-Et-G and cis-$[(NH_3)_2Pt(9\text{-Et-G})Cl]Cl\cdot 0.5H_2O$ was filtered and the colourless filtrate (pH = 4) was allowed to evaporate at 40°C to 5 ml volume, filtered again and crystallized slowly (7 days) at 22°C in air. Several fractions of I were obtained and briefly air-dried. (180 mg, colourless, transparent cubes). Complex II was isolated from a preparation carried out analogously to the one described for complex I but with Pt: (9-Et-G) = 1 and a longer time of crystallization (15 days). The first four fractions of precipitate consisted of cis-$[(NH_3)_2Pt(9\text{-Et-G})Cl]Cl\cdot 0.5H_2O$ [258] (yield 35%) before complex II precipitated (yield 30%). Elemental analyses of complexes I and II were identical within experimental error. The IR spectrum of the product did not show bands caused by HCO_3^-. It is suspected that only a small fraction of the bulk material contained HCO_3^- and that the crystals selected for X-ray measurements happened to be those of the mixed Cl, HCO_3 compound. We further assume that during the

long process of crystallization in air some CO_2 was taken up from the air.

The crystal data for both compounds are shown in Table 29. The atomic parameters and temperature factors are listed in Table 30 for both complexes. The bond lengths and angles are listed in Table 31 and the molecular structure and labelling of the atoms of the cation in I are shown in Figure 47. The two complexes are very similar and differ only in the anions and the number of water molecules present in the lattice. The binding of the platinum atom to the 9-ethylguanine ligand occurs through N(7) as seen in all complexes of platinum with N(9) blocked guanine residues studied so far.[70-72,76,79,84,86-88,253,254] There is no indication in either I or II of an interaction between O(6) on either of the purine ligand and the central platinum atom, the shortest distance being Pt-O(6A) = 3.392(9)Å in complex I and 3.430(7)Å in complex II.

The geometry around the platinum atom is square planar and the platinum to nitrogen bond lengths, ranging from 2.02(1)Å to 2.05(1)Å, are normal for these types of complexes.

The bond lengths and angles within the purine rings are in agreement with the average values calculated from a number of structures of nucleosides and nucleotides,[259] and particularly with those of 9-ethylguanine.[260] The purine rings are almost planar as indicated by the dihedral angles between the pyrimidine and the imidazole ring (range = 1(1)° to 2(1)°). The two rings in the cations differ in the amount in which the ethyl groups extend away from the

Table 29

Crystal data for cis-diamminebis(9-ethylguanine-N^7) platinum(II)dichloride trihydrate (I) and cis-diamminebis (9-ethylguanine-N^7)platinum(II)sesquichloride hemicarbonate sesquihydrate (II)

Compound	$C_{14}H_{30}Cl_2N_{12}O_5Pt$ I	$C_{14.5}H_{27.5}Cl_{1.5}N_{12}O_5Pt$ II
F.W.	712.47	698.21
Crystal size (cm)	0.032 X 0.023 X 0.010	0.040 X 0.040 X 0.015
Space group	$P\bar{1}$	$P\bar{1}$
Unit cell parameters		
a(Å)	12.238(3)	12.378(3)
b(Å)	10.787(2)	10.748(3)
c(Å)	12.883(4)	12.664(4)
α(°)	92.18(2)	92.23(2)
β(°)	123.32(2)	123.40(2)
γ(°)	111.33(2)	112.92(2)
Volume ($Å^3$)	1260.6(6)	1223.2(7)
Z	2	2
$\rho_{calc}(g \cdot cm^{-3})$	1.88	1.90
$\rho_{obs}(g \cdot cm^{-3})$	1.88(1)	1.92(1)
Linear absorption coefficient (cm^{-1})	61.2	62.33
μR	0.52	1.1
Absorption correction factor, limits, A*	2.45, 2.34	4.70, 4.43
Maximum 2θ(°)	45	45

.....cont.

Table 29 (cont.)

	I	II
Standard reflections and e.s.d.(%)	-2, -4, -1; 2, 0, 2 2.09; 1.62	-2, -4, -1; 2, 0, 2 1.10; 2.23
Temperature (°C)	-71	-48
No. of independent reflections	3319	3218
No. with $I > 0$	3162	3124
No. with $I < 0$, rejected	157	94
R_1[a], R_2[a]	0.0617, 0.0618	0.0446, 0.0511
Final shift/error	0.089(0.009)	0.128(0.015)
X(secondary extinction)	0.0008	-0.00042
Final difference map		
highest peak($e \cdot Å^{-3}$)	1.86	1.42
location	0.020, 0.435, 0.155	0.512, 0.241, 0.433
lowest valley($e \cdot Å^{-3}$)	-2.52	-0.73
location		0.58, 0.12, 0.28
Weighting, w	$(\sigma^2 + 0.0001(F_o)^2)^{-1}$	$(\sigma^2 + 0.0003(F_o)^2)^{-1}$
Error in observation of unit weight	0.9397	0.9000
PSI Scan		
2θ Max/Min	42.88/4.25	40.39/6.42
χ Max/Min	291.97/248.03	282.84/257.16
No. refl. used	10	11
PSI increment/range	10°/0-350°	10°/0-350°
Min. correction factor	0.439	0.391

[a]Definitions for R_1 and R_2 are given in Chapter 2, p. 48

Table 30

Atomic parameters and isotropic or equivalent temperature factors ($X10^3$) for [cis-$(NH_3)_2$(9-Et-G)$_2$Pt]$Cl_2 \cdot 3H_2O$(I) and [cis-$(NH_3)_2$(9-Et-G)$_2$Pt]$Cl_{1.5}(HCO_3)_{.5} \cdot 1.5H_2O$(II)

	I				II			
Atom	x	y	z	U_{iso} or U_{eq}*	x	y	z	U_{iso} or U_{eq}*
Pt	34.23(6)	479.26(6)	208.21(5)	30.0(9)*	43.98(4)	483.66(4)	217.09(4)	18.6(6)*
N(12)	17(1)	661(1)	202(1)	60(3)	37(1)	669.8(9)	219.6(9)	46(2)
N(11)	236(1)	575.6(9)	247.1(9)	42(2)	248.3(9)	584.0(8)	258.4(8)	35(2)
N(1A)	-207(1)	11(1)	-95(1)	47(3)	-214.5(9)	1.6(8)	-104.6(8)	38(2)
C(2A)	-182(1)	-93(1)	-41(1)	42(3)	-189(1)	-100(1)	-51(1)	36(2)
N(2A)	-251(1)	-219(1)	-123(1)	49(3)	-262.4(9)	-231.1(9)	-137.9(9)	45(2)
N(3A)	-91(1)	-71(1)	88(1)	43(2)	-95.0(8)	-74.6(8)	79.7(8)	33(2)
C(4A)	-26(1)	65(1)	156(1)	38(3)	-28(1)	62.9(9)	152.4(9)	30(2)
C(5A)	-45(1)	177(1)	112(1)	40(3)	-50(1)	170.6(9)	106.0(9)	31(2)
C(6A)	-144(1)	147(1)	-27(1)	49(3)	-147(1)	145(1)	-31.5(9)	34(2)
O(6A)	-171(1)	235.1(9)	-84.8(9)	63(2)	-176.7(8)	228.5(8)	-90.1(8)	51(2)
N(7A)	43(1)	295.2(9)	-213.8(9)	38(2)	44.9(8)	296.4(8)	216.6(8)	34(2)
C(8A)	115(1)	260(1)	321(1)	43(3)	118(1)	261(1)	324(1)	36(2)
N(9A)	74(1)	120(1)	288.2(9)	43(2)	77.3(8)	120.1(8)	288.9(8)	35(2)
C(9A)	127(1)	37(1)	377(1)	56(3)	130(1)	36(1)	378(1)	56(3)
C(10A)	242(2)	130(2)	520(2)	89(5)	247(2)	129(1)	525(1)	70(4)
N(1B)	-499(1)	391.9(9)	-104.8(9)	44(2)	-486.8(9)	394.3(8)	-99.6(8)	39(2)
C(2B)	-592(1)	303(1)	-84(1)	44(3)	-583(1)	305(1)	-79(1)	40(2)
N(2B)	-736(1)	273(1)	-166(1)	55(3)	-726(1)	276.0(9)	-160.6(9)	50(2)
N(3B)	-550(1)	246.0(9)	13.4(9)	41(2)	-540.6(9)	249.9(8)	20.9(8)	41(2)
C(4B)	-403(1)	287(1)	88(1)	40(3)	-396(1)	289(1)	94(1)	36(2)
C(5B)	-305(1)	371(1)	71(1)	35(3)	-294(1)	375(1)	79(1)	35(2)
C(6B)	-347(1)	436(1)	-30(1)	43(3)	-334(1)	439(1)	-22(1)	34(2)
O(6B)	-270.3(9)	518.4(8)	-53.3(8)	49(2)	-257.9(7)	521.0(7)	-48.4(7)	40(2)
N(7B)	-165(1)	382(1)	171(1)	45(2)	-157.3(9)	383.4(8)	177.0(8)	38(2)

.....cont

Table 30 (cont.)

	I				II			
C(8B)	-190(1)	299(1)	239(1)	46(3)	-182(1)	303(1)	247(1)	46(3)
N(9B)	-332.7(9)	241.0(9)	191.3(9)	35(2)	-326.2(9)	244.3(9)	200.6(9)	43(2)
C(9B)	-397(1)	146(1)	245(1)	46(3)	-391(1)	151(1)	256(1)	54(3)
C(10B)	-469(2)	-3(2)	168(2)	65(4)	-472(2)	-6(1)	171(2)	72(4)
Cl(1)+	22.9(9)	283(1)	550.1(9)	32(11)*	23.6(4)	288.1(4)	562.7(3)	43(5)*
Cl(11)+	29(1)	731(1)	441.6(9)	39(13)*	-	-	-	-
Cl(2)+	484.4(7)	445.2(7)	451.5(7)	40(10)*	495.3(6)	450.6(7)	464.8(6)	37(8)*
Cl(3)+	390.6(7)	948.5(6)	380.3(6)	33(9)*	-	-	-	-
OH(1)+	350(2)	486(2)	694(2)	39(5)	364(2)	488(1)	691(1)	37(3)
OH(11)+	605(3)	501(2)	315(2)	75(8)	426(2)	503(2)	677(2)	63(4)
OH(2)+	-152(2)	473(2)	462(2)	85(6)	193(3)	548(2)	543(2)	102(7)
OH(3)+	569(2)	860(2)	623(2)	59(5)	-	-	-	-
OH(4)+	312(2)	790(2)	442(2)	72(5)	-	-	-	-
OH(5)+	499(3)	677(3)	608(3)	102(7)	-	-	-	-
O(3)+	-	-	-	-	441(2)	153(2)	390(2)	51(4)
O(4)+	-	-	-	-	596(2)	31(2)	610(2)	86(6)
O(5)+	-	-	-	-	395(2)	-115(2)	436(2)	81(5)
CO	-	-	-	-	481(3)	92(3)	443(3)	59(6)

*$U_{eq} = 1/3[U_{11} + U_{12} + U_{13} + 2 (U_{23} \cos \alpha + U_{13} \cos \beta + U_{12} \cos \gamma)]$

+These atoms were given a site occupancy of one-half.

Table 31

Bond lengths (Å) and angles (°) for [cis-$(NH_3)_2Pt(9\text{-Et-G})_2]Cl_2 \cdot 3H_2O$ (I) and [cis-$(NH_3)_2Pt(9\text{-Et-G})_2]Cl_{1.5}(HCO_3)_{.5} \cdot 1.5H_2O$ (II)

	I		II	
	A	B	A	B
Atoms		Distance		
Pt-N(11)	2.04(1)	-	2.05(1)	-
Pt-N(12)	2.05(1)	-	2.04(1)	-
Pt-N(7)	2.03(1)	2.03(1)	2.018(9)	2.03(1)
N(1)-C(2)	1.38(2)	1.36(2)	1.36(2)	1.37(2)
C(2)-N(2)	1.33(2)	1.36(2)	1.36(1)	1.35(2)
C(2)-N(3)	1.34(2)	1.34(2)	1.32(1)	1.34(2)
N(3)-C(4)	1.36(2)	1.36(2)	1.35(1)	1.34(2)
C(4)-C(5)	1.40(2)	1.35(2)	1.37(2)	1.37(2)
C(5)-C(6)	1.44(2)	1.43(2)	1.40(1)	1.41(2)
C(6)-O(6)	1.26(2)	1.22(2)	1.23(1)	1.22(2)
C(6)-N(1)	1.36(2)	1.40(2)	1.40(1)	1.41(1)
C(5)-N(7)	1.36(1)	1.42(2)	1.41(1)	1.40(1)
N(7)-C(8)	1.33(2)	1.34(2)	1.33(1)	1.33(2)
C(8)-N(9)	1.37(2)	1.34(2)	1.36(1)	1.37(2)
C(4)-N(9)	1.36(1)	1.37(2)	1.37(1)	1.37(1)
N(9)-C(9)	1.49(2)	1.49(2)	1.49(2)	1.48(2)
C(9)-C(10)	1.54(2)	1.50(2)	1.53(2)	1.54(2)
CO-O(3)	-	-	1.02(4)	-
CO-O(4)	-	-	1.16(3)	-
CO-O(5)	-	-	1.37(3)	-
		Angles		
N(11)-Pt-N(12)	91.1(5)	-	90.6(4)	-
N(11)-Pt-N(7)	91.5(5)	179.1(4)	91.7(4)	179.5(4)
N(12)-Pt-N(7)	177.5(6)	89.7(5)	177.6(5)	89.9(4)
N(7A)-Pt-N(7B)	87.8(5)	-	87.9(4)	-
C(6)-N(1)-C(2)	125(1)	125(1)	125.0(8)	125.5(9)
N(1)-C(2)-N(2)	117(1)	117(1)	116.2(9)	118(1)
N(1)-C(2)-N(3)	123(1)	125(1)	123.8(9)	123(1)
N(2)-C(2)-N(3)	120(1)	118(1)	120(1)	119(1)
C(2)-N(3)-C(4)	112(1)	111(1)	112.4(9)	112(1)
N(3)-C(4)-C(5)	130(1)	128(1)	127.5(8)	128(1)
N(3)-C(4)-N(9)	125(1)	123(1)	125.1(9)	124(1)
C(5)-C(4)-N(9)	105(1)	109(1)	107.4(8)	108(1)
C(4)-C(5)-C(6)	116(1)	121(1)	120.1(9)	121(1)
C(4)-C(5)-N(7)	110(1)	108(1)	107.9(8)	108(1)

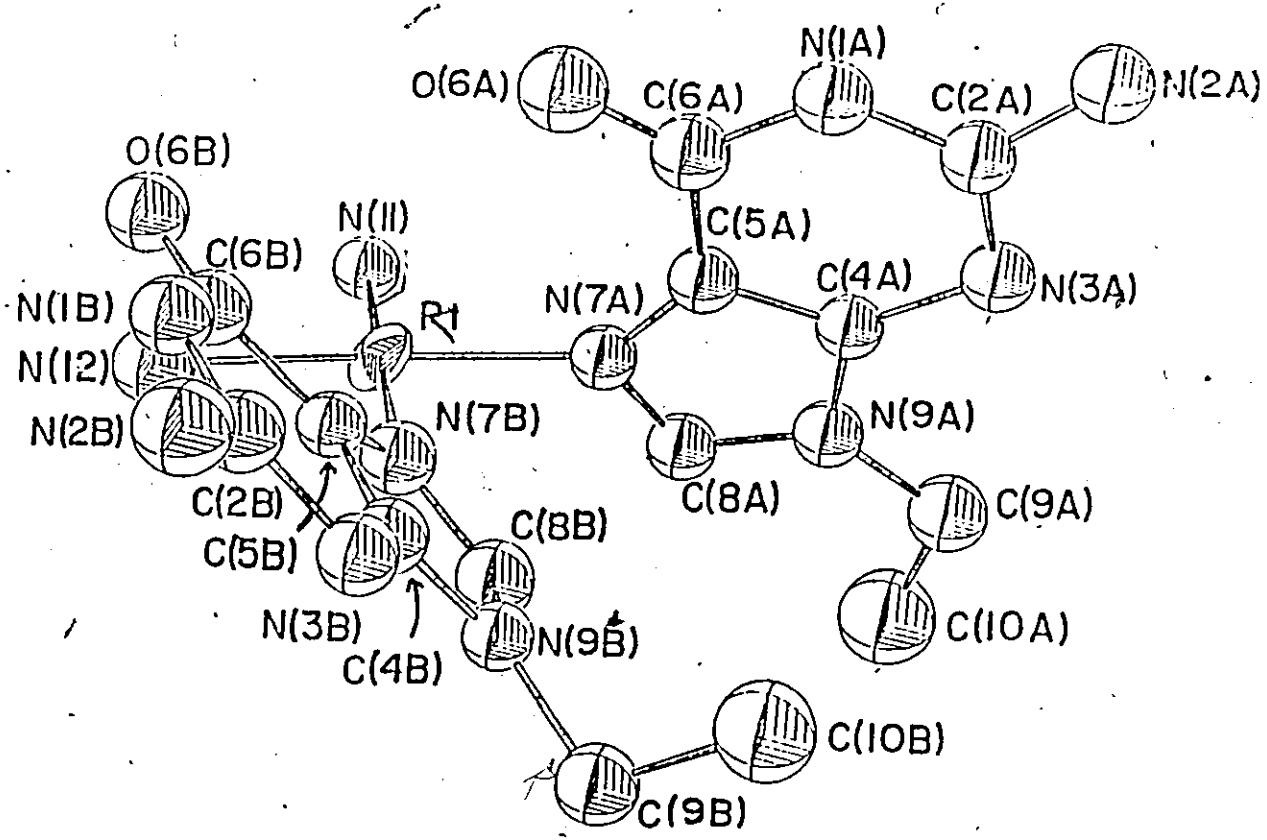
.....cont.

Table 31 (cont.)

C(6)-C(5)-N(7)	134(1)	131(1)	132(1)	131(1)
C(5)-C(6)-O(6)	125(1)	129(1)	128.8(9)	130(1)
N(1)-C(6)-O(6)	121(1)	122(1)	120.0(8)	120(1)
N(1)-C(6)-C(5)	114(1)	110(1)	111.2(9)	110(1)
C(5)-N(7)-Pt	126.1(8)	132(1)	126.7(7)	132.2(9)
C(5)-N(7)-C(8)	107(1)	105(1)	106.4(8)	106(1)
C(8)-N(7)-Pt	126.3(9)	122.8(9)	126.0(7)	121.9(8)
N(7)-C(8)-N(9)	110.3(9)	112(1)	110.8(8)	112(1)
C(8)-N(9)-C(4)	108(1)	107(1)	107.4(9)	106(1)
C(4)-N(9)-C(9)	124(1)	128(1)	124.1(8)	128(1)
C(8)-N(9)-C(9)	127.9(9)	125(1)	128.5(8)	126(1)
N(9)-C(9)-C(10)	111(1)	110(2)	112(1)	109(1)
O(3)-CO-O(4)	-	-	116(2)	-
O(3)-CO-O(5)	-	-	137(2)	-
O(4)-CO-O(5)	-	-	108(3)	-

Figure 47

Molecular structure of the cis-diamminebis(9-ethylguanine-N^7)platinum(II) cation



purine plane. In Ring A, C(10) is 0.07(2)Å out of the purine plane in complex I and 0.04(2)Å in II. In Ring B however, the distance is 1.33(2)Å in I and 1.40(2)Å in II. This leads to three different types of intermolecular base-base stacking in the unit cell (see below).

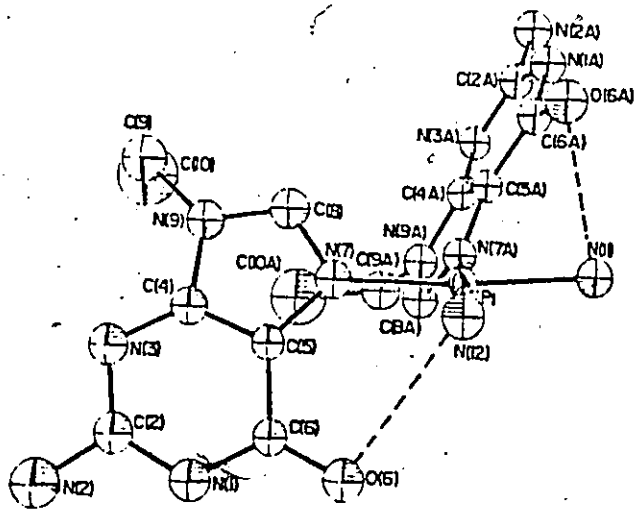
Both structures show large dihedral angles between the purine ligand A and the platinum coordination plane, PtN_4 (A-PtN_4 = 75.4(9)° in I and 74.4(9)° in II). The B ring makes a smaller angle with the platinum coordination plane (49.2(9)° in I and 50.6(9)° in II); this is because of an internal hydrogen bond between O(6) and one of the ammine ligands on the platinum atom.[70,84] These bonds are O(6B)---N(12) = 2.92(1)Å (I) and O(6B)---N(12) = 2.965(8)Å (II). The dihedral angle between the purine ligands is large in both complexes (68(1)° in I and 70(1)° in II) and indicates that there is little or no intra-complex base-base interaction. There is however, substantial inter-complex base stacking between A rings and between B rings of symmetry related cations in the unit cell (see below).

Certainly the most interesting feature of the compounds described here is the head to head arrangement of the two 9-ethylguanine ligands; this is in contrast to all previously reported structures of cis-bis(nucleobase) complexes of platinum(II) (see Figure 48). The head to head arrangement of the purines makes these complexes more likely models for the intrastrand guanine-guanine cross-links.

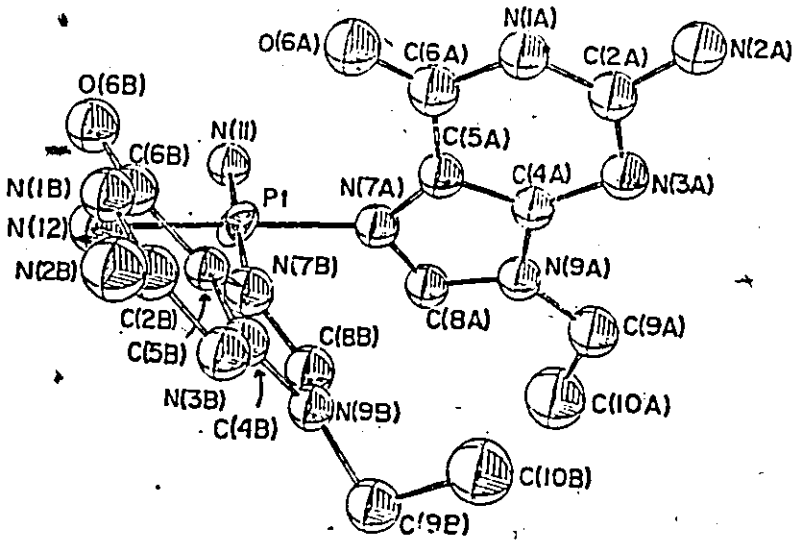
As mentioned earlier, there are three types of intercomplex ring-ring interactions in the unit cells shown in Figures 49 and 50. The first interaction involves the stacking of the A rings. These stack at a distance of 3.36(2)Å and 3.38(2)Å along the a direction

Figure 48

Head to tail arrangement observed in cis-bis(nucleobase)platinum(II) complexes (a) and head to head arrangement observed in cis-bis(9-Et-G)platinum(II) complexes studied here (b)



(a) head to tail arrangement



(b) head to head arrangement

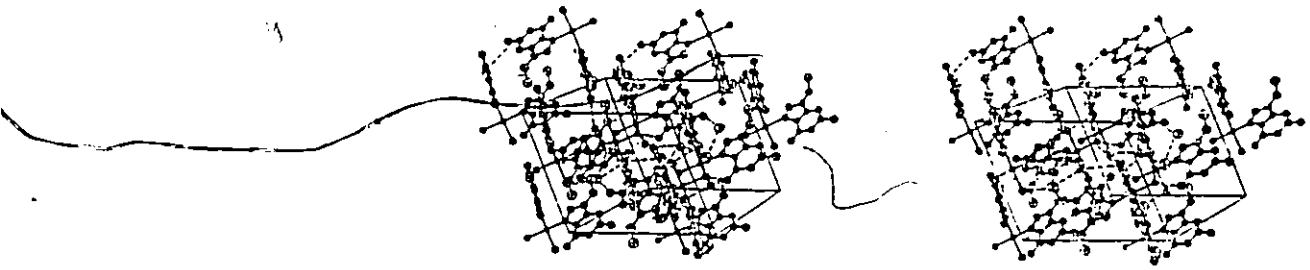
Figure 49

The contents of the unit cell of [cis-$(NH_3)_2Pt(9\text{-Et-G})_2]Cl_2 \cdot 3H_2O$

The a and c* x a axes are parallel to the bottom and side of the page, respectively and the view is down c*.

Figure 50

The contents of the unit cell of
[cis-$(NH_3)_2Pt(9\text{-Et-G})_2]Cl_{1.5}(HCO_3)_{.5}\cdot 1.5H_2O$



The a and c* x a axes are parallel to the bottom and side of the page, respectively and the view is down c*.

in complexes I and II respectively; the rings are related by the centre of symmetry at the origin. In addition, adjacent molecules along a, related by the inversion centre at ½, 0, 0 are hydrogen-bonded together. The A ring of one molecule is hydrogen-bonded to the B ring of the other (N(3A)---N(2B) = 3.07(2)Å).

The B rings are stacked along the b direction at x = ½, z = 0 and there are two types of ring-ring interaction, caused by the orientation of the ethyl groups with respect to the purine plane. At y = ½, the bases are co-stacked to maximize π-π interactions and the rings are 3.37(2)Å (I) and 3.33(2)Å (II) apart. Because the ethyl groups are roughly normal to the purine plane (B ring), adjacent molecules along b related by the inversion centre at ½, 0, 0 have long ring-ring distances (4.86(2)Å (I) and 4.87(2)Å (II)), the contacts being between the terminal methyl groups and the purine planes. In addition, molecules in the b direction are bound by hydrogen bonding between O(6B) of one molecule and N(2A) of a translationally equivalent molecule (O(6B)---N(2A) = 2.97(2)Å in I and 2.94(1)Å in II).

In the c direction, there is hydrogen bonding between pairs of molecules related by the centre of symmetry at 0, ½, 0 from O(6A) to N(11) and N(12).

In both complexes, the anions and lattice water molecules form disordered hydrogen bonded chains which run through the middle of the unit cells at ½, b, ½.

In complex I, there are two chloride ions, Cl(2) and Cl(3) which are disordered about the centres of symmetry at ½, ½, ½ and

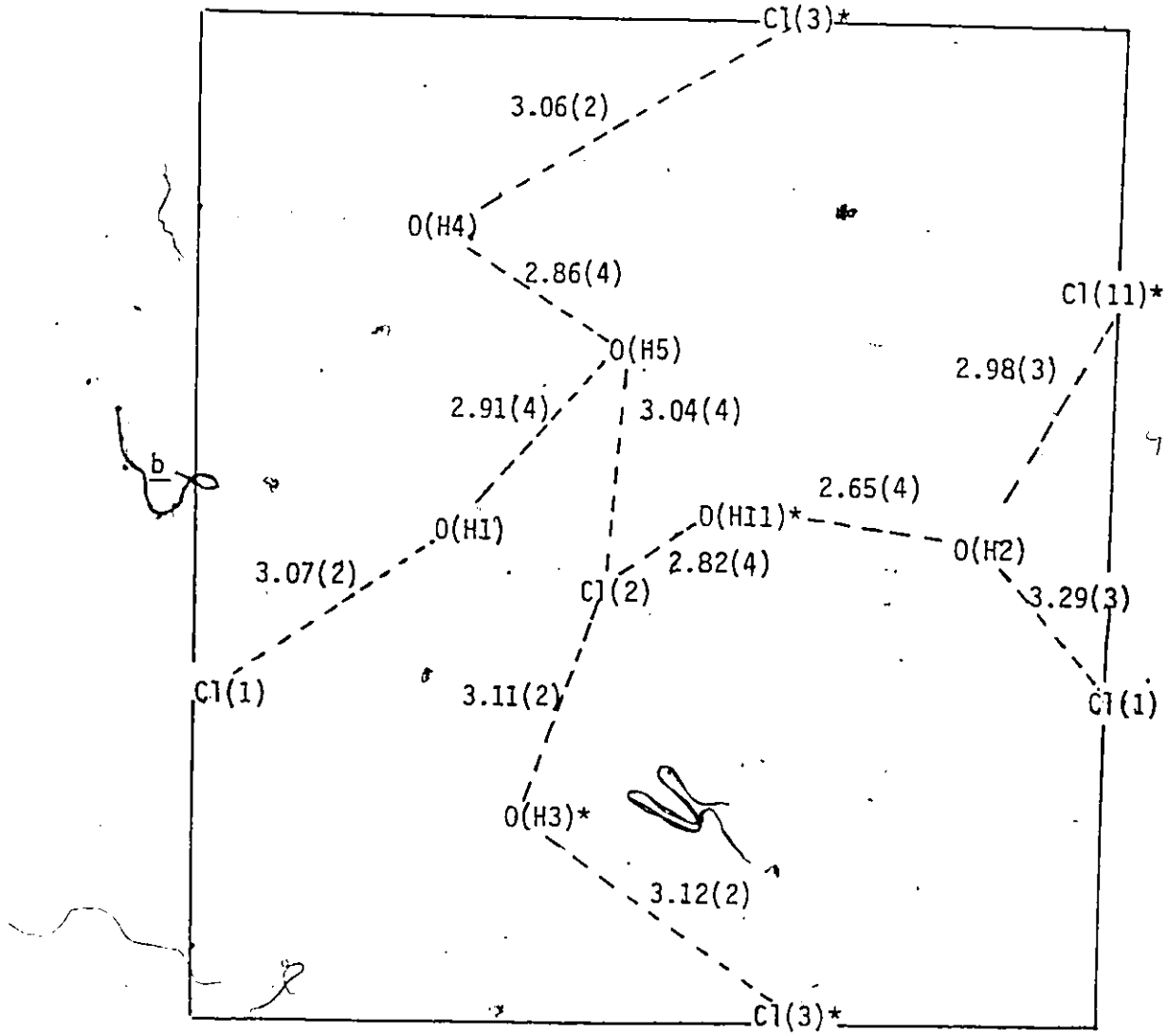
½, 0, ½ respectively. The disordered positions were chosen because the temperature factors were more reasonable than they were with the ions on the special positions. They are part of the hydrogen-bonded chain which consists of the following atoms: Cl(3)*,O(H3)*, Cl(2), O(H5) and O(H4). The interactions between the lattice water molecules and the anions are shown in Figure 51. The half-occupancy of the atoms in the hydrogen-bonded chain running through the crystal results in the observed disorder. The presence of O(H2) in the lattice also causes further disorder: two unacceptable distances were obtained (O(H2)-O(H1) = 2.37(3)Å and O(H2)-Cl(1)* = 2.60(3)Å). O(H1) and Cl(1) were then given half-occupancy. A difference synthesis showed a peak 0.59(5)Å away from O(H1) which was labelled O(H11)* and given half-occupancy. Similarly, a peak was seen 0.66(2)Å away from Cl(1); it was given half-occupancy and labelled Cl(11)*. Joining the chain are thus O(H1), O(H11)*, Cl(1) and Cl(11)* (see Figure 51). O(H1) and O(H11)* form a strong hydrogen bond with N(1B) (2.73(2)Å, 2.79(3)Å respectively). There is a strong interaction between Cl(2) and O(H11) (2.82(4)Å) which is short for normal O---Cl distances but the uncertainty involved is large. Similar Cl---O contacts have been seen ranging between 2.68Å and 2.90(2)Å.[229,261,262]

In complex II, the chain along the b axis consists of two disordered anion: a chloride ion near ½, ½, ½ and a bicarbonate ion near ½, 0, ½. There is a strong interaction between Cl(2) and O(3)

* * These atoms are situated at positions related to those given in Table 30 by a centre of symmetry.

Figure 51

Schematic diagram of the interactions between lattice water molecules and chloride ions in [cis-$(NH_3)_2Pt(9\text{-Et-G})_2]Cl_2 \cdot 3H_2O$



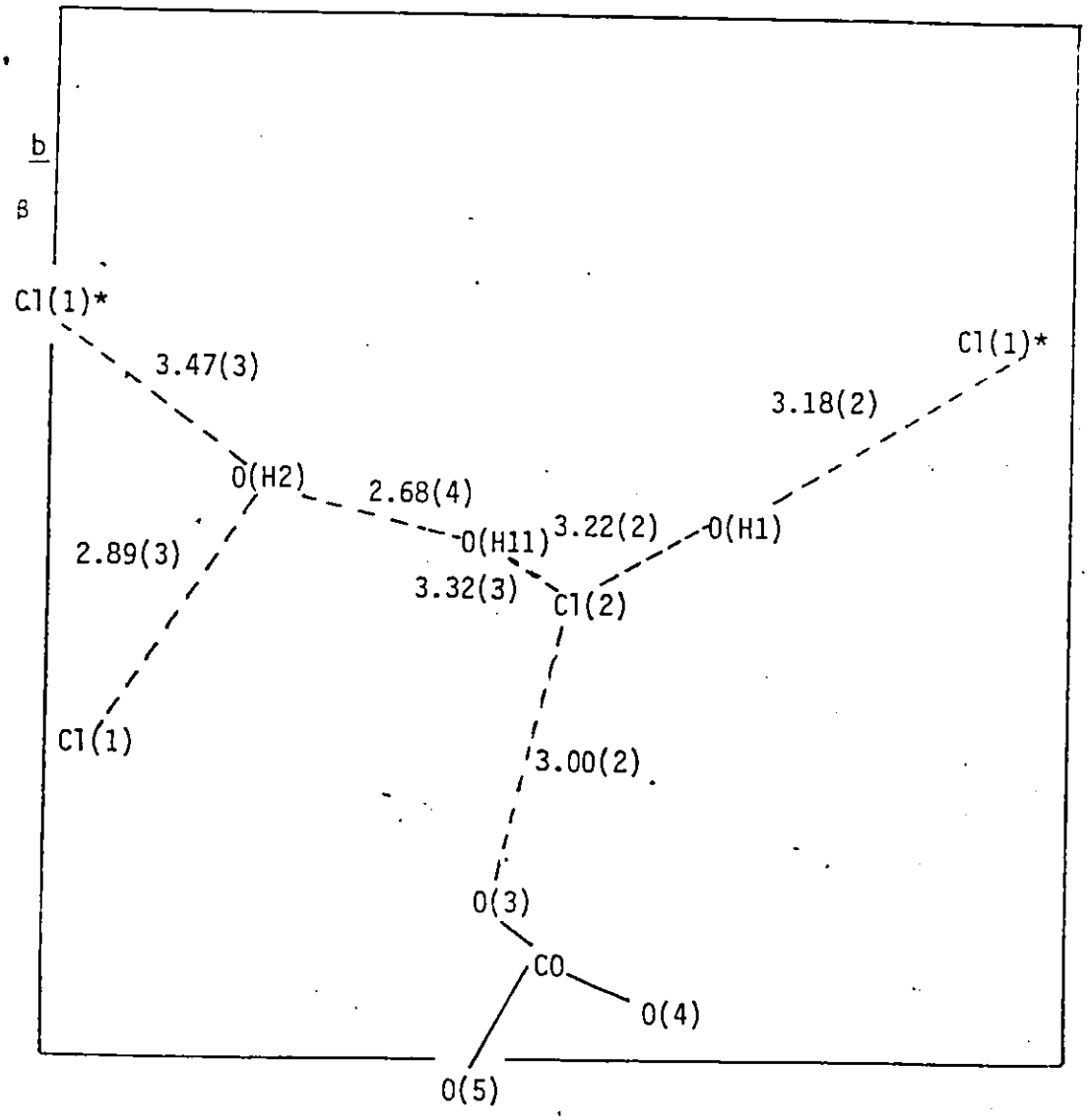
a cos (γ-90°)

of the bicarbonate ion (3.00(2)Å) presumably caused by a hydrogen bond. O(H1) is disordered as it was in complex I because of contact with O(H2), but Cl(1) is not. The interactions between the lattice water molecules and the anions are shown in Figure 52.

Since we have no analytical evidence for the bicarbonate ion and since the geometry is not particularly good (see Table 31), we considered the possibility of other anions such as nitrate or acetate even though neither of these anions had been used in the preparation of complex II. The acetate group can be ruled out from ^{1}H Nmr studies: no CH_3 resonance consistent with an acetate ion was observed. We chose the bicarbonate over the nitrate anion because the unexpected incorporation of carbonate ions into a crystal from water and carbon dioxide in the air is well established.[263,264] The nitrate ion was discarded because it gave no advantage over the bicarbonate ion; the geometric anomalies seen in this structure would apply to it as well.

Figure 52

Schematic diagram of the interactions between lattice water molecules and the anions in [cis-$(NH_3)_2Pt(9\text{-Et-G})_2]_2Cl_3(HCO_3)\cdot 3H_2O$



CHAPTER SIX

CONCLUSIONS

The ultimate goal in anti-cancer drug research is the development of a drug which will cure, or cause remission of, a particular cancer type without showing any dangerous side effects. Cis-dichlorodiammine-platinum(II) (cis-DDP), the original platinum drug, was found to be an effective anti-cancer agent against different types of cancer; yet its efficacy was undermined by its serious side effects, the predominant one being kidney damage. In order to find more effective or less toxic platinum drugs, studies on all aspects of the chemistry of platinum were begun, ranging from the preparation of complexes to their reaction with possible biological targets.

Interesting results have surfaced from the large body of publications now found on platinum anti-cancer drugs in the literature: in order to obtain pure starting materials a common mode of preparation, shown to give a complex of high purity in good yield, should be adopted; it is now believed that some of the early animal tests for toxicity and anti-cancer activity were carried out on mixtures of starting materials. It is known that the drug administered to a patient undergoes hydrolysis before interacting with its biological target; the aqueous chemistry of platinum(II) yields many species, some of which are difficult to isolate and may be very toxic. Finally, the

interaction of the platinum drug with DNA has been studied extensively to determine which of the possible binding modes leads to the anti-cancer activity.

Structural features have played an important part in these aspects of platinum chemistry. It is already known that trans isomers of PtA_2X_2 are not active anti-cancer agents while their cis analogues may be very effective anti-tumour drugs. The interaction of active anti-cancer platinum complexes with DNA causes a major change in the conformation of the macromolecule; this change may be a very important aspect in the determination of anti-cancer activity.

It was with this background in mind that the structures of platinum complexes relevant to the anti-cancer research field were investigated.

The use of dimethylsulfoxide (DMSO) has been studied extensively not only as a solvent for animal tests with cis-DDP but also as a ligand to enhance the water solubility of platinum anti-cancer drugs.[199] The dissolution of cis-DDP in DMSO results however in a complex mixture of products. Thus, there is a need to isolate pure products from the mixture so that each component can be tested for anti-tumour activity and toxicity. Fortunately, DMSO is a good ligand for platinum(II) and the isolation of the different products in solution may be possible. Such is the case for the cis-$(NH_3)_2Pt(Cl)(DMSO)$ cation.

The need for pure starting materials is obvious when the complex being prepared is to be tested as an anti-cancer agent. A method which can be used has been described in detail.[212] It reproducibly

gives cis-DDP in high purity and does not lead to the isomerization of the drug to its trans analogue; this problem has been observed in recrystallization procedures used in the past.[214] The complex cis-dichlorodiammine platinum(II)·dimethylformamide is an intermediate product obtained during the recrystallization. The isolation of this product shows that care must be taken to completely remove the solvent from the platinum complex when using this method of purification.

Because of the toxic side effects of cis-DDP, numerous studies have concentrated on the preparation of "second-generation" drugs which would be more effective and less toxic than the parent drug. 1,2-diaminocyclohexane platinum(II) complexes fulfil these requirements. Furthermore, the platinum complexes of the isolated isomers of the 1,2-diaminocyclohexane ligand have different anti-cancer activities. The study of the 1,2-dac complexes was undertaken with two goals in mind: the first was to compare the structure of platinum complexes of the 1,2-dac ligand with those of anti-cancer drugs containing other amine ligands; the second was to determine whether there is a correlation between the structure of the complexes of the different isomers of 1,2-dac and their anti-tumour activity.

The geometry around the platinum atom in the cis-1,2-dac platinum complexes was not different from that seen in other anti-cancer platinum drugs. The Pt-Cl bond lengths in the three molecules of cis-1,2-dac $PtCl_2$ fall within the range seen in other complexes (range, cis-1,2-dac $PtCl_2$, 2.284(7)-2.310(6)Å; range, other complexes, 2.272(4)-2.326(9)Å [214]); the Pt-N bond lengths are not significantly

different from those in platinum complexes with other amine ligands (range, cis-1,2-dac $PtCl_2$, 2.01(2)-2.06(2)Å; range, other complexes, 2.04(1)-2.07(1)Å[214]). Similarly, the angles around the platinum atom are very close to those seen in other complexes with the exception of the N-Pt-N angle (average = 83.2(8)°) which is smaller than those observed previously (range, 87(1)-91(1)°[214]). This is presumably caused by the chelation of the 1,2-diaminocyclohexane ligand: angles smaller than 90° have been observed for 1,2-diaminocyclohexane complexes of other metals (range = 82.7(9)°-87.5(9)°[158-160,167-169]). Thus the high level of anti-tumour activity of the 1,2-dac platinum complexes cannot be correlated to an unusual structural feature.

A comparison of the spatial distribution of the atoms in cis-1,2-dac and trans-(-)-1,2-dac platinum complexes showed a difference in the orientation of the ligand rings with respect to the platinum coordination plane. There is however no evidence to suggest that this structural difference is the source of the difference in anti-cancer activity.

The hydrolysis of platinum(II) complexes is an important aspect of the chemistry of the anti-cancer drugs. It poses an interesting problem because of the large number of species present in solution. The formation of hydrolysis products can occur under two different conditions. In the first case, hydrolysis of the platinum complex is the first step in the mechanism of action of the drug. The concentration of the platinum complex is believed to be very low. In the second instance, hydrolysis occurs as an intermediate step in

the preparation of water soluble platinum drugs. Here, the concentration of the platinum complex is high and there is a good possibility of forming dimeric or trimeric hydroxo-bridged species. The polymeric products have been shown to be toxic when the amine attached to platinum is NH_3 but to show little toxicity when 1,2-diaminocyclohexane is the ligand. A comparison of the structure of $(1,2\text{-dacPtOH})_3$ with that of $[(NH_3)_2PtOH]_3$ showed no major structural differences which could account for the different results obtained in animal studies.

Other species present in aqueous solutions of platinum complexes are those containing terminal hydroxide groups. These complexes and those with terminal aquo groups occur in aqueous solution but any attempts at isolating these species have failed. The structure of the hydroxo-cis-diammine(1-methylcytosine-N^3) platinum(II) cation is the first example of a platinum(II) complex with a terminal hydroxo ligand. It had been suggested previously that the rapid rate of reaction of square planar d^8 complexes containing Pt-O bonds was caused by the weakness of the Pt-O bond. In the complex, the platinum to oxygen distance was found to be normal, indicating that the bond is not inherently weak. The rapid rate of reaction may be associated with a weakening of the Pt-O bond in a five coordinate intermediate state. This behaviour has been observed previously in rhodium(I) complexes.[144,195] The presence of lattice water molecules is required to stabilize the platinum complex as was predicted by a consideration of the structure using Brown's acid-base model.[198]

The search for the mechanism of action of any drug is probably

the most important aspect in the field of drug research. Once the reason for the activity has been determined, it may be possible to design complexes which will be more effective than the parent drug. It is now widely believed that the biological targets for the platinum anti-cancer drugs are nucleobases in DNA. Crystallographers can only identify molecular fragments in DNA; model systems must be used if one wants to determine the site of attachment of platinum to the bases or to obtain information on the interactions between neighbouring fragments in a molecule. It is hoped that the model complexes mimic the interaction of platinum complexes with the DNA bases.

The bases used in this work were 9-ethylguanine and 1-methyluracil. The primary coordination sites of the bases were the N(7) position of 9-ethylguanine and the deprotonated N(3) position of 1-methyluracil; these are the usual binding sites for these bases.

One of the postulated mechanisms of action of the platinum anti-cancer drugs is the formation of a crosslink between two guanine bases adjacent to one another on the same strand of DNA(intrastrand crosslink). Three complexes studied here contain two DNA bases in cis positions on the platinum atom. The intracomplex dihedral angle between the coordinated bases was large. If one considers these complexes as model systems for an intrastrand crosslink, the results indicate that the dihedral angle between the two bases would change from approximately 0° in native DNA to approximately 70° in the platinated macromolecule. This would be expected to cause a change in the conformation of DNA. Major conformational changes have been observed

in DNA when the macromolecule is reacted with cis-DDP; the model complexes studied here and those investigated previously (see for example Table 32) show how the geometry around the platinum atom may explain the results. Intermolecular base stacking was observed between the 9-ethylguanine ligands. This is always observed when there is no intracomplex base stacking (Table 32).

The complexes with two 9-ethylguanine ligands in cis positions on platinum are the only ones isolated in the solid state where the bases are arranged in a head to head fashion (Table 32). This arrangement may be a more likely model than the cis bis(nucleobase) complexes studied previously for the intrastrand guanine-guanine crosslink; a head to head arrangement of two guanine bases in platinated GpG has been observed previously in solution.[257] Thus, although the bases are not joined through a common backbone in the model complex, the configuration seen in $[cis\text{-}(NH_3)_2Pt(9\text{-Et-G})_2]^{2+}$ should be attainable in DNA.

Although the model complexes studied here cannot differentiate between certain postulated modes of action of the platinum drugs (e.g. intrastrand vs. interstrand crosslink), the geometrical features seen in the cis-bis(nucleobase) platinum complexes would certainly cause major structural changes in localized areas of the DNA. These changes are obtained without binding of platinum to the O(6) position of guanine. In fact, no indication of an interaction between the platinum atom and the O(6) position has been observed in the complexes studied here or investigated previously: there is still no hard

Table 32

Summary of results for cis-bis(nucleobase)platinum(II) complexes

Complex	Intracomplex base stacking (base-base dihedral angle°)	Intercomplex base stacking	Orientation of two bases
cis-$(NH_3)_2Pt(Guo)_2^{2+}$ [a]	No (74)	Yes	Head to tail
cis-$(en)Pt(Guo)_2^{2+}$ [b]	No (71)	Yes	Head to tail
cis-$(NH_3)_2Pt(GMP)_2$ [c]	Yes (39.6)	No	Head to tail
cis-$(NH_3)_2Pt(9\text{-Et-G-H})_2$ [d,e]	No (67.1[d]; 87(1)[e])	Yes	Head to tail
cis-$(NH_3)_2Pt(9\text{-Et-G})_2^{2+}$ [f]	No (68(1); 70(1))	Yes	Head to head

[a] Guo = guanosine, values are from reference 76

[b] en = ethylenediamine, values are from reference 79

[c] GMP = guanosinemonophosphate, values are from reference 86

[d] 9-Et-G-H = 9-ethylguanine, deprotonated at N(1), values are from reference 70

[e] values are from reference 71

[f] 9-Et-G = 9-ethylguanine, this work

evidence for N(7)-O(6) chelation of the guanine ligand to platinum.

The results presented in this work have attempted to bridge certain gaps in the major areas of research on platinum anti-cancer drugs. The important structural features of the complexes studied have been outlined and, where possible, the molecular conformations have been associated with previous chemical information. It is hoped that the information available here will help future workers in this field to obtain a better understanding of the general chemistry and the mechanism of action of the platinum anti-tumour complexes.

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APPENDICES

ANISOTROPIC TEMPERATURE FACTORS ($Å^2$) FOR SELECTED ATOMS

A tris[cis-dichloro-cis-(1,2-diaminocyclohexane)platinum(II)]hydrate

($\times 10^3$)

Atoms	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt(1)	27.1(5)	15.7(4)	33.0(5)	-9(4)	7.7(4)	0.1(4)
Pt(1A)	27.4(5)	18.3(4)	28.6(5)	2.2(4)	8.1(3)	1.1(4)
Pt(1B)	25.8(5)	16.1(4)	33.4(5)	-0.1(4)	13.0(4)	0.4(4)
Cl(1)	51(4)	22(3)	29(3)	-5(3)	1(3)	1(3)
Cl(2)	45(4)	24(3)	58(4)	-1(3)	4(3)	-12(3)
Cl(1A)	39(3)	25(3)	59(4)	5(3)	15(3)	-11(3)
Cl(2A)	37(3)	40(4)	48(4)	2(3)	5(3)	-18(3)
Cl(1B)	48(4)	28(3)	40(4)	6(3)	18(3)	4(3)
Cl(2B)	45(4)	26(3)	44(4)	-6(3)	22(3)	-5(3)

B cis-dibromo-cis(1,2-diaminocyclohexane)platinum(II)

($\times 10^4$)

Atoms	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	234(2)	265(3)	307(3)	-20(2)	158(2)	-40(2)
Br(1)	432(7)	474(8)	502(8)	140(6)	264(6)	50(6)
Br(2)	437(7)	407(7)	411(7)	-48(6)	256(6)	-86(6)

C cyclo-tri-μ-hydroxotris[trans-1,2-diaminocyclohexaneplatinum(II)] nitrate hydrate

($\times 10^3$)

Atoms	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt(1)	53(1)	50(1)	70(1)	1(1)	-3(1)	-16(1)
Pt(2)	62(1)	56(1)	67(1)	-14(1)	16(1)	-13(1)
Pt(3)	55(1)	47(1)	80(1)	-4(1)	1(1)	-18(1)

D hydroxo-cis-diammine(1-methylcytosine-N^3)platinum(II) nitrate dihydrate

($X10^3$)

Atoms	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	13.3(2)	16.2(2)	16.2(2)	0.2(2)	3.7(2)	2.6(2)
O(2)	16(4)	32(5)	30(4)	-4(4)	3(3)	8(4)
O(71)	36(5)	38(5)	24(4)	-1(5)	3(4)	10(4)
O(72)	58(8)	71(10)	99(11)	1(7)	32(8)	44(9)
O(73)	35(6)	93(10)	33(5)	25(6)	-4(5)	-18(6)

E chloro-cis-diammine(dimethylsulfoxide-S)platinum(II) nitrate

($X10^3$)

Atoms	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	30.6(5)	37.2(5)	21.8(5)	0	0	3(6)
Cl	49(4)	47(4)	36(3)	0	0	0(3)
S	30(3)	52(4)	21(3)	0	0	-9(3)

F cis-dichlorodiammineplatinum(II)dimethylformamide

($X10^3$)

Atoms	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	21.1(2)	31.9(2)	24.1(2)	1.0(4)	5.6(9)	-4.3(7)
Cl(1)	29(4)	62(4)	32(4)	6(3)	-6(3)	13(3)
Cl(2)	29(4)	50(3)	48(4)	0(3)	-2(3)	16(3)

G potassium thyminate trihydrate

($\times 10^3$)

Atoms	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
K	35.5(8)	57.5(10)	38.3(7)	-2.8(8)	12.8(6)	-6.4(8)
N(1)	33(3)	39(3)	37(3)	-6(3)	8(2)	-9(2)
C(2)	28(3)	38(4)	26(3)	-8(3)	9(2)	-2(3)
O(2)	26(2)	43(3)	41(2)	0(2)	8(2)	-5(2)
N(3)	29(2)	26(3)	34(3)	-1(2)	10(2)	-3(2)
C(4)	26(3)	35(3)	29(3)	8(3)	9(2)	0(3)
O(4)	26(2)	47(3)	52(3)	-5(2)	9(2)	-19(2)
C(5)	34(3)	33(3)	29(3)	2(3)	13(3)	2(3)
C(51)	44(4)	50(4)	44(4)	16(4)	19(3)	-3(3)
C(6)	48(4)	35(4)	38(4)	-1(3)	18(3)	-5(3)
O(1)	29(2)	55(4)	53(3)	4(2)	6(2)	1(3)
O(3)	45(3)	78(4)	38(3)	-6(3)	10(2)	0(3)
O(5)	35(3)	59(3)	47(3)	-1(2)	11(2)	1(3)

H cis-(9-ethylguaninato-N^7)(1-methyluracilato-N^3)diammineplatinum(II) dihydrate

($\times 10^2$)

Atoms	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	2.97(5)	4.09(5)	5.90(5)	-0.07(7)	2.01(4)	-0.84(7)
C(10)	6(1)	5(1)	10(2)	-2(1)	5(2)	0(1)

I cis-diamminebis(9-ethylguanine-N^7)platinum(II)dichloride trihydrate

($\times 10^3$)

Atoms	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	58.3(4)	62.8(4)	59.4(4)	50.6(3)	45.5(3)	47.5(3)
Cl(1)	46(5)	73(5)	35(4)	39(4)	27(4)	29(4)
Cl(11)*	77(7)	57(5)	43(5)	41(5)	24(5)	25(4)
Cl(2)	44(4)	52(4)	59(5)	21(3)	15(4)	22(3)
Cl(3)	44(6)	42(4)	34(4)	14(3)	9(3)	9(3)

J cis-diamminebis(9-ethylguanine-N^7)platinum(II)sesquichloride hemicarbonate sesquihydrate

($\times 10^3$)

Atoms	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	28.2(2)	35.9(3)	31.7(3)	20.8(2)	20.5(2)	18.7(2)
Cl(1)	83(2)	82(2)	39(2)	49(2)	31(2)	32(2)
Cl(2)	37(3)	67(4)	43(3)	21(3)	16(3)	19(3)