DNA BASE COMPLEXES OF PLATINUM AND THE ANTITUMOR ACTION OF cis-$Pt(NH_3)_2Cl_2$

By

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A Thesis

Submitted to the Faculty of Graduate Studies

in Partial Fulfilment of the Requirements

for the Degree

Doctor of Philosophy

McMaster University

June, 1980

THE ANTITUMOR ACTION OF <u>cis</u>-$Pt(NH_3)_2Cl_2$

To My Fiancée and Parents

We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.

T.S. Eliot
Four Quartets (Little Gidding).

Look to this day -
For yesterday is but a dream and
Tomorrow is only a vision;
But today well-lived, makes
Every yesterday a dream of happiness -
And every tomorrow a vision of hope.
Look well therefore to this day.

Author unknown.

DOCTOR OF PHILOSOPHY (1980)
Department of Chemistry

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TITLE: DNA BASE COMPLEXES OF PLATINUM AND THE ANTITUMOR ACTION OF cis-$Pt(NH_3)_2Cl_2$

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NUMBER OF PAGES: xxi, 237

ABSTRACT

A previously unknown mode of binding of platinum complexes to the DNA bases is described. The binding mode is characteristic of *cis* and not *trans*-$Pt(NH_3)_2Cl_2$, and is thought to be related to the ability of *cis* compounds to form hydroxobridged dimers. It is suggested that the differing anticancer activity of *cis* and *trans*-$Pt(NH_3)_2Cl_2$ may result from this difference in chemistry which is based on the differing stereochemical requirements of *cis* and *trans* isomers.

ACKNOWLEDGEMENTS

I am very grateful to Professor Colin Lock for the guidance, encouragement and friendship which he has shown me.

I would like to thank the members of my committee Professors Brown, Eaton and Neilson for their helpful criticisms.

Thanks are also due to Romolo Faggiani, whose technical help was invaluable.

I am especially grateful to my fiancée, Irene, and my parents for their faith in me, for their constant encouragement and for their patience.

Finally, I would like to thank Mrs. Jan Gallo for typing this thesis.

Financial support in the form of the C.W. Sherman Science and Engineering Scholarship (1977-1979), and from the Chemistry Department, McMaster University, in the form of Scholarships and Teaching Assistantships is gratefully acknowledged.

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

LIST OF TABLES

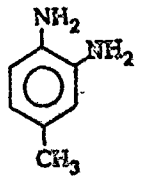
LIST OF FIGURES

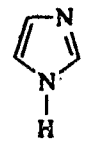
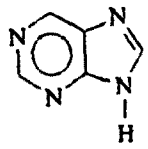
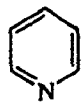
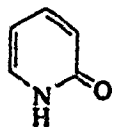
Miscellaneous Abbreviations

Abbreviation	Name
Å	Angstrom (10^{-8} cm)
°C	degrees celsius
cm	centimeter
ESCA	electron spectroscopy for chemical analysis
g	gram
h	hour
ir	infrared
L	liter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
M	a transition metal
nm	nanometer
nmr	nuclear magnetic resonance
rms	root mean square (deviation from the mean)
uv	ultraviolet
X	a halogen atom
wt	weight

Ligands and Molecules

am	amino
dat	3,4-diaminotoluene



Abbreviation	Name
dien	diethylenetriamine, $H_2NCH_2CH_2NHCH_2CH_2NH_2$
en	ethylenediamine, $NH_2CH_2CH_2NH_2$
	imidazole 
i-Pr_2SO	isopropylsulfoxide, $(i\text{-}C_3H_7)_2SO$
L,Y	ligand
Me_2SO	dimethylsulfoxide, $(CH_3)_2SO$
	purine 
	pyrazine 
py	pyridine 
	α-pyridone 
	pyrrole 
R	alkyl or aryl group
-SH	sulfhydryl

DNA Abbreviations	Name
1-MeCyt	1-methylcytosine
9-EtGua	9-ethylguanine
9-MeAde	9-methyladenine
	thymine
Cyd	cytidine
dCyd	2'-deoxycytidine
Guo	guanosine
dGuo	2'-deoxyguanosine
Ado	adenosine
dAdo	2'-deoxyadenosine
Thy	thymidine
Uri	uridine
5'-CMP	cytidine 5'-monophosphate
5'-dCMP	2'-deoxycytidine 5'-monophosphate
5'-dGMP	2'-deoxyguanosine 5'-monophosphate
5'-dAMP	2'-deoxyadenosine 5'-monophosphate
G-C	guanine-cytosine base pair in DNA
A-T	adenine-thymine base pair in DNA
GpG	guanylyl[3',5']guanosine
GpA	guanylyl[3',5']adenosine
d(GpG)	deoxyguanosine-phosphate-deoxyguanosine in DNA
d(GpA)	deoxyguanosine-phosphate-deoxyadenosine
DNA	deoxyribonucleic acid

CHAPTER 1

PLATINUM COMPOUNDS AS ANTITUMOR DRUGS

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PLATINUM COMPOUNDS AS ANTITUMOR DRUGS

1.1 PREAMBLE

Since the discovery made by Rosenberg *et al.* that *cis*-$Pt(NH_3)_2Cl_2$ was a potent antitumor agent,[1,2] (see Section 1.2) a considerable amount of effort has been directed at deducing the mechanism of the drug's action.[3-5] Initial biochemical experiments (see Section 1.3) showed that *cis*-$Pt(NH_3)_2Cl_2$ and other platinum compounds interacted with nuclear DNA.[6-9] Subsequent studies (see Section 1.4) suggested that it was the peculiar way in which *cis*-$Pt(NH_3)_2Cl_2$ bound to the DNA bases that caused tumor cell death.[10,11] At the start of this work, there was very little reliable structural information available as to how Pt complexes interacted with the DNA bases. Some of the proposed interactions appeared to be sterically unreasonable,[12] so, it was considered important to examine model platinum-base compounds to determine what the possible and probable modes of binding were. Since unambiguous structural information was sought, the model compounds were studied crystallographically.

This thesis has been organized so that the large volume of crystallographic data (and relevant discussion of the structures and packing) does not interfere with the logical development of the theme. All of the data

is reported in Chapter 2, hence, continuity is maintained simply by skipping this chapter on initial reading. The crystallographic data is assimilated in Section 2.6, p. 140 and inductive effects in DNA bases caused by platinum compounds and other electrophiles are discussed in Section 2.7, p. 154. Deductions made in these sections (2.6 and 2.7) are directly related to the theme of the thesis (as outlined in Chapters 1, 3 and 4), so they should be read next. Sections 2.1, 2.2, 2.3, 2.4 and 2.5 can be read as independent units. Although of secondary importance to the theme, the material in these sections is fundamental and is relevant to any discussion of platinum complex-DNA base binding. Abbreviations, nomenclature and DNA base numbering have been listed on pp. xix-xxi and p. 143.

1.2 COMPARISON OF CIS AND TRANS-$Pt(NH_3)_2Cl_2$: INITIAL CORRELATION ATTEMPTS

Although cis-$Pt(NH_3)_2Cl_2$ was shown to be the most potent[a] of the original platinum compounds which were investigated by Rosenberg et al.[1,2,3] (cis-$Pt(NH_3)_2Cl_2$, cis-$Pt(NH_3)_2Cl_4$, $Pt(en)Cl_2$ and $Pt(en)Cl_4$[b]), the others also showed antitumor activity. All of these original active compounds contain at least two cis chloride ligands. Any trans isomers that were tested were found to be inactive.[5] Rosenberg has suggested[15] that this stereo-selectivity implies that the cis and trans isomers retain their structural integrity throughout the biological systems (during

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[a] In the initial tests,[2] using, for example, single 8 mg/kg doses of cis-$Pt(NH_3)_2Cl_2$ against Sarcoma 180, complete remission of the tumor (as evidenced by tumor drop out) was effected within 10 to 16 days of injection of the drug.

[b] The Pt(IV) complexes, cis-$Pt(NH_3)_2Cl_4$ (and $Pt(en)Cl_4$) are presumed[13] or have been suggested[14] to be reduced in vivo according to:

$$2e^- + \text{cis-}Pt(NH_3)_2Cl_4 \rightarrow \text{cis-}Pt(NH_3)_2Cl_2 + 2Cl^-$$

The reduced species retain the cis arrangement of chloride ligands.

binding) and that they do not act as heavy metal poisons (with non-specific toxicity)[c].

Hoeschele and L. Van Camp[17] studied the distribution and retention of cis and trans-$Pt(NH_3)_2Cl_2$ in Swiss white mice with and without tumors (Sarcoma 180). They found that it was not possible to correlate variations in body retention and distribution of cis and trans isomers with antitumor and toxicity effects of the cis and trans isomers (see Appendix 1a for details).

Cleare[5] considered whether the differing rates of reactivity of the two isomers could explain their differing biological effects. He suggested that since the trans isomers of platinum compounds were usually more reactive than the corresponding cis isomers, they would react "more quickly and with a wider variety of body constituents"[5] than the cis compounds. The trans compounds then would be less specific in their action. The small difference in specificity was not

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[c] Nucleophilic substitutions in square planar platinum complexes proceed with complete retention of configuration. Isomerisms that do occur, proceed slowly by way of a two step mechanism.[16] (These reactions are discussed in more detail in Section 2.5, p. 136.)

considered large enough to describe the significant differences in antitumor activity of cis and trans isomers.

In spite of their higher reactivity, the trans compounds are, in general, less toxic than the corresponding cis compounds. This higher toxicity associated with the active cis compounds implies that the mechanism of toxicity may be related to the biological activity that is responsible for the antitumor activity. Such a link has not been confirmed to-date.

The initial reactions of cis and trans-$Pt(NH_3)_2Cl_2$ with body constituents almost certainly involve substitution by nucleophiles, such as H_2O, OH^-, $R\text{-}NH_2$, RS^-, or $R\text{-}S\text{-}CH_3$.[13,14] In such substitution reactions of $Pt(NH_3)_2Cl_2$, the chloride ions are replaced.[18-20] The ammines are very difficult to replace for thermodynamic (they are very strongly bound) and kinetic (NH_3 is a poor leaving group) reasons,[21] although exchange of the ammines can be induced in either of two ways (see Section 2.5, p. 136). Substitution reactions in square planar complexes of the type

$$PtL_nCl_{4-n} + Y \rightleftarrows PtL_nCl_{3-n}Y^+ + Cl^- \qquad (1)$$

are assumed to proceed by associative mechanisms along either of two pathways:[16,21] a direct nucleophilic substitution of Cl^- by incoming ligand Y as illustrated in (1); and, a solvent assisted pathway in which Cl^- is first replaced by H_2O, as in (2).

$$PtL_nCl_{4-n} + H_2O \underset{}{\overset{\text{slow}}{\rightleftharpoons}} PtL_nCl_{3-n}(OH_2)^+ + Cl^- \qquad (2)$$

$$PtL_nCl_{3-n}(OH_2)^+ + Y \overset{\text{fast}}{\rightleftharpoons} PtL_nCl_{3-n}Y^+ + H_2O$$

The rate law describing these substitution reactions is:

$$\text{rate} = k[PtL_nCl_{4-n}] + k'[PtL_nCl_{4-n}][Y]$$

Basolo and Pearson[21] have suggested that the mechanisms are associative (S_N2 involving $Pt...OH_2$ or $Pt...Y$ bond formation as the slow rate determining step followed by Pt-Cl bond breaking). This suggestion was based on kinetic results obtained for the hydrolysis of a range of platinum chloride complexes:

$$Pt(NH_3)_nCl_{4-n} + H_2O \rightarrow Pt(NH_3)_nCl_{3-n}(OH_2)^+ + Cl^-$$

where n = 0 - 3

As the charge of the complexes varied from -2 to +1 (as n varied from 0 to 3; e.g., $PtCl_4^{2-}$ to $Pt(NH_3)_3Cl^+$), the rates of hydrolysis varied only by a factor of 2. If Pt-Cl bond breaking was rate determining, the rate for hydrolysis of $PtCl_4^{2-}$ should be considerably higher than for $Pt(NH_3)_3Cl^+$.

Results from other studies,[20,22] however, show that bond breaking can be very important in determining rates of reactions. For the reaction:

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

the order of decreasing rate constants as determined by the leaving group X are,[20]

$$NO_3^- > H_2O > Cl^- > Br^- > I^- > SCN^- > NO_2^-$$

(where the rates vary by $\sim 10^6$).

Cleare and Hoeschele[23] tried correlating the anticancer activity of the cis-platinum complexes with leaving group X (as defined above) in a series of compounds of the type cis-$Pt(NH_3)_2X_2$. They found that compounds with weakly bound ligands such as H_2O and NO_3^-, showed no anticancer activity but were very toxic. They suggested that these labile compounds were metabolized quickly so that sufficient quantities of the compounds did not reach the site responsible for antitumor activity. No antitumor activity was shown for compounds with tightly bound ligands SCN^- and NO_2^-. According to Cleare and Hoeschele, no reactions occurred in the body (since the SCN^- and NO_2^- ligands were not displaced in vivo) and hence relatively high doses could be tolerated. Although compounds with ligands of intermediate leaving ability (Br^-) showed considerable antitumor activity, the optimum activity was shown for compounds with Cl^- as intermediate leaving group. Chloride, as leaving group, has the advantage of being compatible with the body system.

In recent studies, Rosenberg[24] has shown that pure cis-$Pt(NH_3)_2(NO_3)_2$ does show considerable antitumor activity

and low toxicity. This work has raised doubts about Cleare and Hoeschele's correlations of antitumor activity and Pt-X bond strength. Doubts are raised, particularly in view of the intermediate hydroxobridged species of platinum which have been characterized[25-27] (see detailed discussion in Chapter 3, p. 184) and which have been shown to have very high toxicities.

Because of the relatively high concentrations of chloride in human blood plasma[28] (~ 103 mM), it has generally been assumed that hydrolysis of cis and trans-$Pt(NH_3)_2Cl_2$ in the plasma is minimal (see discussion on next page). This results in an effective (thermodynamic and kinetic) inhibition of nucleophilic substitutions of the platinum bound chlorides. Thermodynamic inhibition is effected in that the equilibria of the type described previously [(1) and (2)] are shifted to the left. Kinetically substitution reactions are inhibited because hydrolysis is inhibited (see (2)). Since H_2O is replaced 70 times faster than Cl^- in substitution reactions of platinum(II), by lowering the equilibrium concentrations of aquo species of platinum in solutions, (note that OH^- is inert to substitution[22]) the rates of substitution are lowered considerably. These previous values can be deduced from the study by Basolo et al.[20] of the reactions of $Pt(dien)X^+$ with pyridine as reported earlier. Their results are supported by radiotracer studies of chloride exchange in $Pt(NH_3)_2Cl_2$ done by Reishus and Martin.[18] They suggested that exchange occurs with $Pt(NH_3)_2Cl(OH_2)^+$ rather than with $Pt(NH_3)_2Cl_2$.

Thomson[14] and Lim and Martin[28] have used equilibrium constants (see Table 1) for the hydrolysis of $Pt(NH_3)_2Cl_2$ and $Pt(en)Cl_2$:

$$Pt(NH_3)_2Cl_2 + H_2O \overset{k_1}{\rightleftharpoons} Pt(NH_3)_2Cl(OH_2)^+ + Cl^- \qquad K_1$$

$$Pt(NH_3)_2Cl(OH_2)^+ + H_2O \overset{k_2}{\rightleftharpoons} Pt(NH_3)_2(OH_2)_2^{2+} + Cl^- \qquad K_2$$

as well as pK_a values for:

$$Pt(NH_3)_2(OH_2)_2^{2+} \rightleftarrows Pt(NH_3)_2(OH_2)(OH)^+ + H^+ \qquad K_a^1$$

$$Pt(NH_3)_2(OH_2)(OH)^+ \rightleftarrows Pt(NH_3)_2(OH)_2 + H^+ \qquad K_a^2$$

to characterize possible reactions which could occur *in vivo* (Tables 2 and 3). Lim and Martin suggested, on the basis of their calculations, that no substitution reactions would occur *in vivo* until the inert compound $Pt(NH_3)_2Cl_2$ passed from the blood plasma (where $[Cl^-] \approx 103$ mM) into the cells ($[Cl^-] \approx 4$ mM) where it would be hydrolyzed. They calculated *equilibrium* concentrations of platinum species in the plasma and cells (Table 2) and suggested that, in cells, at least 42% of the platinum complexes had labile H_2O groups. In the plasma, less than 3% of platinum species contained aquo groups and $Pt(NH_3)_2Cl_2$ was the predominant species ($\sim$ 95%).

These predictions are similar to Thomson's that in saline solutions (such as blood plasma), $Pt(NH_3)_2Cl_2$ is the predominant species while in water at pH 6.5 and $[Cl^-] \approx 0$, the predominant species is $Pt(NH_3)_2(OH_2)(OH)^+$.

TABLE 1

(a) Equilibrium and rate constants for hydrolysis of cis and trans-$Pt(NH_3)_2Cl_2$ and $Pt(en)Cl_2$

	K_1(M)	$k_1(s^{-1})$	K_2(M)	$k_2(s^{-1})$
cis[18]	3.3×10^{-3}	2.5×10^{-5}	4.0×10^{-5}	3.3×10^{-5}
trans[18]	3.2×10^{-4}		2.0×10^{-5}	
$Pt(en)Cl_2$[29]	2.2×10^{-3}	3.4×10^{-5}	1.4×10^{-4}	4.4×10^{-5}

(b) pK_a values for cis and trans-$Pt(NH_3)_2Cl_2$

	pK_a^1	pK_a^2
cis[30]	5.56	7.32
cis[31]	5.63	9.25
cis[32]	5.46	7.16
cis[33]	5.51	7.37
trans[18]	4.32	7.00

TABLE 2

Fractions of species of $Pt(en)Cl_2$ in aqueous solution at equilibrium (T = 35°C)

	$[Cl^-]$	(a)	(b)	(c)	(d)	(e)	(f)
Plasma	103 mM	94.7%	2.5%	2.5%	0.1%	0.1%	--
Cell	4 mM	25.3%	17.5%	17.5%	24.1%	15.0%	0.1%

Data from Ref. 28.

(a) $Pt(NH_3)_2Cl_2$; (b) $Pt(NH_3)_2Cl(OH_2)^+$; (c) $Pt(NH_3)_2ClOH$;
(d) $Pt(NH_3)_2(OH_2)OH^+$; (e) $Pt(NH_3)_2(OH)_2$; (f) $Pt(NH_3)_2(OH_2)_2^{2+}$

TABLE 3

Fractions of species of $Pt(NH_3)_2Cl_2$ in aqueous solution at equilibrium (T = 25°C)

$[Cl^-]$	$Pt(NH_3)_2Cl_2$	$Pt(NH_3)_2Cl(OH_2)^+$	$Pt(NH_3)_2(OH_2)_2^{2+}$
1 mM	40%	52%	8%
0	33%	54%	12%

Data from Ref. 14.

Thomson suggested that $Pt(NH_3)_2Cl_2$ (in saline solutions) would react with only very strong nucleophiles such as -SH. This suggestion is, of course, consistent with the known kidney toxicity of the $Pt(NH_3)_2Cl_2$ drug. Platinum complexes have been postulated to bind to sulfhydryl-containing proteins in the kidneys.[34]

Thomson concluded, from his analysis, that his predictions were applicable to both cis and trans platinum compounds on the basis of similarity of equilibrium K and K_a constants. Hence, the differing antitumor and toxicity effects could not be explained by a differing chemistry of the two isomers. He suggested that the differing steric demands of the two isomers could explain the differing antitumor effects.

As has been described, others were also unable to correlate physical and chemical properties of the platinum compounds with antitumor properties. Because the obvious difference between cis and trans complexes is structural, this has been assumed to be the major factor in explaining the differing antitumor and toxicity effects.

It is important to note that aquo complexes of platinum, e.g., $Pt(NH_3)_2(OH_2)(OH)^+$, $Pt(NH_3)_2(OH_2)Cl^+$, $Pt(NH_3)_2(OH_2)^{2+}$, have been deduced by Thomson and by Lim and Martin and assumed by others to be the active species of platinum which are responsible for antitumor action, and which are the predominant species in aqueous solutions.

This deduction may be wrong (see Chapter 3).

In many studies, which will be described in the next sections, no pH or pCl controls were used. Temperatures used vary from 25°C to 65°C. Although this does not necessarily invalidate the results of these studies, care must be taken in evaluating the binding sites observed and in assessing their relevance in biological systems (where T, pH and pCl are rigorously maintained).

1.3 THE INTERACTION OF PLATINUM(II) COMPOUNDS WITH BIOLOGICAL MOLECULES

Early studies showed that DNA was the site for binding of cis-$Pt(NH_3)_2Cl_2$ and that the mechanism of antitumor action was associated with this binding. The reason (high $[Cl^-]$) that $Pt(NH_3)_2Cl_2$ does not bind to other nucleophilies in the plasma has been described.

Harder and Rosenberg[7] studied the effects of Pt(II) complexes on DNA, RNA and protein synthesis in cells grown in tissue culture (i.e., human amnion AV3 cells in vitro). They found that for concentrations of cis-$Pt(NH_3)_2Cl_2$ corresponding to therapeutic doses ($\sim$ 5 μM), DNA synthesis was selectively inhibited. At higher concentrations (25 μM), DNA, RNA and protein synthesis were all inhibited, but DNA synthesis was most rapidly inhibited. The platinum compounds which were inactive against Sarcoma 180 were also unable to inhibit DNA, RNA and protein synthesis. Hence, Harder and Rosenberg could correlate the ability of cis-$Pt(NH_3)_2Cl_2$ to inhibit DNA synthesis with its activity against Sarcoma 180 tumors.

Howle and Gale[8] studied the effects of platinum compounds on DNA, RNA and protein synthesis in Ehrlich Ascites tumor cells grown in vivo. The cells were periodically removed from rats up to 4 days after treatment with a single injection of 10 mg/kg of cis-$Pt(NH_3)_2Cl_2$. The

subsequent synthesis of DNA, RNA and protein was followed *in vitro*. A striking suppression in DNA synthesis was found. DNA synthesis was more depressed than RNA or protein synthesis.

Harder and Rosenberg[7] showed that the inhibition of DNA synthesis (in their studies) was not caused by any effect of the platinum compounds on tritiated thymidine uptake or because of inhibition of a DNA polymerase.

Roberts and Pascoe[35,36] considered that *trans*-$Pt(NH_3)_2Cl_2$ could be inactive because it was not able to enter cells and react with DNA, RNA and protein. They showed, however, (using HeLa cells grown *in vitro*) that at low concentrations, where cell kill was effected by only *cis* isomer, that twice as much *trans*-$Pt(NH_3)_2Cl_2$ was bound to DNA, RNA and protein as the *cis* isomer.

In view of these studies, it was concluded that the platinum compound bound to DNA and that this was the basis for the preferential effects on DNA synthesis. It was further assumed that the ability of platinum complexes to bind to DNA *and* inhibit DNA synthesis was the primary mechanism for its antitumor action.

1.4 POSTULATED DNA LESIONS CAUSED BY PLATINUM(II) COMPOUNDS

Since it was not possible to correlate the physical and chemical properties of cis and trans-$Pt(NH_3)_2Cl_2$ with their antitumor properties and since both cis and trans-$Pt(NH_3)_2Cl_2$ were shown to bind to DNA, researchers postulated that the differing way in which the cis and trans isomers bound to the DNA base molecules would account for the differing activity[15,37] (see Figure 1). Selectivity was supposedly based on the differing stereochemical requirements of the cis and trans isomers. It was argued that bifunctional binding (i.e., interstrand and intrastrand crosslinking) could form the basis for selectivity while monofunctional binding could not (since it is an option for both the inactive trans isomer and the active cis isomer). The possibility of crosslinking between base pairs in the same plane was also considered not a likely binding option as this would interfere with the hydrogen bonding above and below the plane of the crosslink. Experimental evidence has been sought to verify that one of these reactions could cause the primary lesion (abnormal structural change in DNA responsible for cell death). Attempts to identify possible (cell killing) lesions in DNA were based, in large part, on physical studies: uv, nmr, ir and Raman studies of the interactions of cis and trans-$Pt(NH_3)_2Cl_2$ with DNA and its components in model systems. Because of the large number

Figure 1

Postulated modes of binding of cis-$Pt(NH_3)_2Cl_2$ to DNA

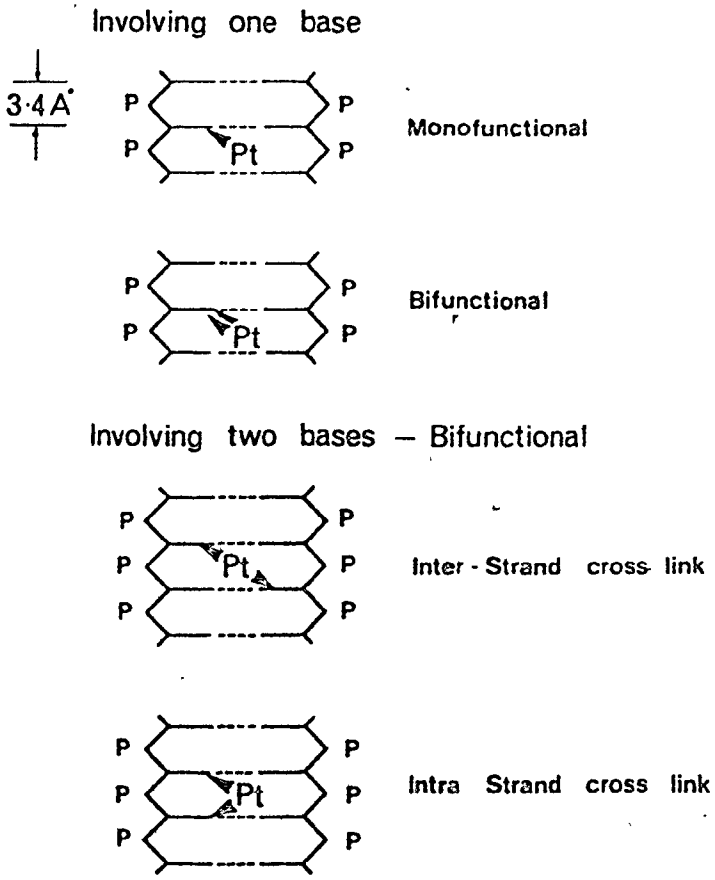

Fig. 1 was reproduced from ref. 37(a), I.A.G. Roos and M.C. Arnold, J. Clin. Hematol. Oncol., 7, 374 (1977).

of these binding studies, no attempt is made here to review comprehensively all of this work. Several reviews of this work have been published recently.[5,38-40] Studies that are presented are, in general, related to the postulates that cis-$Pt(NH_3)_2Cl_2$ binds bifunctionally to the DNA bases (to form chelates), or that cis-$Pt(NH_3)_2Cl_2$ forms inter- or intrastrand crosslinks in DNA.

1.4.1 Interstrand Crosslinks

To detect possible DNA interstrand crosslinking, Roberts and Pascoe[35,36] treated radioactive and density labelled HeLa cells with cis-$Pt(NH_3)_2Cl_2$. (Since the HeLa cells had been grown in radioactively (^3H) labelled 5-bromo-2'-deoxyuridine for one generation (24 h), only one of the strands was "heavy labelled".) Density gradient centrifugation was used to isolate DNA from treated and untreated cells. DNA from untreated cells (no cis-$Pt(NH_3)_2Cl_2$) yielded gradients having two DNA peaks, a "heavy labelled" DNA peak and a "light unlabelled" DNA peak. DNA from treated cells (containing interstrand crosslinks) gave a third "labelled hybrid" peak. From the areas under the three peaks, the percentage of crosslinked DNA could be calculated. The percentage of crosslinks for cis-$Pt(NH_3)_2Cl_2$ reacting with DNA was about 12 times higher than for trans-$Pt(NH_3)_2Cl_2$. This correlated well with the relative ability of cis and trans-$Pt(NH_3)_2Cl_2$ to kill cells implying that the cis-

$Pt(NH_3)_2Cl_2$ crosslinks could be cytotoxic. With the cis-$Pt(NH_3)_2Cl_2$, however, only 1 in 400 reactions with DNA resulted in a crosslink. This compares with 1 in 8 reactions with DNA which result in interstrand crosslinks for the bifunctional alkylating agent, mustard gas (which is another known antitumor agent). Roberts and Pascoe concluded that the much lower frequency of formation of interstrand crosslinks for cis-$Pt(NH_3)_2Cl_2$ indicated that it was not the cytotoxic lesion.

1.4.2 Guanine N(7)-O(6) Chelate

The following evaluation of possible chelation is, admittedly, long and involved (based in part on the large amount of discussion that this suggested lesion has generated). Since the author believes that the evidence (used to support the model of N(7)-O(6) chelation) can be interpreted in another way (see Chapter 3), it is presented comprehensively.

Mansy et al.[10] studied the binding of cis and trans-$Pt(NH_3)_2Cl_2$ (aqueous solutions 10^{-3} M) to nucleosides. They assigned binding sites on the basis of uv spectral changes which occurred upon platination (the nucleosides absorb between 220-300 nm). They suggested that the cis isomer formed a bidentate

chelate with either N(6) and N(7) or N(6) and N(1) of adenosine and with N(4) and N(3) of cytidine.[d] Binding at the exocyclic nitrogen atoms, N(6) of adenosine and N(4) of cytidine, was suggested to occur only after deprotonation. The trans isomer was suggested to bind monofunctionally at N(7) and N(1) of adenosine and at N(3) of cytidine. Cis and trans isomers were found to bind monofunctionally at N(7) of guanosine. No binding was observed to uridine or thymidine or to the phosphate groups of any of the nucleotides by either isomer. In their studies, Mansy et al. presumed that the dichloride isomers were hydrolyzed to reactive species, such as $Pt(NH_3)_2(OH_2)_2^{2+}$, $Pt(NH_3)_2(OH_2)(OH)^+$ and $Pt(NH_3)_2(OH)_2$, where the equilibrium concentrations of these species varied as the pH of the solutions. They generalized in concluding that the sites bound to $Pt(NH_3)_2Cl_2$ were also favourable to proton binding and to binding by other metal cations (CH_3Hg^+, Hg^{2+} and Ag^+).

Other studies suggested that chelation (bifunctional binding) could be important in describing the DNA lesion associated with antitumor

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[d] See base structures and numbering on p. 143.

activity. In particular, metal ion chelation involving the guanosine N(7)-O(6) atoms has been proposed many times (see Figure 2), although chelation to guanosine was not observed by Mansy et al.[10] in their uv study.

In part, this proposal is based on experiments supposedly pointing to the guanine base as the preferred site of electrophilic attack by cis-$Pt(NH_3)_2Cl_2$ on polynucleotides. In some of these experiments,[41,42] guanine is mistakenly cited as the preferred site for binding of cis-$Pt(NH_3)_2Cl_2$, when, in fact, preferential binding by platinum complexes can only be correlated with G-C content, i.e., since the percentages of guanine and cytosine are equivalent in double strand DNA's, it would be necessary to use single strand polynucleotides to verify proportionalities to any single base.

Using uv spectroscopy, Mansy[43] found that the rate of reaction of cis-$Pt(NH_3)_2Cl_2$ with DNA's varied directly as G-C content.

Stone et al.[44] reported that large increases in buoyant density of cis-$Pt(NH_3)_2Cl_2$ bound DNA's were proportional to G-C content (pH ~ 6.5, 25°C, $[Cl^-]$ = 15 mM).

Scovell and O'Connor[45] calculated equilibrium constants for the binding of cis-$Pt(NH_3)_2Cl_2$ to ribonucleosides using uv spectroscopic data (4 weeks to equilibrium, pH 6.5, 25°C). The cis-$Pt(NH_3)_2Cl_2$ was first aquated by reacting it with silver nitrate. The log K values calculated

Figure 2

Postulated chelate formed by cis-$Pt(NH_3)_2Cl_2$ and dGMP

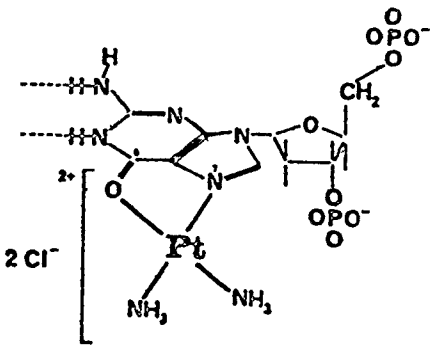


Figure 2 was reproduced from ref. 15, B. Rosenberg, J. Clin. Hematol. Oncol., 7, 817 (1977).

(assuming only mono complexes) were nearly the same: guanosine, 3.7; adenosine, 3.6; cytidine, 3.5.

Geidarova et al.[46] studied reactions of $PtCl_4^{2-}$ with G-C enriched DNA's (using uv spectroscopy) and found that the platinum complexes were most strongly bound to cytosine molecules (where binding was suggested to occur at N(3)).

As noted by Mansy et al.[10] platinum complexes bind at base sites which are favourable to proton binding. We would expect, then, a rough correlation between equilibrium constants for platinum based compounds and basicity of binding sites. The pK_a[47] for the 5'-dGMP imidazole site N(7) is 2.9 which is slightly lower than the pK_a's for the pyrimidine sites of 5'-dAMP, N(1), 4.4, and of 5'-dCMP, N(3), 4.6. Binding of platinum complexes should be almost equally favoured at cytosine and adenine with cytosine being most strongly bound. Binding should be less favoured at guanine. This prediction is consistent with the uv results of Geidarova et al.[46]

Kong and Theophanides[48] have argued in favour of such a correlation between basicity and binding sites. They suggested that since tertiary amines are more basic than secondary amines, pyrimidine sites (e.g., N(3) of cytosine and N(1) of adenine) should bind more strongly to platinum complexes than do imidazole sites (e.g., N(7) and N(9) of guanine and adenine). If such a correlation does exist, which is unlikely (see Appendix 1,b), it would

be based on thermodynamics because no correlations have been established between nucleophilicity of ligands (in general) and their basicity for reactions with platinum(II).[16]

Munchausen and Rahn[49] used ^{195}Pt nmr to study the binding of cis-$^{195}Pt(NH_3)_2Cl_2$ with DNA's of varying G-C content (24 h, pH 7, 37°C, $[Cl^-]$ = 50 mM or 2-3 h, pH 7, 60°C, $[Cl^-]$ = 50 mM). They found that the amount of bound platinum was proportional to G-C content. When they hydrolyzed the polynucleotides with acid, (15 min, 66% formic, 100°C) they found that only the purines and Pt-bound purines were stable under the conditions used. Cis-$Pt(NH_3)_2Cl_2$ was bound to both adenine and guanine. By varying the ratios of cis-$Pt(NH_3)_2Cl_2$ to bases before hydrolysis and determining the ratios of free and bound bases after hydrolysis, they were able to show that cis-$Pt(NH_3)_2Cl_2$ bound preferentially to guanine and no binding to adenine occurred until 25% of the guanine had reacted. They implied because of this that guanine determines the G-C proportionality. The experiment does not, however, indicate what the contribution of cytosine is to the proportionality.

More convincing evidence indicates that guanine is the preferred site for binding of platinum compounds. Robins[50] studied the kinetics of reactions of $Pt(^{14}C\text{-en})Cl_2$ with nucleosides (no pH control, 37°C) and found that deoxyguanosine reacted faster ($t_{1/2}$ of 12 h). Deoxycytidine and deoxyadenosine reacted with half-lives of

130 h and 120 h. Deoxythymidine showed no reaction. This experiment would suggest that the specificity for binding of $Pt(en)Cl_2$ to guanine might be kinetically favoured. It should be noted, however, that adenosine 5'-monophosphate reacted considerably faster than deoxyguanosine with $t_{1/2} = 2$ h.

Stone et al.[50] showed that the extent of binding of cis-$Pt(NH_3)_2Cl_2$ to DNA's (no pH control, 22°C) could be correlated with the occurrence of guanine in DNA strands.

On the basis of these experiments, one can deduce that the specificity of cis-$Pt(NH_3)_2Cl_2$ for guanine is probably real. However, the evidence for the existence of platinum-guanine chelated N(7)-O(6) structure is indirect and not convincing.

Millard et al.[52] studied the binding of cis-$Pt(NH_3)_2Cl_2$ with DNA using ESCA. They attributed a decrease in 1s binding energy for oxygen (of ~ 1 ev from 532 ev) to binding of platinum atoms at O(6). On the basis of this result, they suggested that cis-$Pt(NH_3)_2Cl_2$ chelates to guanine, in spite of their nmr data which does not show such an interaction.[53] Both Chu et al.[41,54] and Kelman et al.[37b] have argued that since O(6) contributes to only a minor portion of the 1s intensity of oxygen (phosphate oxygens also contribute), the assignment of chelation is inaccurate.

Dehand and Jordanov[55] studied the reactions of

$Pt(dat)Cl_2$ with the ribonucleosides, adenosine, cytidine and guanosine ($HCONMe_2$, 60°C). They suggested that chelation occurs on the basis of elemental analyses, nmr and ir data. A shift in the O(6)-C(6) stretching frequency at $\sim$ 1665 cm^{-1}, which occurred when $[Pt(dat)guo]Cl_2$ was recrystallized, was attributed to the following rearrangement

$$[Pt(dat)guo]Cl_2 \rightarrow [Pt(dat)guoCl]Cl$$

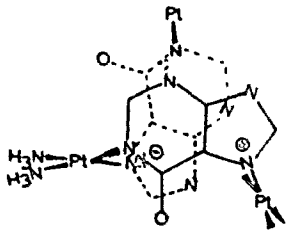
Similar shifts have been attributed by others[41,63] to intermolecular interactions. Chu et al.[41] have recently studied platinum compound base binding using ir, Raman and nmr spectroscopy. In their studies (which will be discussed in more detail in Chapter 3), they observed binding of platinum atoms at guanosine sites N(7), N(1) and O(6). As illustrated in Figure 3, although platinum atoms do bind at O(6), guanosine is suggested to act as a bridging bidentate ligand rather than as a bidentate chelate.

Roos et al.[56] studied the binding of cis and trans-$Pt(NH_3)_2Cl_2$ and other $Pt(am)_2Cl_2$ compounds with methyl substituted bases 9-methyladenine, 9-methylguanine, 1-methylcytosine and 1-methylthymine using mass spectroscopy. They suggested that 9-methylguanine chelated to cis-$Pt(NH_3)_2Cl_2$ on the basis of peaks which were not observed in their spectra rather than on peaks which were observed. They postulated that the doubly charged species $[Pt(NH_3)_2$(9-methylguanine-

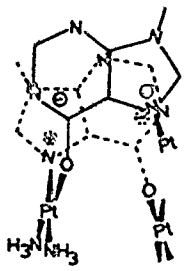
Figure 3

Polymerization via: (A) N(7)-N(1) bridges;

(B) N(7)-O(6) bridged



A



B

Figure 3 was reproduced from ref. 41, G.Y.H. Chu, S. Mansy, R.E. Duncan and R.S. Tobias, J. Amer. Chem. Soc., 100, 593 (1978).

$N(7)\text{-}O(6)]^{2+}$ could be involatile and explained why no peak appeared in the spectrum for the product of the reaction of $Pt(NH_3)_2Cl_2$ and 9-methylguanine.

Kelman et al.[37b] have argued against formation of the platinum guanine O(6)-N(7) chelate on the basis of their buoyant density measurements. They suggested that if chelation was an important binding mode for cis-$Pt(NH_3)_2Cl_2$, no correlations should exist between DNA enriched in GpG sequences and DNA not enriched (a correlation which they have shown to exist[51]).

X-ray diffraction studies on single crystals of $Pt(en)(guanosine)_2Cl_{3/2}I_{1/2}\cdot 2H_2O$ [57] and cis-$Pt(NH_3)_2(guanosine)_2Cl_{3/2}(ClO_4)_{1/2}\cdot 7H_2O$ [58] show only monodentate binding to platinum atoms by N(7) of guanosine. In fact, the possibility that N(7)-O(6) chelation occurs was suggested by Goodgame et al.[12] in their discussion of $Pt(NH_3)_2(5'\text{-inosine-monophosphate})_2$ which showed only N(7) binding by inosine to platinum. An N(7)-S(6) chelation has been crystallographically characterized[59] in a copper 6-mercaptopurine complex. The Cu-N(7) bond length was 1.992(4) Å while the Cu-S(6) bond length was 2.424(1) Å and appears to be strained. A second chelate structure[60] between palladium and 6-mercaptopurine has been characterized. The Pd-N(7) bond lengths were 2.047(9) Å and 2.08(1) Å, while the Pd-S(6) bond lengths were 2.305(3) and 2.311(3) Å and are all normal. Although a copper 1,3-dimethyl-2,6-dioxopurine

complex with a Cu-O(6) bond distance of 2.919(3) Å (a weak interaction) has been synthesized,[61] both Sletten,[62] and Kuntz and Kotowycz,[63] have described why the N(7)-O(6) chelate is sterically improbable. At the very least, it would be necessary to obtain X-ray crystallographic proof of the platinum guanine N(7)-O(6) chelate in a model system to prove its existence.

In view of the supposed preferential binding to guanine by cis-$Pt(NH_3)_2Cl_2$ and in spite of the unconvincing evidence for chelate formation, Rosenberg has proposed that the reaction of cis-$Pt(NH_3)_2Cl_2$ with guanosine to form an intramolecular N(7)-O(6) chelate is the primary cytotoxic lesion.[15] The platinum binding alters the interbase hydrogen bonding enough to cause base mispairing. The base mispairing causes increased antigenicity[e] of the cancer cells and the immune system destroys the tumor. Rosenberg has suggested that the platinum compounds do not cause extensive direct cell kill on the basis of distribution and retention studies. Toth Allen[65] (see Appendix 1,c) found that

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[e] An antigen is any object which stimulates antibody synthesis.[64] "Antibody synthesis is a defence response found in higher vertebrates that helps combat the harmful effects of pathogenic microorganisms. Antibodies accomplish this task by combining with the microorganisms to form complexes that are then destroyed by scavenger white blood cells."

there was no selective uptake of cis-$Pt(NH_3)_2Cl_2$ in tumor tissues but that it appeared in relatively high concentrations in normal tissues such as kidney and liver. There were no toxic effects on healthy tissues and only the tumor cells disappeared.

The mutagenic effects of alkylating agents have been explained according to a similar mechanism.[66] Alkylation of guanine at N(7) (to produce 7,9-disubstituted species) induces a pK_a shift in the N(1) hydrogen, increasing its acidity. The deprotonated guanine is then suggested to mispair with thymine as illustrated in Figure 4. Very recently, a mispairing of this type (but involving two guanine molecules) has been characterized[163] (see Figure 5, and see p. 212 for details). This mispairing was induced, however, not by cis-$Pt(NH_3)_2Cl_2$ chelating at N(7)-O(6), but simply by Pt monofunctionally binding at N(7).

1.4.3 Intrastrand crosslink

The final mode of binding which has been postulated to describe the cytotoxic effects of cis-$Pt(NH_3)_2Cl_2$ is the intrastrand crosslink. This postulate is supported by the wealth of crystallographic data[12,57,58] which suggests that platinum can bind to two adjacent DNA bases, where each base acts as a unidentate ligand. The bite distance of cis-$Pt(NH_3)_2Cl_2$ (~ 3.3 Å) is considered similar to the 3.4 Å interplanar stacking distance of the DNA bases. This

Figure 4

Mispairing induced by alkylation at N(7) of guanine

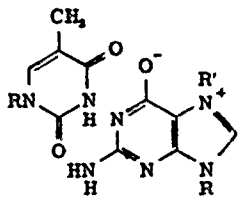

Figure 4 was reproduced from ref. 66, R. Shapiro, Prog. in Nucl. Acid Res. and Mol. Biol., 8, 73 (1968).

Figure 5

Mispairing induced by platination at N(7) of guanine

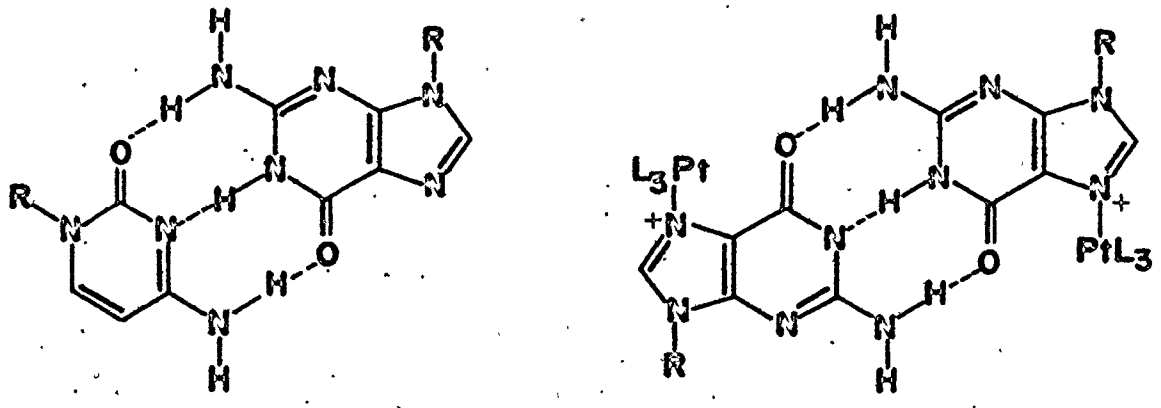

Figure 5 was reproduced from ref. 163, C.J.L. Lock, "Inorganic Chemistry in Biology and Medicine", A.C.S. Symposium Series, to be published.

supposedly permits a ready clipping of base pairs, especially GpG sequences,[51] since the N(7) sites are not involved in hydrogen bonding. Although a number of experiments show the tendency for Pt complexes to bind to adjacent bases[11,51,54,56] on the same strand, the intrastrand mode of binding is not sterically reasonable (as will be discussed in Section 2.3.4). As well, it does not account for the increasing evidence that platinum compounds can interact with certain exocyclic base atoms. (Note, however, that the bases do not act as chelates, but as ligand bridges, see Figure 3 and reference 41.)

In the Discussion (Chapter 3), another mode of binding will be suggested which accounts for all of the apparently conflicting evidence, including that for base stacking and for platinum-exocyclic atom interaction.

1.5 SPECTRAL EVIDENCE FOR PLATINUM BINDING TO DNA

A considerable number of physical measurements have been recorded by researchers in their attempts to deduce how cis and trans-$Pt(NH_3)_2Cl_2$ bind to DNA. It is very important to assess critically the techniques which have been used in eliciting this information. Both Mansy and Tobias[67] and Kelman, Peresie and Stone[37b] have done this.

Although uv measurements are very sensitive and can be used with very dilute solutions, relatively small changes occur in the base absorption spectra when platinum atoms bind. The different bases also all absorb in the same region of the spectrum and binding at different sites induces similar shifts in the spectra. As noted by Mansy and Tobias, "it is easy to tell when a reaction occurs but difficult to tell exactly what it is".[67] Assignments of chelation,[10] as based on uv measurements where platinum-to-base ratios are as high as 10 to 1, are suspect. It is more likely (especially at the platinum-to-base ratios used) that if platinum atoms do bind to exocyclic base atoms, it is by a second $Pt(NH_3)_2Cl_2$ moiety monofunctionally bound.[41]

Nmr has been used extensively in studies of interactions of paramagnetic metals with DNA. With diamagnetic metals such as platinum(II) (since easily measured line broadening does not occur) effects are sometimes ambiguous;

e.g., when $CH_3Hg(II)$ binds at either N(1) or N(7) of inosine, the resonances of both H(2) and H(8) shift.[67] Similar effects were observed by Kong and Theophanides for platinum-base interactions,[48,53] and by Chu and Tobias for platinum-inosine interactions.[54] Since the shifts are also small (typically < 0.5 ppm[54]), it is difficult to use these data to assign binding sites.

In assigning binding sites, it is usually assumed that the largest proton resonance shifts occur for protons nearest the binding site of the electrophile because they feel the largest inductive effects. The electron density of the DNA base, however, is so delocalized that the largest resonance shift does not necessarily correspond to the closest site of binding. Upon protonation of cytosine, for example, the resonances of H(5), H(6) and the NH_2 protons all shift, but the NH_2 proton resonances shift the farthest. This was first thought to imply proton binding at NH_2.[68] Protonation was later shown to occur at N(3).[69,70]

In a study of Zn binding to cytidine, broadening of the NH_2 peak was first attributed to Cu^{2+} paramagnetic impurity rather than incipient splitting associated with hindered rotation about the C-NH_2 bond as caused by Zn binding at N(3).[71]

To examine the amino-imino tautomerism in cytosine, Lee et al. studied the pD (and temperature) dependence of shifts of the H(5) resonances, and deduced that

the imino tautomer was in 15% abundance.[72] They subsequently disavowed this claim.[180] Wong, later showed that these results could not be reproduced with purified samples of 5'-CMP. With addition of paramagnetic impurities, the pD and temperature dependence of carbon H(5) proton line width broadening could be reproduced.[73]

Although ir and Raman spectroscopy can be very useful in assigning base binding sites, unambiguous assignments are based on large amounts of data.

These problems in interpretation of uv, nmr and ir, Raman spectra are compounded by the extreme delocalization of electron density in the DNA bases. Although this feature of the DNA bases will be discussed in greater detail in Section 2.7, it is very important to realize that changes in electronic structure of a DNA base could result from inductive effects caused by Pt binding at a remote site.

1.6 SUMMARY

At the outset of this work, there was very little reliable information available as to how platinum complexes interacted with the DNA bases. Information which was available was deduced from uv-visible, nmr, ir and Raman spectra. There were virtually no crystal structures of Pt-base compounds available. It was necessary, therefore, to establish to which bases it was possible to bind platinum complexes. It was also important to verify which sites on the bases were most likely to bind to Pt. The unequivocal assignment of binding sites afforded by X-ray crystallography was thought essential, especially in view of repeated proposals of Pt-base interactions which appeared to be sterically unreasonable. It was hoped that by narrowing down the possible binding sites to a few, useful information about the mechanism of action of cis-$Pt(NH_3)_2Cl_2$ could be elicited. It was also presumed that by studying the stereochemical requirements of model compounds (i.e., products of reactions of cis-$Pt(NH_3)_2Cl_2$ with the DNA bases), information could be deduced which would favour or discredit certain of the binding modes suggested. It was also considered inappropriate to restrict this investigation to a study of platinum compounds binding to guanine on the basis of the unconvincing evidence for selectivity cited previously. Hence, a systematic study of the interactions of cis and trans-$Pt(NH_3)_2Cl_2$ with all

the bases was undertaken. The results reported in this thesis are those related to the study of platinum(II) compounds with cytosine. The work done with cytosine can be justified in that a peculiar mode of binding of cis-$Pt(NH_3)_2Cl_2$ with cytosine has been characterized which has not yet been shown to exist for adenine or guanine. This example of peculiar binding is used as a basis for postulating another possible lesion which can explain the antitumor action of cis-$Pt(NH_3)_2Cl_2$ (see Chapter 4).

CHAPTER 2

EXPERIMENTS AND RESULTS

CHAPTER 2

EXPERIMENTS AND RESULTS

2.1 EXPERIMENTS

(i) Preparation and analysis

The conditions for the preparation of compounds used in the crystallographic studies are given in the appropriate crystallography sections. All compounds are original compositions as prepared by:

John Powell, Lash Miller Chemical Laboratories, University of Toronto,

and

Bernhard Lippert, Institute for Inorganic Chemistry of the Technical University Munich.

J. Powell and B. Lippert are also responsible for obtaining analytical data and infrared and Raman spectra for their respective compounds. Elemental analyses of compounds synthesized by B. Lippert were done by E.O. Fischer, Institute for Inorganic Chemistry of the Technical University, Munich. Compounds synthesized by J. Powell were analyzed by A.B. Gygli, Microanalyses Laboratory, Toronto.

The densities of all but one of the crystalline compounds were measured. It was not possible to measure the density of μ-(9-methyladenine-N1,N7)bis(trans-dichloro-

(diisopropylsulfoxide-S)platinum(II)) because the crystals fractured and powdered in the several flotation mixtures tried. The density of trans-dichloro(diisopropylsulfoxide-S)(1-methylcytosine-N3)platinum(II) was measured by flotation in a methylene iodide-carbon tetrachloride mixture and the other crystals were measured in methylene iodide-chloroform mixtures.

(ii) X-ray Crystallography

Collection of the Diffraction Data

Crystals to be studied were mounted on thin glass fibers. Crystals of $[PtCl_2((CH_3)_2CH)_2SO]_2(C_6H_7N_5)$ which were recrystallized from acetone/water, were sealed in (Lindemann) capilliaries with mother liquor to prevent decomposition. Capilliaries made with Lindemann glass were used because they are transparent to X-rays[74] and will not affect absorption corrections. For the air stable crystals, if the faces could not be identified for absorption corrections, or if the crystals were too large, they were manually ground to cylinders using emery paper.

Mounted crystals were examined under a polarizing microscope for homogeneity and precession photographs of zero and first layers were taken using MoK_α to identify lattice symmetry. On the basis of this symmetry, possible space groups were assigned and unit cells calculated. The crystals were then transferred to a Syntex

$P2_1$ diffractometer and accurate unit cell parameters were obtained by least squares refinement from 15 centered medium angle reflections.

Intensity data were recorded on the Syntex $P2_1$ diffractometer using graphite momochromatized MoK_α radiation (λ = 0.71069 Å) for the appropriate hemisphere or quadrant (depending on the space group) up to a maximum 2θ = 55°. The Syntex $P\bar{1}$ diffractometer was used to measure unit cell parameters and collect intensity data for trans-dichloro(diisopropylsulfoxide-S)(1-methylcytosine-N3)platinum(II) and for one of the two data sets recorded for μ-(9-methyladenine-N1,N7)bis(trans-dichloro(diisopropylsulfoxide-S)platinum(II)).

Data were collected[75] by using a coupled θ(crystal)-2θ(counter) scan from 1.0° below the K_{α_1} position to 1.0° above the K_{α_2} position. Scan rates ranged from 5.9 to 29.3 deg min^{-1} (8 to 24 deg min^{-1} for $P\bar{1}$) and were selected by the program supplied with the instrument. The stability of each system was monitored by measuring one or two standard reflections after every 49 or 48 reflections. Stationary counts at the limits of each scan were made for half the scan time to establish the background. The intensity of a reflection was taken as $I = N_T - N_{BG_1} - N_{BG_2}$, where N_T is the total peak count and N_{BG_1} and N_{BG_2} are the background counts. σ(I)'s were taken as $(N_T + N_{BG_1} + N_{BG_2})^{1/2}$.

Data Processing[76]

Of the total symmetry-independent reflections measured, a reflection was labelled "observed" if $I > 3\sigma_I$. Reflections which were not significantly above background, $I < \sigma_I$, were not used in the refinement. Those reflections, for which $3\sigma_I > I > \sigma_I$, were used with the "observed" reflections in the refinement only if $F_C > F_O$ for the reflections. Absorption corrections were applied to the intensity data according to the dimensions of the individual crystals.

Unscaled structure factor amplitudes, F_O, and their standard deviations, σ_F, were calculated from the expression, $F_O = (\frac{I}{Lp})^{1/2}$

$$\sigma_F = \frac{1}{2}\frac{1}{\sqrt{Lp}}\sqrt{\frac{\sigma_I}{I}}$$

Lp, the Lorentz polarization factor was $(1 + \cos^2 2\theta)/(2 \sin 2\theta)$. Isotropic secondary extinction corrections were applied to structure factor amplitudes, when necessary, using the method of Larson.[77]

Unscaled structure amplitudes, F_C, were calculated according to

$$F_C(hkl) = \sum_{j=1}^{n} T_j f_j \exp 2\pi i(hx_j + ky_j + lz_j)$$

where f_j is the scattering factor of the jth atom in the

unit cell and x_j, y_j and z_j are the fractional coordinates of the jth atom along the three crystallographic axes $\underset{\sim}{a}$, $\underset{\sim}{b}$, and $\underset{\sim}{c}$, respectively. The value calculated for the structure factor is the amplitude of X-ray diffraction from a particular plane in the crystal (in terms of an equivalent number of electrons) as caused by the electron density of the j atoms in the unit cell.

The magnitude of vibration of the atoms about their mean positions (thermal motion) is described by the temperature factor[76a]

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

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

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

where U_{ij} are the anisotropic thermal parameters expressed in terms of mean square amplitudes of vibration in $\mathring{A}^2$, and a^*, b^*, c^* are the reciprocal cell axes.

All calculations were carried out on a CDC 6400 computer. The programs DATCO3, ABSORB, DATRDN from the

X-RAY 71 package were used for preliminary treatment of data for all structures except trans-dichloroammine(1-methylcytosine-N3)platinum(II) for which the programs DATCOS, ABSORB, DATRDN from the X-RAY 76 package were used.

The full matrix least squares program CUDLS was used for structure refinement and the Fourier program SYMFOU was used for generating electron density difference syntheses. Both programs were written locally by J.S. Stephens and J.S. Rutherford, respectively. CUDLS was enlarged to the program BIGLS by G. Turner to permit full matrix least squares refinement of cis-diammine(1-methylcytosine-N3)(9-ethylguanine-N7)platinum(II) diperchlorate.

Least square planes were calculated by the local program PALS by P.G. Ashmore and diagrams were prepared by the program ORTEP by C.K. Johnson.[78]

Throughout the refinements, the scattering curves and the anomolous dispersion corrections were those from the "International Tables for X-ray Crystallography",[101] Vol. IV, Tables 2.2A, p. 72ff and 2.3.1, pp. 149-150, respectively. Anomolous dispersion corrections were only applied to the curves for Pt, Cl and S atoms.

Solution of the Structures

All structures except one were solved by the heavy atom method, i.e., the coordinates of the platinum atoms were found from three-dimensional Patterson syntheses. For μ-(9-

methyladenine-N1,N7)-bis(trans-dichloro(diisopropyl-sulfoxide-S)platinum(II)) direct methods were used to locate the two Pt atoms. In all cases, least squares refinement of the Pt atom positions followed by successive three-dimensional electron density difference syntheses and calculations of the likely geometries of the ligands revealed all the remaining non-hydrogen atoms. In the initial stages of the structure solutions, isotropic temperature factors were used for all atoms. As the refinements progressed, the temperature factors for Pt, Cl and S atoms were made anisotropic. In the full matrix least square refinements, the function minimized is $\Sigma w(|F_o| - |kF_c|)^2$ where w is the weighting term. The two residuals which are used in CUDLS to follow the refinement are

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

and

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

In the last cycle of refinement, for all structures, no parameter shifted by more than 1/20 of its esd.

The specifics of each structure solution and refinement as well as atom parameters and selected interatomic distances and angles, are reported in Sections 2.2 through 2.7. The corresponding moduli of F_o and F_c are

listed in reference 179. Interesting problems associated with particular structure determinations are reported in the appropriate section.

(iii) Measurement of the nmr spectra

The solution for spectrum a, Fig. 26, Sect. 2.7.2, was prepared by stirring 0.125 g of 1-methylcytosine in 10 mL of dimethylsulfoxide for 3 h at 22°C. The sample only dissolved slowly, so after 3 h saturation (~ 0.1 M) was assumed and the sample was used to obtain a spectrum. The solution for spectrum b was obtained by adding 0.410 g of K_2PtCl_4 (an equimolar amount) to the initial sample of 1-methylcytosine. After ~ 20 min, a yellow solution developed. Spectrum b was obtained 1 h after mixing.

Spectra were recorded on a Varian EM390 Spectrometer at 90 MHz. The internal reference used was tetramethylsilane. The probe temperature was 34°C.

2.2 STRUCTURES RELEVANT TO LABELLING OF DNA STRANDS WITH PLATINUM

2.2.1 Introduction

The first two molecular structures were investigated to determine the primary sites for binding of platinum complexes (specifically $PtCl_3(i\text{-}Pr_2SO)^-$) to DNA bases. Previous studies had shown that $K[PtCl_3(Me_2SO)]$ complexed directly to the bases of denatured DNA;[79] 1:1 complexation was observed with cytosine, guanine and thymine bases, while 2:1 complexation was observed for adenine. The possibility that certain platinum complexes could be designed to bind preferentially to a particular base (e.g., adenine) suggested a potentially useful method of sequencing the bases in DNA. Electron microscopy is one method of detecting platinum atoms[80] bound to DNA and hence of determining the sequences of the bases.

2.2.2 The Crystal and Molecular Structure of trans-dichloro-(diisopropylsulfoxide-S)(1-methylcytosine-N3)-platinum(II)[81]

Preparation (by J. Powell)

Potassium trichloro(diisopropylsulfoxide)platinate(II) was prepared according to the method of Kukushkin et al.[82] for potassium trichloro(dimethylsulfoxide)platinate(II). To an aqueous solution of potassium trichloro(diisopropylsulfoxide)platinate(II) (0.36 g in 10 mL) was added an aqueous solution of 1-methylcytosine (0.115 g in 15 mL)

and the mixture stirred for 0.5 h. The mixture was then evaporated to dryness and the residue washed with a little water to remove excess HCl. Recrystallization of the residue from an isopropanol-water mixture gave the title compound as yellow prisms. Yield 70%, m.p. 220-224°C (dec.). Analysis: Calcd. for $C_{11}H_{21}Cl_2N_3O_2SPt$: C 25.2, H 4.03; Found: C 25.2, H 4.0.

Solution of the Structure

Precession photographs revealed no lattice symmetry, nor did a Delaunay reduction show any hidden symmetry. The possible space groups were thus P1 (No. 1) or $P\bar{1}$ (No. 2). The second space group was assumed and confirmed by the successful refinement of the structure in this space group.

Discussion

Crystal data and other numbers related to data collection and structure refinement are summarized in Table 4. The atom parameters from the final refinement are listed in Table 5 and the corresponding moluli of F_0 and F_C are listed in reference 179. Selected bond lengths and angles are given in Table 6 and the molecule, trans-$PtCl_2$-(i-Pr_2SO)($C_5H_7N_3O$) is illustrated in Figure 6. It can be seen that the platinum atom is in rough square planar coordination with the chlorine atoms trans. The bis(isopropyl)-sulfoxide molecule is bonded to the platinum atom through

TABLE 4

Compound	$C_{11}H_{21}Cl_2N_3O_2PtS$
F.W.	525.37
Crystal size	Polyhedron with faces: {100}, 0.10 mm apart; {001}, 0.18 mm apart; $(1\bar{1}0)$, $(\bar{1}10)$, 0.13 mm apart.
Crystal colour	yellow
ρ_{calc}	2.09 g cm^{-3}
ρ_{obs}	2.08(2) g cm^{-3}
Systematic absences	none
Space group	$P\bar{1}$ (No. 2)
Unit cell parameters	a = 16.205(5) Å, α = 106.53(2)° b = 8.078(2) Å, β = 96.35(2)° c = 6.776(2) Å, γ = 98.54(2)°
Volume	834(1) $Å^3$
Z	2
Crystal mount axis	roughly along c
Linear absorption coefficient	68.9 cm^{-1}
Transmission coefficient limits	1.68 - 2.43
Max 2θ; quadrant	50°; h, ± k, ± l
Standard reflections	-2, 1, 0
Overall e.s.d.	1.21%
Temperature	22°C
No. of independent reflections	2293
No. with $I > 3\sigma(I)$	2023
$3\sigma(I) > I > \sigma(I)$ where $F_c > F_o$	81
$3\sigma(I) > I > \sigma(I)$ where $F_c < F_o$	95
$I < \sigma(I)$, rejected	94

Continued.....

TABLE 4 (Continued)

Compound	$C_{11}H_{21}Cl_2N_3O_2PtS$
Final R_1	0.0459
Final R_2	0.0464
Final shift in e.s.d. Max.	0.011
Ave.	0.001
g (secondary extinction)	not required
Final difference map	
Highest peak; location	0.60 e/Å^3; 0.33, 0.04, 0.10
Lowest valley; location	-0.65 e/Å^3; 0.21, -0.04, 0.08
Weighting	$\frac{1}{\omega} = (23.0 - 0.558\|F_o\| + 0.00457\|F_o\|^2)$

TABLE 5

Atom parameters and temperature factors ($Å^2$) for

trans-dichloro(diisopropylsulfoxide-S)(1-methylcytosine-N3)

platinum(II) (x 10^3) *

	x	y	z	U
Pt	272.66(3)	92.57(6)	156.11(7)	
Cl(1)	399.6(2)	31.8(4)	61.4(5)	
Cl(2)	153.4(2)	164.7(5)	283.7(6)	
S	205.4(2)	-138.2(4)	-111.0(4)	
O(1)	239.5(5)	-162(1)	-307(1)	41(2)
O(2)	341.8(5)	461(1)	164(1)	47(2)
N(1)	403.8(6)	607(1)	496(1)	34(2)
N(3)	339.9(6)	305(1)	396(1)	28(2)
N(4)	335.2(8)	159(1)	639(2)	52(3)
C(1)	423(1)	772(2)	443(2)	58(4)
C(2)	360.4(7)	459(1)	344(2)	26(2)
C(4)	360.4(7)	306(1)	592(2)	31(3)
C(5)	407(1)	457(2)	749(2)	41(3)
C(6)	426(1)	605(2)	694(2)	45(3)
C(7)	211(1)	-332(2)	- 28(2)	40(3)
C(8)	193(1)	-499(2)	-210(2)	50(3)
C(9)	158(1)	-338(2)	147(3)	62(4)
C(10)	94(1)	-130(2)	-174(2)	42(3)
C(11)	48(1)	-293(2)	-339(2)	52(4)
C(12)	92(1)	36(2)	-243(2)	61(4)

Anisotropic temperature factors U_{ij} (x 10^3) *

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	27.8(3)	22.0(2)	24.6(2)	-2.5(2)	0.9(2)	0.4(1)
Cl(1)	27(2)	40(2)	42(2)	3(1)	1(1)	-1(1)
Cl(2)	35(2)	64(2)	50(2)	6(2)	10(2)	-15(2)
S	32(2)	27(1)	28(1)	-2(1)	3(1)	1(1)

* Estimated standard deviations (esd) from the least squares programs are given in parentheses.

TABLE 6

Selected interatomic distances (Å) and angles (deg) for trans-dichloro-(diisopropylsulfoxide-S)(1-methylcytosine-N3)platinum(II) (esd's in terms of the least significant figure are given in parentheses).

Atoms	Distance	Atoms	Distance	Atoms	Distance
Pt-Cl(1)	2.302(3)	Pt-N(3)	2.058(7)	Pt-Cl(2)	2.288(4)
N(3)-C(2)	1.39(2)	Pt-S	2.231(2)	C(2)-N(1)	1.37(1)
S-O(1)	1.46(1)	C(2)-O(2)	1.23(2)	S-C(7)	1.82(2)
N(1)-C(6)	1.35(2)	S-C(10)	1.83(1)	N(1)-C(1)	1.47(2)
C(7)-C(8)	1.51(2)	C(6)-C(5)	1.35(2)	C(7)-C(9)	1.54(2)
C(5)-C(4)	1.42(1)	C(10)-C(11)	1.50(2)	C(4)-N(3)	1.33(2)
C(10)-C(12)	1.54(2)	C(4)-N(4)	1.33(2)		
Nonbonded Distances					
Cl(1)-S	3.19(1)	Cl(1)-N(3)	3.04(1)	Cl(2)-S	3.35(1)
Cl(2)-N(3)	3.00(1)				

Atoms	Angle	Atoms	Angle	Atoms	Angle
Cl(1)-Pt-Cl(2)	174.3(1)	C(5)-C(4)-N(3)	122(1)	Cl(1)-Pt-S	89.3(1)
C(5)-C(4)-N(4)	120(1)	Cl(2)-Pt-S	95.7(1)	N(4)-C(4)-N(3)	118(1)
Cl(1)-Pt-N(3)	88.1(3)	C(4)-N(3)-C(2)	120(1)	Cl(2)-Pt-N(3)	87.0(3)
Pt-S-O(1)	116.0(3)	S-Pt-N(3)	177.2(3)	Pt-S-C(7)	106.6(4)
Pt-N(3)-C(2)	115.3(7)	Pt-S-C(10)	111.9(4)	Pt-N(3)-C(4)	125.1(8)
O(1)-S-C(7)	108.5(6)	N(3)-C(2)-O(2)	121(1)	O(1)-S-C(10)	106.1(6)
N(3)-C(2)-N(1)	119(1)	C(7)-S-C(10)	107.5(6)	N(1)-C(2)-O(2)	120(1)
S-C(7)-C(8)	112(1)	C(2)-N(1)-C(1)	119(1)	S-C(7)-C(9)	112(1)
C(2)-N(1)-C(6)	121(1)	C(8)-C(7)-C(9)	114(1)	C(6)-N(1)-C(1)	120(1)
S-C(10)-C(11)	111(1)	N(1)-C(6)-C(5)	122(1)	S-C(10)-C(12)	106(1)
C(6)-C(5)-C(4)	117(1)	C(11)-C(10)-C(12)	112(1)		

TABLE 7

Least squares planes and dihedral angles between planes for trans-dichloro(diisopropylsulfoxide-S)(1-methylcytosine-N3)platinum(II)

Plane	Atoms	Distance from best plane (Å)
1	N(1)C(2)N(3)C(4)C(5)C(6)C(1)* O(2)*N(4)*	N(1),0.0;C(2),0.0;N(3),0.02;C(4),-0.02; C(5),0.01;C(6),0.0;C(1),-0.06;O(2)0.03; N(4),-0.09
2	S(1)N(3)Cl(I)Cl(2)Pt*	S(1),0.032;N(3),0.037;Cl(1),-0.03; Cl(2),-0.034;Pt0.022.

Dihedral angle for planes 1 and 2 is 84.4°.

*Atoms given no weight in determining the best plane; other atoms are given unit weight. Errors in atom positions about 0.02Å. Rms deviation for Plane 1, 0.013Å; Plane 2, 0.038Å.

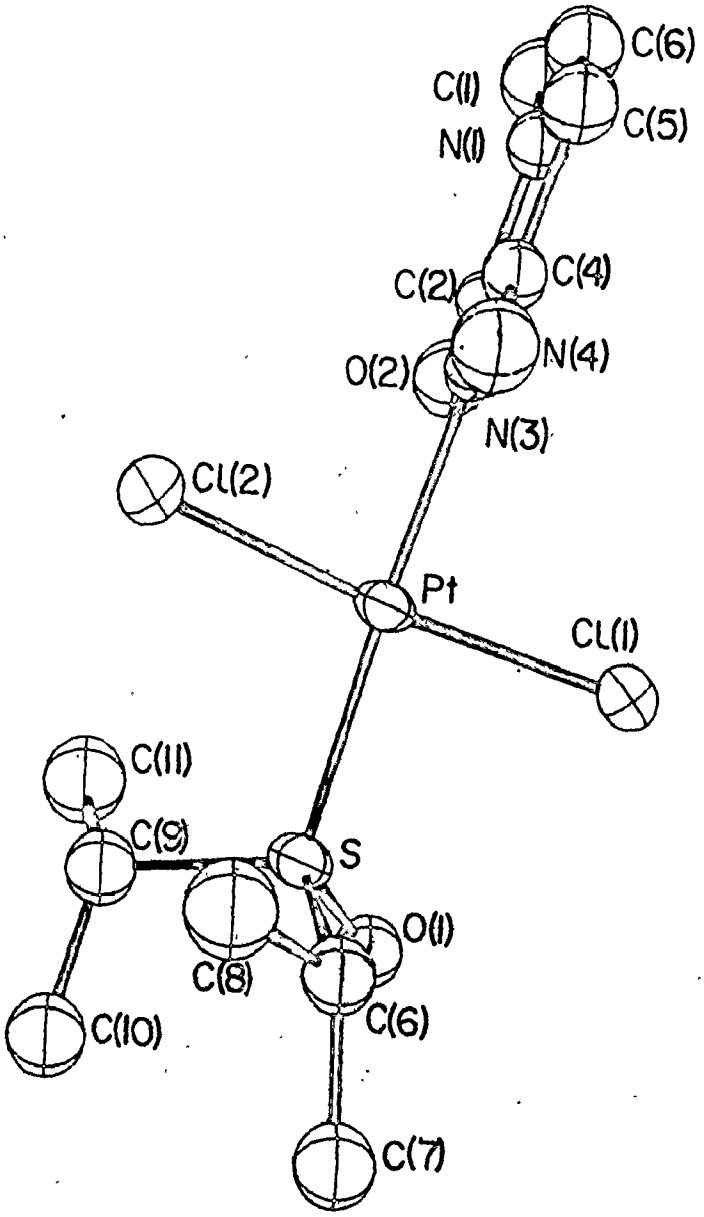

Figure 6

The molecule <u>trans</u>-$PtCl_2(i\text{-}Pr_2SO)(C_5H_7N_3O)$ showing the atom numbering. The plane of the cytosine ring is almost perpendicular to the plane defined by the atoms bonded to platinum.

the sulphur atom and the 1-methylcytosine ring is attached to the platinum atom through the ring nitrogen, N(3),[f] atom. The four nearest neighbour ligand atoms are close to planar although there is a slight distortion towards the tetrahedral arrangement. Cl(1) and Cl(2) lie 0.035 and 0.034 Å below the best plane through the four atoms while S and N(3) lie 0.032 and 0.037 Å above the plane.

There are some angular deviations from the ideal square planar arrangement. Cl(1)-Pt-Cl(2) is only 174.3(1)° (compared with 178.4(1)° for trans-$PtCl_2(NH_3)(C_5H_7N_3O)$ in Sect. 2.5 and 176.1(1)° for trans-$[PtCl_2(Me_2SO)(Cyd)]$ in ref. 83) such that the chlorine atoms bend away from the bulky bis(isopropyl)sulfoxide group. This repulsion is less for dimethylsulfoxide. Cl(2)-Pt-S is large, 95.7(1)°, apparently because of the Cl(2)-C(12) (methyl) repulsion. This compares with 92.9(2)° for Cl(2)-Pt-S for trans-$[PtCl_2(Me_2SO)(Cyd)]$ where Cl(2) appears to interact with O(1) of the sulfoxide group. Cl(1)-Pt-S is normal in both cases (89.3(1) and 90.8(1)) because the Cl(1) atoms are staggered with C(7) and O(1) of i-Pr_2SO in the title compound and with C(10) and C(11) of Me_2SO in trans-$[PtCl_2$-

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[f] The ring numbering in this and subsequent structures is conventional as accepted by North American biochemists and molecular biologists[39] (see p. 143).

(Me_2SO)(Cyd)]. Hence, the bis(isopropyl)sulfoxide and dimethylsulfoxide groups are arranged to minimize interactior with the Cl(1) atoms. The other angles around the platinum atom are much closer to ideal values.

The bond lengths around the platinum atom are normal. Pt-Cl bond lengths are 2.288(4) and 2.302(3) and agree well with values found in other similar structures reported in this work (see Table 8, where values range from 2.288(5) to 2.334(9) Å) and in the literature (where values range from 2.289(7) to 2.361(5) Å for ref. 83-92). The Pt-S bond length, 2.231(2), agrees well with the values (2.244(2), 2.229(2),[92] and 2.220(4) Å[82]) found by Melanson and Rochon for cis-$PtCl_2(Me_2SO)_2$ and trans-$PtCl_2(Me_2SO)$(Cyd). The distances and angles found in the bis(isopropyl)sulfoxide group agree fairly well with equivalent values found by Melanson and Rochon. The Pt-N(3) distance of 2.058(7) Å is about the expected value. S-bonded sulfoxides have an intermediate trans influence,[88] about equal to Cl^-. Typical values for nitrogen ligands bonded to Pt(II) and subjected to an intermediate trans influence (i.e., of Cl and olefins) are 2.04(1)-2.10(1) Å.[86-91, 93-100] These values are slightly larger than the range of values reported in this work (Table 8, 5 structures) for Pt-N(3) (where 1-methylcytosine is subjected to the weak trans influence of NH_3) of 2.023(8)-2.06(1). Pt-N distances for the ammonia groups (trans to N(3) of 1-methylcytosine)

TABLE 8

Summary of bond lengths around platinum for Pt(II)-(1-methylcytosine-N(3))compounds

Ligand Trans	Pt-N for Ammonia	Ligand Trans	Pt-N(3) for Cytosine	Ligand Trans	Pt-Cl	Reference Section
		S	2.058(7)	Cl	2.302(3)	2.2.2
				Cl	2.288(4)	"
				Cl	2.312(8)	2.2.3
				Cl	2.316(8)	"
				Cl	2.334(9)	"
				Cl	2.315(8)	"
NH_3	2.067(10)	Cyt-N(3)	2.023(5)			2.3.3
Cyt-N(3)	2.047(7)	NH_3	2.026(6)	NH_3	2.299(2)	2.4.2 A
Cl	2.053(8)					"
Cyt-N(3)	2.04(1)	NH_3	2.06(1)	NH_3	2.300(2)	2.4.2 B
Cl	2.05(1)					"
Cyt-N(3)	2.04(1)	NH_3	2.03(1)	Cl	2.288(5)	2.5.2
				Cl	2.296(5)	"
Cyt-N(3)	2.06(2)	NH_3	2.03(2)			2.3.2
Gua-N(7)	2.05(1)	NH_3	2.04(2)			"
Gua-N(7)	2.07(2)					"
Cyt-N(3)	2.06(2)					"
Average	2.054(10)	Average	2.038(15)	Average	2.305(14)	
Range	2.04 - 2.07	Range	2.023 - 2.06	Range	2.288 - 2.334	
Average (N(3) trans)	2.060(10)	Average (NH_3 trans)	2.037(14)	Average (Cl trans)	2.306(16)	
		Average (NH_3 trans)*	2.031(6)			

* 2.[illegible]

range from 2.04(1) to 2.06(2) Å and average 2.05(1) Å. It appears that the trans influence of coordinated oxygen atoms is slightly less than for nitrogen atoms: where the trans ligand is a bridging hydroxide group, Pt-N distances range from 1.97(5) to 2.06(2) Å,[25,27b] and average 2.02 Å. Where the trans ligand is a nitrate ion, Pt-N distances range from 1.99(1) to 2.00(1),[102] and average 1.995 Å. Because of the limited number of results and high errors, the differences are difficult to verify.

The dihedral angle between the plane of the pyrimidine ring and the plane of the four ligand atoms around Pt is 84.4°. Hence, there are no intermolecular interactions between the 1-methylcytosine atoms N(4) and O(2) and the chlorine atoms bound to the platinum atom. The 1-methylcytosine ring is planar within the errors. Bond lengths and angles within the ring are discussed in Sect. 2.6, p. 149.

The packing of the molecules is shown in Figure 7. In the a direction there are two main types of contact. Near x = 0.5, contact is primarily between the cytosine rings, which lie parallel to each other, and which are interspersed with Cl(1) atoms. At x = 0, contact is primarily between C(10) and C(11) methyl groups interspersed with Cl(2) atoms. In the b direction, contact is primarily between the Cl(1) on one molecule and O(2) and the C(1) methyl group on the next. In the c direction, packing is primarily between pairs of cytosine rings on adjacent

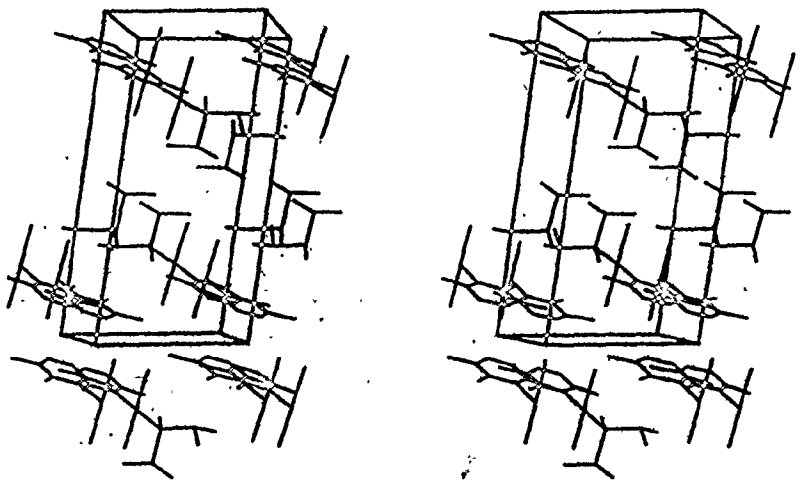


Figure 7

The unit cell contents of trans-$PtCl_2(i\text{-}Pr_2SO)(C_5H_7N_3O)$, plus portions of other molecules. $\underset{\sim}{b}$ and $\underset{\sim}{a}^*$ are parallel to the bottom and side of the page, respectively. The view is down $\underset{\sim}{c}^*$. The cell outline shown is shifted by 1/2,1/2,1/2 from the cell used in the structure determination.

molecules. All contact distances mentioned above are at or greater than the van der Waals contact distance. There are no short distances to N(4) suggesting no intermolecular hydrogen bonding.

2.2.3 The Crystal and Molecular Structure of μ-(9-methyladenine-N1,N7)-bis(trans-dichloro)diisopropylsulfoxide-S)platinum(II)) hydrate[103]

Preparation (by J. Powell)

9-Methyladenine (0.1827 g) was dissolved in ∿ 30 mL of water by heating. The solution was allowed to cool. An aqueous solution of potassium trichloro(diisopropylsulfoxide-S)platinate(II) (1.2091 g in 10 mL) was added with stirring. A pale yellow precipitate formed and the mixture was stirred for one hour, and then filtered. The yellow crystals of the title compound were dried in vacuo over phosphorus pentoxide overnight. Yield, 0.9559 g (82%). A sample for analysis was recrystallized from a chloroform-tetrahydrofuran mixture.

Analysis: Calcd. for $C_{18}H_{37}Cl_4N_5O_3Pt_2S_2$: C 22.8, H 3.7, N 7.4, Cl 14.9; Found: C 22.8, H 3.8, N 7.7, Cl 14.7. Crystals for diffraction studies were prepared by recrystallizating the title compound from acetone at 5°C over a period of 14 days.

Collection of the Diffraction Data

The first data set was collected at room temperature (295°K) on the Syntex $P\bar{1}$ diffractometer using a yellow crystal of the title compound mounted in a sealed Lindemann capillary tube containing mother liquor to inhibit decomposition. The crystals appeared to be thermally sensitive but decomposition was inhibited by using mother liquor. A total of 1661 independent reflections were measured up to about $2\theta = 35°$ before the crystal suddenly and completely decomposed (after approximately 24 h). Although the crystal structure was solved and refined using this data set, large bond length errors resulted from this refinement. These were thought to result from inaccuracies in measured intensities. This was confirmed by the high estimated standard deviation from the mean, 4.4%, for the standard reflection, 2,2,-1 measured 40 times. Although there was no systematic variation with time for this reflection, the large apparently random deviation could have resulted from the crystal shifting in the capilliary tube in which it was sealed.

To improve the accuracy of the structure, a second data set was recorded at low temperature using the Syntex $P2_1$ diffractometer. The temperature was maintained at $T = 243°K$ by using a low temperature device supplied with the diffractometer. A second crystal was used which was again mounted in a sealed Lindemann capilliary tube containing mother liquor. The crystal again decomposed but

after approximately 48 h. This was enough time in which to record a complete data set to $2\theta = 45°$.

To monitor more closely the decomposition of the crystal, the standard reflection intensities were measured every 15 reflections (a total of 195 measurements). There was a marked variation in intensity for the standard reflection 1,-8,-1 (esd, 7.3%). (The esd for the second standard reflection, 5,5,3, which was measured 101 times, was normal, 2.1%). Although there was no systematic decrease in either the 1,-8,-1 or 5,4,3 intensity correlating with crystal decomposition, there was a rough oscillation of the intensity of 1,-8,-1 about the mean (7 cycles with an average period of 27 measurements and maximum deviations from the mean of 6σ). Standard 5,4,3 was randomly distributed about the mean. Unsuccessful attempts were made to correlate the oscillation of 1,-8,-1 with the crystal orientation to check the possibility of the crystal shifting in the capilliary tube. Examples of correlations attempted were to plot the differences in ϕ (or χ) of a reflection measured just before each standard and the corresponding value of ϕ (or χ) for the subsequent standard reflection against the positive or negative deviation from the mean for the intensity of the standard reflection. No meaningful correlations could be determined. Since most of the movement in crystal orientation is associated with ϕ and χ, differences in these values were thought to result in

good assessments of crystal motion.

Solution of the Structure

The main features of the structure were found from the intensities measured using the first crystal. The two crystallographically independent platinum atoms were located by direct methods. (The pseudo symmetry between the coordinates of the two platinum atoms precluded a unique solution to the Patterson map.) Subsequent electron density difference syntheses and full matrix least squares refinements revealed the positions of all non-hydrogen atoms except for the water of crystallization. Refinement converged to a value of $R_1 = 0.069$ for the 1581 reflections used in the refinement. Relatively large errors resulted from this refinement because of the inaccuracies in the measured intensities (described previously). Hence, the low temperature data set was obtained and used to continue the refinement.

Discussion

Crystal data and other numbers related to data collection and structure refinement for the two temperatures 243 and 295°K are summarized in Tables 9A and 9B, respectively. The atom parameters from the two final refinements are listed in Tables 10A and 10B, and the corresponding moduli of F_o and F_c are listed in reference 179. For the two refinements, there are some small but significant differences in some of the atom parameters of the heavier atoms. For the lighter atoms (C,N,O) 67% differ by < 1σ,

TABLE 9A

Compound	$C_{18}H_{37}Cl_4N_5O_3Pt_2S_2$
F.W.	967.65
Crystal size	Cylinder, r, 0.15 mm, l, 0.37 mm
Crystal colour	yellow
ρ_{calc}	1.81 g cm^{-3}
ρ_{obs}	
Systematic absences	0k0, k = 2n + 1 h0l, l = 2n + 1
Space group	$P2_1/c$ (No. 14)
Unit cell parameters	a = 15.620(8) Å b = 17.357(5) Å, β=104.79(7)° c = 14.05(2) Å
Volume	3682(5) Å
Z	4
Crystal mount axis	roughly along b
Linear absorption coefficient	83.3 cm^{-1}
Transmission coefficient limits	
Max 2θ; quadrant	35°; h, k, ± l
Standard reflections	2, 2, -1
Overall e.s.d.	4.40%
Temperature	295°K
No. of independent reflections	1661
No. with $I > 3\sigma(I)$	1344
$3\sigma(I) > I > \sigma(I)$ where $F_c > F_o$	114
$3\sigma(I) > I > \sigma(I)$ where $F_c < F_o$	123
$I < \sigma(I)$, (rejected)	80

Continued.....

TABLE 9A (Continued)

Compound	$C_{18}H_{37}Cl_4N_5O_3Pt_2S_2$
Final R_1	0.0691
Final R_2	0.0788
Final shift in e.s.d. Max.	0.410
Ave.	0.052
g (secondary extinction)	no correction made
Final difference map	
Highest peak; location	
Lowest valley; location	
Weighting	$\frac{1}{\omega} = (301.3 - 3.200\|F_o\| + 0.01139\|F_o\|^2)$

TABLE 9B

Compound	$C_{18}H_{37}Cl_4N_5O_3Pt_2S_2$
F.W.	967.65
Crystal size	Polyhedron with faces: {010} 0.40 mm apart; (101),(1̄0Ī) 0.20 mm apart; (1̄01),(10Ī) 0.32 mm apart.
Crystal colour	yellow
ρ_{calc}	1.81 g cm^{-3}
ρ_{obs}	
Systematic absences	0k0, k = 2n + 1 h0l, l = 2n + 1
Space group	$P2_1/c$ (No. 14)
Unit cell parameters	a = 15.46(1) Å, b = 17.073(8) Å, β=104.61(5)° c = 13.895(4) Å
Volume	3548(4) $Å^3$
Z	4
Crystal mount axis	roughly along b
Linear absorption coefficient	83.3 cm^{-1}
Transmission coefficient limits	4.37 - 8.97
Max 2θ; quadrant	45°, h, k, ± l
Standard reflections	(1) 1, -8, -1 (2) 5, 4, 3
Overall e.s.d.	(1) 7.32% (2) 2.11%
Temperature	243°K
No. of independent reflections	2628
No. with $I > 3\sigma(I)$	2187
$3\sigma(I) > I > \sigma(I)$ where $F_c > F_o$	104
$3\sigma(I) > I > \sigma(I)$ where $F_c < F_o$	139
$I < \sigma(I)$, (rejected)	198

Continued.....

TABLE 9B (Continued)

Compound	$C_{18}H_{37}Cl_4N_5O_3Pt_2S_2$
Final R_1	0.0718
Final R_2	0.0909
Final shift in e.s.d. Max	0.015
Ave.	0.002
g (secondary extinction)	no correction made
Final difference map	
Highest peak; location	2.65 e/Å^3; 0.73, 0.42, -0.03
Lowest valley; location	-2.18 e/Å^3; 0.30, 0.18, -0.13
Weighting	$\frac{1}{\omega} = (377.5 - 5.007\|F_o\| + 0.02096\|F_o\|^2)$

TABLE 10A

Atom parameters and temperature factors ($Å^2$) for μ-(9-methyladenine-N_1,N_7)-bis(trans-dichloro(diisopropyl-sulfoxide-S)platinum(II)) hydrate from data recorded at 295°K ($\times 10^3$) *

	x	y	z	U
Pt(1)	340.6(1)	174.6(1)	-185.1(1)	
Pt(7)	677.6(1)	415.5(1)	- 21.9(1)	
Cl(11)	440.4(8)	75.7(6)	-144.7(8)	
Cl(12)	255.5(9)	284.1(9)	-226.6(8)	
Cl(71)	640(1)	542.0(6)	- 60.5(8)	
Cl(72)	711.6(9)	287.0(6)	1.2(9)	
S(1)	231.4(9)	105.7(6)	-151.3(7)	
S(7)	752.6(9)	440.3(6)	134.0(7)	
O(1)	240(2)	21(1)	-161(2)	57(8)
O(7)	820(2)	386(1)	181(2)	57(8)
N(1)	438(2)	240(1)	-224(2)	22(8)
N(3)	487(3)	278(2)	-365(2)	49(10)
N(6)	492(2)	286(2)	- 65(2)	43(10)
N(7)	613(2)	388(2)	-166(2)	38(10)
N(9)	600(2)	378(2)	-326(2)	30(9)
C(2)	439(3)	234(2)	-323(3)	38(12)
C(4)	546(3)	328(2)	-303(2)	22(10)
C(5)	552(3)	333(2)	-204(2)	25(10)
C(6)	493(3)	286(2)	-159(2)	21(10)
C(8)	647(3)	412(2)	-240(2)	26(11)
C(9)	615(3)	390(2)	-427(3)	56(14)
C(11)	216(3)	121(2)	- 26(3)	58(14)
C(12)	213(3)	209(2)	- 11(3)	57(14)
C(13)	308(3)	91(2)	44(3)	53(13)
C(14)	123(3)	132(2)	-230(3)	48(13)
C(15)	128(4)	117(3)	-335(3)	75(15)
C(16)	49(4)	60(3)	-197(3)	93(17)

Continued.....

TABLE 10A (Continued)

	x	y	z	U
C(71)	672(3)	452(2)	215(3)	52(13)
C(72)	629(5)	377(4)	219(5)	133(24)
C(73)	601(4)	514(3)	171(4)	105(20)
C(74)	806(3)	536(2)	144(3)	42(12)
C(75)	866(3)	527(2)	75(3)	56(14)
C(76)	859(3)	552(2)	250(3)	43(12)

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

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt(1)	29(2)	33(1)	42(1)	-1(1)	14(1)	-1(1)
Pt(7)	32(2)	35(1)	41(1)	0(1)	4(1)	0(1)
Cl(11)	12(14)	57(7)	84(8)	11(7)	15(7)	12(6)
Cl(12)	52(15)	40(7)	93(9)	11(8)	37(8)	12(6)
Cl(71)	93(15)	48(7)	54(7)	3(8)	-9(7)	2(6)
Cl(72)	67(14)	38(7)	71(8)	3(7)	-1(8)	11(6)
S(1)	19(7)	40(7)	59(7)	3(7)	20(7)	-6(5)
S(7)	27(13)	58(8)	44(7)	-9(8)	-3(7)	7(6)

* Estimated standard deviations from the least squares programs are given in parentheses.

TABLE 10B

Atom parameters and temperature factors ($Å^2$) for μ-(9-methyladenine-N_1,N_7)-bis(trans-dichloro(diisopropyl-sulfoxide-S)platinum(II)) hydrate from data recorded at 243°K ($\times 10^3$) *

	x	y	z	U
Pt(1)	339.20(7)	174.51(7)	-186.69(9)	
Pt(7)	678.59(7)	415.86(7)	- 21.07(9)	
Cl(11)	439.6(4)	74.6(5)	-144.4(6)	
Cl(12)	253.6(5)	284.2(5)	-229.0(6)	
Cl(71)	640.6(6)	544.1(5)	- 60.0(6)	
Cl(72)	714.8(5)	286.7(5)	1.9(6)	
S(1)	228.3(5)	105.2(4)	-152.8(6)	
S(7)	751.9(5)	441.9(5)	135.4(6)	
O(1)	233(1)	20(1)	-164(1)	41(6)
O(7)	821(1)	384(1)	183(2)	40(6)
N(1)	436(1)	237(1)	-227(2)	25(6)
N(3)	484(2)	278(1)	-367(2)	30(7)
N(6)	496(1)	287(1)	- 64(2)	31(7)
N(7)	617(1)	387(1)	-163(2)	24(6)
N(9)	600(1)	377(1)	-329(2)	21(6)
C(2)	435(1)	236(2)	-324(2)	12(7)
C(4)	545(2)	325(2)	-305(2)	21(7)
C(5)	553(2)	331(2)	-205(2)	22(7)
C(6)	493(2)	283(2)	-163(2)	18(7)
C(8)	642(2)	414(2)	-245(2)	21(7)
C(9)	615(2)	391(2)	-427(3)	31(8)
C(11)	221(2)	124(2)	- 28(2)	36(9)
C(12)	208(3)	216(2)	- 10(3)	68(12)
C(13)	306(2)	93(2)	49(2)	39(9)
C(14)	123(2)	136(2)	-227(2)	25(7)
C(15)	125(2)	115(2)	-337(2)	39(9)

Continued.....

TABLE 10B (Continued)

	x	y	z	U
C(16)	47(2)	93(2)	-200(3)	52(10)
C(71)	673(2)	451(2)	215(2)	25(8)
C(72)	633(2)	370(2)	218(3)	66(12)
C(73)	603(2)	517(2)	178(3)	55(11)
C(74)	808(2)	537(2)	142(2)	29(8)
C(75)	873(2)	528(2)	79(3)	51(10)
C(76)	858(2)	556(2)	252(2)	44(10)
O(2)	8(2)	710(2)	167(3)	111(11)

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

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt(1)	24.6(7)	17(1)	25(1)	-2.3(6)	13.4(6)	0.0(7)
Pt(7)	26.1(7)	20(1)	25(1)	-0.6(6)	8.7(6)	-1.3(7)
Cl(11)	26(4)	25(5)	47(6)	3(4)	16(4)	5(4)
Cl(12)	39(4)	24(5)	48(6)	8(4)	16(4)	6(5)
Cl(71)	64(6)	28(6)	38(6)	4(5)	-4(5)	0(5)
Cl(72)	43(4)	24(6)	44(6)	0(4)	7(4)	6(4)
S(1)	28(4)	15(5)	32(5)	-2(4)	18(4)	-4(4)
S(7)	28(4)	21(5)	33(6)	3(4)	14(4)	-1(4)

* Estimated standard deviation from the least squares programs are given in parentheses.

91% by < 2σ and 100% by < 3σ. Lowering the temperature produced smaller temperature factors as might be expected. This effect is most marked for the terminal methyl groups on the sulfoxide groups which showed the largest temperature factors in the first place. Selected bond lengths and angles for only the more statistically significant low temperature refinement are given in Table II. Although an absorption correction was attempted, no corrected data were used in the final refinements. When the correction was applied to the low temperature data, the refinement worsened (i.e., R_1 = 0.0718 without absorption and R_1 = 0.0748 with absorption). Since the crystal decomposed before it was removed from the diffractometer, it was not possible to check if the initial absorption correction was applied correctly. As well, the crystal could have moved in the capilliary tube, while the data set was being recorded (as discussed previously).

The molecule, [<u>trans</u>-$PtCl_2$(i-Pr_2SO)]$_2$(9-methyladenine-N1,N7), is illustrated in Fig. 8. The arrangement of ligand atoms about each platinum atom is essentially square planar. The four nearest neighbour ligand atoms around Pt(7) are planar (within the errors) and Pt(7) lies slightly (-0.03 Å) below this plane. The plane around Pt(1) is tetrahedrally distorted as in <u>trans</u>-$PtCl_2$(i-Pr_2SO)($C_5H_7N_3O$) (Sect. 2.2.2). In this case, Cl(11) and Cl(12) lie 0.05 and 0.05 Å <u>above</u> the best plane while S(1) and N(1) lie 0.04 and 0.05 Å <u>below</u> the best plane. Pt(1) lies 0.02 Å

TABLE 11

Selected interatomic distances (Å) and angles (deg) for μ-(9-methyladenine-N1,N7)-bis-(trans-dichloro(diisopropylsulfoxide-S)platinum(II))hydrate from data recorded at 243°K (esd's in terms of the least significant figure are given in parentheses).

Atoms	Distance	Atoms	Distance	Atoms	Distance
Pt(1)-Cl(11)	2.312(8)	Pt(1)-Cl(12)	2.316(8)	Pt(1)-S(1)	2.257(8)
Pt(1)-N(1)	2.06(2)	Pt(7)-Cl(71)	2.334(9)	Pt(7)-Cl(72)	2.315(8)
Pt(7)-S(7)	2.251(8)	Pt(7)-N(7)	2.04(2)	S(1)-O(1)	1.50(2)
C(11)-C(12)	1.65(5)	S(1)-C(11)	1.81(4)	S(1)-C(14)	1.79(3)
C(14)-C(16)	1.53(5)	C(11)-C(13)	1.57(4)	C(14)-C(15)	1.60(5)
S(7)-C(74)	1.86(3)	S(7)-O(7)	1.50(2)	S(7)-C(71)	1.88(3)
C(74)-C(75)	1.53(5)	C(71)-C(72)	1.54(5)	C(71)-C(73)	1.57(5)
C(2)-N(3)	1.33(4)	C(74)-C(76)	1.37(4)	N(1)-C(2)	1.35(4)
C(5)-C(6)	1.47(4)	N(3)-C(4)	1.38(3)	C(4)-C(5)	1.39(4)
C(4)-N(9)	1.35(4)	C(6)-N(6)	1.38(4)	C(6)-N(1)	1.35(3)
N(7)-C(5)	1.41(3)	N(9)-C(8)	1.34(3)	C(8)-N(7)	1.39(4)

Atoms	Angle	Atoms	Angle	Atoms	Angle
Cl(11)-Pt(1)-Cl(12)	172.9(3)	Cl(11)-Pt(1)-N(1)	88.4(7)	Cl(11)-Pt(1)-S(1)	93.0(3)
Cl(12)-Pt(1)-N(1)	84.8(7)	Cl(12)-Pt(1)-S(1)	93.9(3)	N(1)-Pt(1)-S(1)	176.2(7)
Cl(71)-Pt(7)-Cl(72)	174.6(3)	Cl(71)-Pt(7)-N(7)	88.8(7)	Cl(71)-Pt(7)-S(7)	94.2(3)
Cl(72)-Pt(7)-N(7)	86.2(7)	Cl(72)-Pt(7)-S(7)	90.7(3)	N(7)-Pt(7)-S(7)	176.5(7)
Pt(1)-S(1)-O(1)	116(1)	Pt(1)-S(1)-C(11)	111(1)	Pt(1)-S(1)-C(14)	111(1)
O(1)-S(1)-C(11)	107(1)	O(1)-S(1)-C(14)	107(1)	C(11)-S(1)-C(14)	103(1)
S(1)-C(11)-C(12)	111(2)	S(1)-C(11)-C(13)	111(2)	C(12)-C(11)-C(13)	110(2)
Pt(7)-S(7)-O(7)	116(1)	Pt(7)-S(7)-C(71)	110.8(8)	Pt(7)-S(7)-C(74)	110(1)
O(7)-S(7)-C(71)	107(1)	O(7)-S(7)-C(74)	107(1)	C(71)-S(7)-C(74)	105(1)
S(7)-C(71)-C(72)	105(2)	S(7)-C(71)-C(73)	112(2)	C(72)-C(71)-C(73)	115(2)
Pt(1)-N(1)-C(2)	116(2)	Pt(1)-N(1)-C(6)	122(2)	Pt(7)-N(7)-C(8)	125(2)
Pt(7)-N(7)-C(5)	132(2)	N(1)-C(2)-N(3)	126(2)	C(2)-N(3)-C(4)	115(3)
N(3)-C(4)-N(9)	128(3)	N(3)-C(4)-C(5)	124(3)	C(4)-C(5)-N(7)	110(3)
C(4)-C(5)-C(6)	117(3)	C(5)-C(6)-N(6)	121(2)	C(5)-C(6)-N(1)	116(3)
C(6)-N(1)-C(2)	121(3)	N(6)-C(6)-N(1)	123(3)	C(4)-N(9)-C(9)	127(2)
C(4)-N(9)-C(8)	107(3)	C(9)-N(9)-C(8)	126(2)	N(9)-C(8)-N(7)	113(2)
C(8)-N(7)-C(5)	102(2)	N(7)-C(5)-C(6)	133(3)	C(5)-C(4)-N(9)	108(2)

TABLE 11 (cont'd)

Non-bonded distances

Cl(11)-O(1)	3.31(2)	Cl(71)-C(74)	3.33(3)
Cl(72)-O(7)	3.15(2)	Cl(12)-C(14)	3.29(3)

Possible hydrogen bond distances

Cl(12)-C(76)^{b}	3.24(4)	Cl(72)-N(6)	3.30(2)
C(8)-O(1)^{a}	3.17(4)	N(3)-N(6)^{b}	3.03(4)
Cl(11)^{a}-C(8)	3.29(3)	C(9)-O(1)^{a}	3.26(4)

Possible hydrogen bond angles

N(3)-N(6)^{b}-C(6)^{b}	155(2)	N(9)-C(9)-O(1)^{a}	91(1)
C(8)-Cl(11)^{a}-Pt(1)^{a}	111.2(5)	C(74)^{b}-C(76)^{b}-Cl(12)	88(2)
C(8)-O(1)^{a}-S(1)^{a}	132(1)	C(9)-O(1)^{a}-S(1)^{a}	133(1)
C(6)-N(6)-Cl(72)	93(2)	Pt(7)-N(7)-C(5)	133(2)
Pt(7)-Cl(72)-N(6)	76(5)		

Atoms are related to those given in Table 10B by

a,-x,1/2 + y, 1/2 - z ;b,x,1/2 - y, 1/2 + z

TABLE 12

Least squares planes and dihedral angles between planes for μ-(9-methyladenine-N1,N7)-bis(trans-dichloro(diisopropylsulfoxide-S) platinum(II) hydrate (at 243°K)

Plane	Atom	Distance from best plane (Å)
1	N(1)C(2)N(3)C(4)C(5)C(6)N(7) C(8)N(9)N(6)*C(9)*Pt(1)* Pt(7)*	N(1),-0.02;C(2),0.01;N(3),0.00;C(4),0.02; C(5),0.02;C(6)-0.01;N(7),0.02;C(8),-0.03; N(9),-0.01;N(6),-0.02;C(9),-0.02;Pt(1), -0.26;Pt(7),0.26.
2	Cl(11)Cl(12)S(1)N(1)Pt(1)*	Cl(11),0.05;Cl(12),0.05;S(1),-0.04; N(1),-0.05;Pt(1),0.02.
3	Cl(71)Cl(72)S(7)N(7)Pt(7)*	Cl(71),0.01;Cl(72),0.01;S(7),0.0;N(7), 0.0;Pt(1),-0.03.

Dihedral angle for planes

1-2 89.2°
1-3 54.9°
2-3 95.8°

Errors in atom positions about 0.04 Å. Rms deviation for Plane 1, 0.019Å; Plane 2, 0.055Å; Plane 3, 0.006Å.

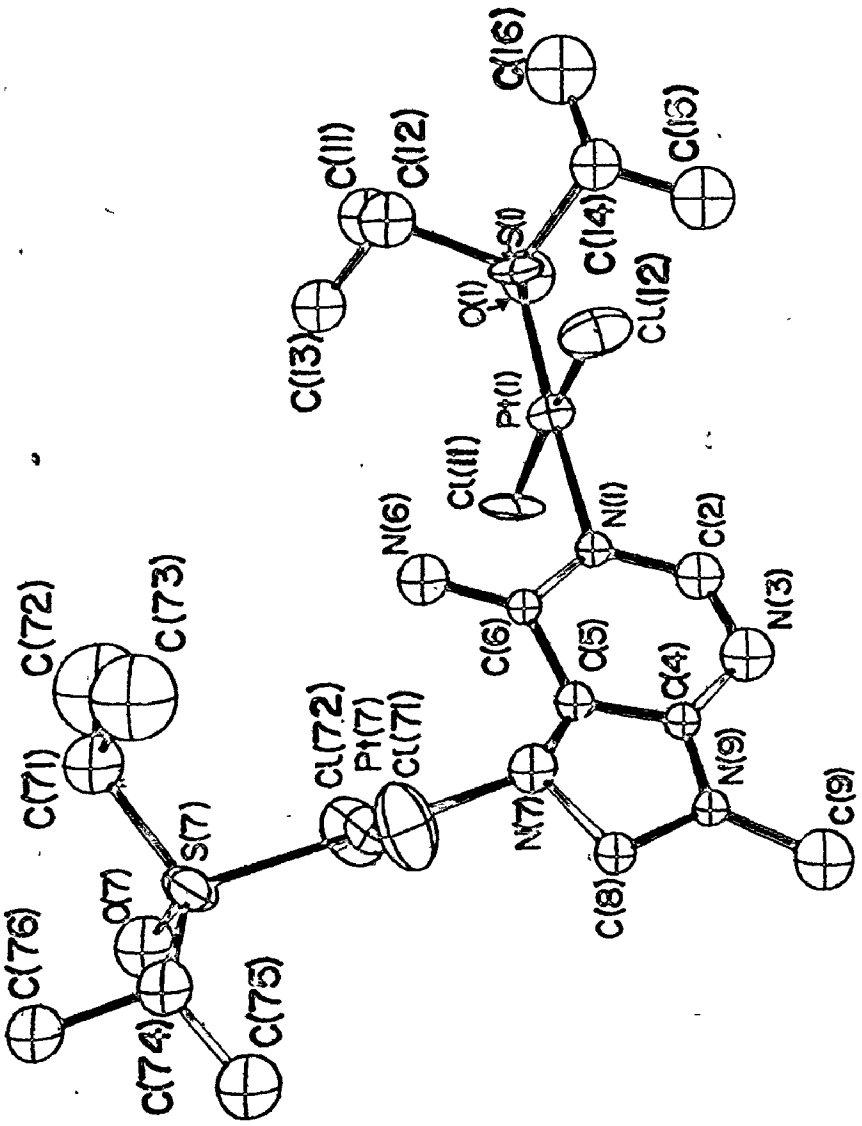


Figure 8. The molecule [trans-$PtCl_2(i\text{-}Pr_2SO)]_2(C_6H_7N_5)$ showing the atom numbering.

above the best plane.

The angular deviations from the ideal square plane for Pt(1) are similar to those described for trans-$PtCl_2$-(i-Pr_2SO)($C_5H_7N_3O$), A, and trans-$PtCl_2(Me_2SO)$(Cyd),[83] B. The Cl(11)-Pt(1)-Cl(12) angle is 172.9(3)°, as compared to 174.3(1)° and 178.4(1)°.[83] This results, in part, from an intramolecular repulsion, i.e., between Cl(12) and C(14) of the isopropyl group (distance is 3.29(3) Å) as occurred in A. The Cl(12)-Pt(1)-S(1) angle is, therefore, 93.9(3)° as compared to 95.7(1)° in A. Although Cl(1)-Pt-S is normal (89.3°) in A, the equivalent angle, Cl(11)-Pt(1)-S(1) in the title compound is 93.0(3)°. The increase is the result of an intramolecular repulsion (O(1)-Cl(1) distance is 3.31(2)) and of packing (see Fig. 9), where an intermolecular repulsion (C(8) of a second adenine, to Cl(11) distance is 3.29(3) Å) forces the angle open. The Cl(71)-Pt(7)-Cl(72) angle is 174.6(3) and is less distorted than Cl(10)-Pt(1)-Cl(12). The distortion is peculiar, however, in that S(7)-Pt(7)-Cl(72) is 90.7(3)° and Cl(71)-Pt(7)-N(7) is 88.8(7)°. The S(7)-Pt(7)-Cl(7) angle opens up to 94.2(3) and the complement Cl(72)-Pt(7)-N(7) closes in to 86.2(7). The C(74)-Cl(71) distance is 3.33(3) and C(74) is the closest non-bonded atom (except for N(7), 3.07(3)). The C(74)-Cl(71) repulsion does not completely explain the distortion. The small dihedral angle between the Pt(7) plane (defined by Cl(71), Cl(72), S(7) and N(7)) and adenine

(~ 55°) suggested that Cl(72) could be interacting with the exocyclic atom N(6) of adenine. Closer examination of the distances showed this to be true, i.e., the Cl(72)-N(6) distance is 3.30(2) Å and Cl(72)-N(6)-C(6) is 93(2), implying that an intramolecular hydrogen bond of the type N-H...Cl exists. The bond is stronger than the weak intramolecular interaction reported in Sect. 2.5.2 for trans-$PtCl_2(NH_3)_2(C_5H_7N_3O)$ (i.e., N(4)-Cl(1) distance is 3.48(1) Å). The 3.30(2) Å N-Cl distance agrees well with intermolecular hydrogen bond distances (N-Cl distances of 3.31 and 3.38 Å) found for trans-$PtCl_2$(benzylamine)(olefin)[88] and trans-$PtCl_2(MeC_6H_4NH_2)$(acetylene)[86] complexes and is within the range specified by Hamilton and Ibers[104] (3.15-3.51 Å) for N-H...Cl hydrogen bonds. The chlorine-N(6) interaction described is similar to one described for a Cu-9-methylhypoxanthine structure,[62] where Cu is bound at N(7) of hypoxanthine and H_2O, coordinated to Cu, hydrogen bonds with O(6) of hypoxanthine. Distances and angles within this complex agree well with those found in the title compound, i.e., Cu-N(7)-C(5) is 135° vs. Pt(7)-N(7)-C(5), 133(2)°; Cu-N(7), 2.054 Å vs. Pt(7)-N(7), 2.04(2) Å; Cu-O(6), 3.74 Å vs. Pt(7)-N(6), 3.88(3) Å. In ref. 62, Sletten argues that chelation between Cu and O(6) is not probable because of the large distortion that would occur in the Cu-N(7)-C(5) angle (i.e., the angle would have to

decrease by ~35-40°). The large dihedral angle between adenine and the Pt(1) plane, 89°, suggests that there are no intramolecular interactions between N(6) and the chlorine atoms bound to the platinum atoms.

The bond lengths around each platinum atom are normal and are in agreement with values found in other similar structures reported in this work (see Table 8, p. 56) and those values reported in Sect. 2.2.2. The Pt(1)-N(1) distance is 2.06(2) and is similar to the values recorded for platinum atom binding to N(3) of cytosine, also a tertiary amine site (2.023-2.06, Table 8). The Pt(7)-N(7) distance is 2.04(2) and is not significantly larger than values for platinum atom binding at the imidazole site of guanine, 2.01(1) and 2.01(2) as reported in Sect. 2.3.2. The Pt-N distance in a trans imidazole complex, trans-$[Pt(N_2C_4H_6)_2(NH_3)_2]Cl_2 \cdot 2H_2O$, was reported[96] to be 2.01(2) Å. Bond lengths and angles within the bis(isopropyl)sulfoxide group do not differ significantly from values reported for A and B. Bond lengths and angles within the 9-methyladenine group do not differ significantly from the average values listed by Voet and Rich.[105]

The packing of the molecules is shown in Figure 9. As in the $(i\text{-}Pr_2SO)PtCl_2(1\text{-}MeCyt\text{-}N3)$ cell, this is essentially a close packed structure with some weak hydrogen bonding. In the $\underset{\sim}{b}$ direction at y = 0 and 1/2, weak interactions are between O(1) of the sulfoxide group with C(8) and C(9) of adjacent molecules. In the $\underset{\sim}{c}$ direction at

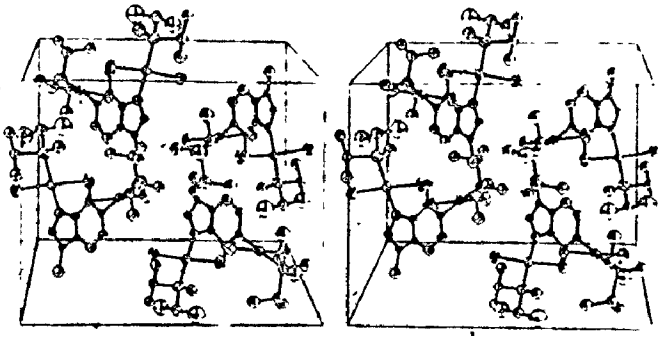


Figure 9. The unit cell contents of [<u>trans</u>-$PtCl_2(i\text{-}Pr_2SO)]_2$-$(C_6H_7N_5)\cdot H_2O$. $\underset{\sim}{c}$ and $\underset{\sim}{b}$ are parallel to the side and bottom of the page, respectively. The view is down $\underset{\sim}{a}^*$.

z = 0 and 1/2, weak interactions occur between N(3) and N(6) of adjacent molecules. Other distances are close to van der Waals contact distances.

2.2.4 Discussion

The potential for sequencing of DNA was verified since one to one complexation was observed for Pt binding to cytosine in trans-$(i\text{-}Pr_2SO)PtCl_2$(1-Me-cytosine-N3) as well as in trans-$(Me_2SO)PtCl_2$(cytidine-N3),[83] while 2:1 complexation was observed for trans-$(i\text{-}Pr_2SO)PtCl_2$ binding to adenine.

The adenine complex is the first isolable complex in which platinum has been shown to bind to N(1) and N(7) of adenine. Solution of this molecular structure verified Kong and Theophanides[48] contention, based on nmr evidence, that adenosine acted as a bidentate ligand linking two platinum atoms through N(1) and N(7). Robins[50] had also detected binding of 2 platinum atoms to adenosine and ATP in his studies.

The large dihedral angles between the plane of the base and the ligand planes for the cytosine and adenine structures are very important. The adenine-Pt(7) plane angle is 55° and the adenine-Pt(1) plane angle is 89°. The cytosine-Pt plane angle is 84°. These large angles are caused by the steric requirements of the groups attached to the carbon atoms adjacent to the bound nitrogen atom,

and similar large dihedral angles will occur in any square planar platinum-DNA-base complex. This will cause a marked distortion in a coiled DNA chain, when platinum complexes are bound to the bases. This distortion may be the reason why cis-dichloro diammineplatinum (II), in addition to being a useful anticancer agent, is an activator of other anticancer drugs.[106]

2.3 STEREOCHEMICAL REQUIREMENTS OF MODEL COMPOUNDS

2.3.1 Introduction

When researchers established that cis-$Pt(NH_3)_2Cl_2$ bound preferentially to the G-C base pair, a study of the stereochemical requirements of model cytosine and guanine compounds was undertaken in hopes of deducing information which would favour any of the crosslinking theories. Few of these complexes had been adequately characterized. The first of these studied was the mixed base compound, cis-$[(H_3N)_2$-Pt(1-MeCyt)(9-EtGua)$]^{2+}$. The second was trans-$[(H_3N)_2Pt(1\text{-MeCyt})_2]^{++}$.

2.3.2 The Crystal and Molecular Structure of cis-diammine-(1-methylcytosine-N3)(9-ethylguanine-N7)platinum-(II) diperchlorate[107]

Preparation (by B. Lippert)

Cis-$[PtCl(NH_3)_2(C_5H_7N_3O)]Cl\cdot H_2O$ (0.665 g, 25 mL H_2O) was reacted with two equivalents of $AgClO_4$ (0.675 g, 5 mL H_2O). After 45 min one equivalent (0.270 g, 15 mL H_2O) of 9-ethylguanine was added. After 30-40 h (at 40°C), the AgCl was filtered off. The solution was concentrated and the title compound crystallized at room temperature. Yield 1.1 g. Crystals suitable for crystallographic work were prepared by recrystallization from H_2O.

Analysis: Calcd. for $C_{24}H_{44}Cl_4N_{20}O_{20}Pt_2$: C 19.4, H 3.1, N 18.9, Pt 26.3; Found: C 19.7, H 3.0, N 18.8, Pt 26.0.

Solution of the Structure

Precession photographs of zero and first layers

for the title compound showed that the crystal was monoclinic with systematic absences, 0k0, k = 2n + 1 and h0l, h + l = 2n + 1 suggested that the space group was $P2_1/n$. The zero layer photographs, only, had suggested a C2/c cell. Density measurements suggested about 8 molecular units (based on elemental analyses) per unit cell, which was consistent with the C2/c cell (with the molecule in a general position). When upper layer photographs eliminated C2/c as a possible space group, the density of the crystals implied (for the $P2_1/n$ cell) that there were two crystallographically independent platinum atoms. In spite of this, there were relatively few problems encountered in solving the Patterson map for the platinum atoms. Possible x, y and z values were obtained from the Harker lines and planes. The number of possible combinations of x_1,y_1,z_1 with x_2,y_2,z_2 was reduced by calculating cross peaks and comparing these peaks with the Patterson map. The solution to the Patterson was one of several possible solutions which resulted from this procedure.

Discussion

Crystal data and other numbers related to data collection and structure refinement are summarized in Table 13. The atom parameters from the final refinement are listed in Table 14 and the corresponding moduli of F_o and F_c are listed in reference 179. Selected bond lengths and angles are given in Table 15 and the molecular cation

TABLE 13

Compound	$C_{24}H_{44}Cl_4N_{20}O_{20}Pt_2$
F.W.	1464.73
Crystal size	Cylinder, r, 0.087mm, l, 0.40 mm
Crystal colour	colourless
ρ_{calc}	2.11 g cm^{-3}
ρ_{obs}	2.10(2) g cm^{-3}
Systematic absences	0k0, k = 2n + 1 h0l, h + l = 2n + 1
Space group	$P2_1/n$
Unit cell parameters	a = 20.117(7) Å b = 27.017(5) Å, β=105.13(2)° c = 8.727(2) Å
Volume	4602(2) $Å^3$
Z	4
Crystal mount axis	roughly along c
Linear absorption coefficient	67.2 cm^{-1}
Transmission coefficient limits	2.64 - 2.69
Max 2θ; quadrant	45°, h, k, ± l
Standard reflections	(1) -4,0,-2 (2) -1,-1,-2
Overall e.s.d.	(1) 1.44% (2) 1.77%
Temperature	22°C
No. of independent reflections	3875
No. with $I > 3\sigma(I)$	2815
$3\sigma(I) > I > \sigma(I)$ where $F_c > F_o$	206
$3\sigma(I) > I > \sigma(I)$ where $F_c < F_o$	315
$I < \sigma(I)$, (rejected)	539

Continued.....

TABLE 13 (Continued)

Compound	$C_{24}H_{44}Cl_4N_{20}O_{20}Pt_2$
Final R_1	0.0552
Final R_2	0.0662
Final shift in e.s.d. Max.	0.023
Ave.	0.007
g (secondary extinction)	3.84×10^{-8}
Final difference map	
Highest peak; location	1.83 e/Å^3; -0.06, 0.23, 0.65
Lowest valley; location	-0.89 e/Å^3; 0.74 0.10, 0.50
Weighting	$\frac{1}{\varepsilon} = (99.51 - 0.8942\|F_o\| + 0.00385\|F_o\|^2)$

TABLE 14

Atom parameters and temperature factors ($Å^2$) for

cis-diammine(1-methylcytosine-N3)(9-ethylguanine-N7)

platinum(II) diperchlorate (x 10^3) *

	x	y	z	U
Pt(1)	271.35(4)	161.32(3)	942.07(9)	
N(11)	204.3(9)	200.1(6)	1039(2)	47(5)
N(12)	351.6(9)	174.3(6)	1137(2)	43(4)
N(1)	149.8(8)	232.9(6)	417(2)	32(4)
C(2)	103(1)	202.5(8)	321(2)	42(5)
N(2)	74(1)	218.3(7)	167(2)	57(5)
N(3)	84.1(9)	159.1(6)	366(2)	41(4)
C(4)	120(1)	146.6(7)	510(2)	37(5)
C(5)	169.3(9)	172.5(6)	618(2)	23(4)
C(6)	183(1)	220.8(7)	578(3)	35(5)
O(6)	219.3(7)	253.7(5)	658(1)	42(3)
N(7)	193.6(8)	145.7(6)	750(2)	35(4)
C(8)	159(1)	102.1(8)	738(2)	45(6)
N(9)	114.3(9)	102.5(6)	584(2)	48(5)
C(9)	72(2)	58(1)	502(4)	98(10)
C(10)	2(2)	69(1)	465(4)	130(13)
N(1A)	404(1)	123.4(7)	663(2)	57(5)
C(1A)	438(1)	152(1)	554(3)	74(8)
C(2A)	366(1)	149.1(8)	748(2)	41(5)
O(2A)	366.2(7)	194.0(6)	748(2)	57(4)
N(3A)	335.4(8)	121.9(6)	843(2)	37(4)
C(4A)	340(1)	71.3(8)	850(2)	42(5)
N(4A)	308.8(9)	47.4(6)	939(2)	49(5)
C(5A)	379(1)	46.5(8)	759(3)	52(6)
C(6A)	409(1)	74(1)	666(3)	69(7)
Pt(2)	739.66(4)	152.18(3)	517.66(9)	
N(21)	804.9(9)	189.7(6)	410(2)	44(4)
N(22)	657.8(9)	165.1(6)	321(2)	47(5)

Continued.....

TABLE 14 (Continued)

	x	y	z	U
N(1B)	858.3(9)	224.2(6)	1040(2)	42(4)
C(2B)	907(1)	194.0(7)	1130(2)	35(5)
N(2B)	935(1)	210.8(7)	1285(2)	59(5)
N(3B)	931.5(9)	153.5(6)	1088(3)	43(4)
C(4B)	894(1)	140.1(8)	941(2)	43(5)
C(5B)	842(1)	166.1(7)	840(2)	29(4)
C(6B)	825(1)	212.9(7)	881(2)	32(5)
O(6B)	784.4(7)	243.7(5)	802(1)	41(3)
N(7B)	820.1(8)	137.3(6)	704(2)	40(4)
C(8B)	858(1)	96.5(8)	719(2)	48(6)
N(9B)	904.4(9)	97.9(6)	866(2)	46(4)
C(9B)	956(1)	57.9(9)	931(3)	59(6)
C(10B)	1032(1)	78(1)	952(3)	90(9)
N(1C)	607(1)	115.8(7)	803(2)	58(5)
C(1C)	575(1)	146.8(9)	902(3)	64(7)
C(2C)	643(1)	141.0(8)	708(2)	38(5)
O(2C)	642.0(8)	186.2(6)	708(2)	56(4)
N(3C)	677.9(9)	112.9(6)	625(2)	46(4)
C(4C)	674(1)	62.9(8)	625(2)	42(5)
N(4C)	706.6(9)	38.5(7)	537(2)	53(5)
C(5C)	635(1)	38.5(9)	714(3)	59(6)
C(6C)	605(1)	65(1)	803(3)	66(7)
Cl(1)	508.2(3)	74.2(2)	241.1(8)	
O(11)	476(3)	35(2)	129(7)	349(28)
O(12)	498(2)	43(1)	354(4)	202(13)
O(13)	466(2)	107(1)	159(4)	211(14)
O(14)	571(1)	71(1)	198(3)	131(8)
Cl(2)	246.4(3)	91.7(2)	320.4(8)	
O(21)	195(1)	84.0(8)	178(3)	123(8)
O(22)	252(1)	143.2(7)	357(2)	90(6)
O(23)	309(1)	75.9(7)	293(2)	91(6)
O(24)	235(1)	65.4(7)	450(2)	94(6)

Continued.....

TABLE 14 (Continued)

	x	y	z	U
Cl(3)	785.3(5)	69.5(3)	177(1)	
O(31)	826(2)	68(1)	330(4)	190(13)
O(32)	718(1)	56.3(8)	177(2)	105(6)
O(33)	809(1)	38(1)	77(3)	158(10)
O(34)	782(1)	119(1)	127(3)	159(10)
Cl(4)	4.7(3)	232.7(2)	726.4(7)	
O(41)	-27(1)	249(1)	845(3)	158(10)
O(42)	4(2)	185(2)	710(5)	244(18)
O(43)	18(2)	261(1)	601(5)	213(14)
O(44)	68(3)	243(2)	810(6)	302(23)

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

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt(1)	29.8(6)	32.4(5)	26.8(5)	1.9(3)	2.8(4)	0.4(3)
Pt(2)	35.1(6)	28.8(5)	27.3(5)	-2.1(3)	1.0(4)	1.5(3)
Cl(1)	45(4)	71(4)	78(4)	10(3)	24(3)	16(3)
Cl(2)	71(5)	61(4)	66(4)	22(3)	29(4)	18(3)
Cl(3)	126(7)	92(6)	113(6)	-56(5)	78(6)	-51(4)
Cl(4)	53(4)	57(4)	59(4)	5(3)	13(3)	5(3)

* Estimated standard deviations from the least squares programs are given in parentheses.

TABLE 15

Selected interatomic distances (Å) and angles (deg) for cis-diammine(1-methylcytosine-N3)(9-ethylquanine-N7)platinum(II) diperchlorate (esd's in terms of the least significant figure are given in parentheses).

Atoms	Distance	Atoms	Distance	Atoms	Distance
		Molecular Unit 1			
Pt(1)-N(11)	2.06(2)	Pt(1)-N(12)	2.05(1)	Pt(1)-N(7)	2.01(1)
Pt(1)-N(3A)	2.03(2)	N(1)-C(2)	1.36(2)	C(2)-N(2)	1.38(3)
C(2)-N(3)	1.32(3)	N(3)-C(4)	1.33(2)	C(4)-C(5)	1.36(2)
C(5)-C(6)	1.40(3)	C(6)-N(1)	1.43(2)	C(6)-O(6)	1.24(2)
C(5)-N(7)	1.34(2)	N(7)-C(8)	1.35(3)	C(8)-N(9)	1.35(2)
N(9)-C(9)	1.54(4)	C(9)-C(10)	1.41(5)	N(9)-C(4)	1.37(3)
N(1A)-C(1A)	1.51(4)	N(1A)-C(2A)	1.39(3)	C(2A)-O(2A)	1.21(3)
C(2A)-N(3A)	1.37(3)	N(3A)-C(4A)	1.37(3)	C(4A)-N(4A)	1.30(3)
C(4A)-C(5A)	1.42(3)	C(5A)-C(6A)	1.36(4)	C(6A)-N(1A)	1.33(3)
		Molecular Unit 2			
Pt(2)-N(21)	2.06(2)	Pt(2)-N(22)	2.07(1)	Pt(2)-N(7B)	2.01(2)
Pt(2)-N(3C)	2.04(2)	N(1B)-C(2B)	1.36(2)	C(2B)-N(2B)	1.40(3)
C(2B)-N(3B)	1.29(3)	N(3B)-C(4B)	1.35(3)	C(4B)-C(5B)	1.37(3)
C(5B)-C(6B)	1.38(3)	C(6B)-N(1B)	1.41(2)	C(6B)-O(6B)	1.24(2)
C(5B)-N(7B)	1.39(2)	N(7B)-C(8B)	1.33(3)	C(8B)-N(9B)	1.38(3)
N(9B)-C(9B)	1.51(3)	C(9B)-C(10B)	1.58(4)	N(9B)-C(4B)	1.36(3)
N(1C)-C(1C)	1.48(4)	N(1C)-C(2C)	1.39(3)	C(2C)-O(2C)	1.22(3)
C(2C)-N(3C)	1.37(3)	N(3C)-C(4C)	1.35(3)	C(4C)-N(4C)	1.31(3)
C(4C)-C(5C)	1.40(4)	C(5C)-C(6C)	1.31(4)	C(6C)-N(1C)	1.38(3)

Atoms	Angle	Atoms	Angle	Atoms	Angle
		Molecular Unit 1			
N(11)-Pt(1)-N(12)	91.7(7)	N(11)-Pt(1)-N(3A)	178.5(7)	N(11)-Pt(1)-N(7)	89.9(7)
N(12)-Pt(1)-N(7)	177.7(6)	N(12)-Pt(1)-N(3A)	89.6(7)	N(3A)-Pt(1)-N(7)	88.8(6)
C(2)-N(1)-C(6)	123(2)	N(1)-C(2)-N(2)	117(2)	N(1)-C(2)-N(3)	124(2)
N(2)-C(2)-N(3)	119(2)	C(2)-N(3)-C(4)	112(2)	N(3)-C(4)-C(5)	130(2)
N(3)-C(4)-N(9)	125(2)	C(4)-C(5)-C(6)	117(2)	C(5)-C(6)-N(1)	113(2)

.....Cont.

TABLE 15 (continued)

C(5)-C(6)-O(6)	130(2)	O(6)-C(6)-N(1)	117(2)	C(6)-C(5)-N(7)	132(2)
C(5)-N(7)-C(8)	107(1)	C(5)-N(7)-Pt(1)	129(1)	Pt(1)-N(7)-C(8)	124(1)
N(7)-C(8)-N(9)	109(2)	C(8)-N(9)-C(4)	109(2)	C(8)-N(9)-C(9)	125(2)
C(4)-N(9)-C(9)	125(2)	N(9)-C(9)-C(10)	109(3)	C(5)-C(4)-N(9)	105(2)
C(4)-C(5)-N(7)	110(2)	O(2A)-C(2A)-N(3A)	122(2)	N(1A)-C(2A)-N(3A)	117(2)
C(2A)-N(3A)-C(4A)	121(2)	C(2A)-N(3A)-Pt(1)	114(1)	C(4A)-N(3A)-Pt(1)	123(2)
N(3A)-C(4A)-N(4A)	119(2)	N(3A)-C(4A)-C(5A)	119(2)	N(4A)-C(4A)-C(5A)	122(2)
C(4A)-C(5A)-C(6A)	118(2)	C(5A)-C(6A)-N(1A)	121(3)	C(6A)-N(1A)-C(1A)	119(2)
C(6A)-N(1A)-C(2A)	122(2)	C(2A)-N(1A)-C(1A)	118(2)	N(1A)-C(2A)-O(2A)	120(2)

Molecular Unit 2

N(21)-Pt(2)-N(22)	90.3(7)	N(21)-Pt(2)-N(3C)	177.8(7)	N(21)-Pt(2)-N(7B)	89.6(7)
N(22)-Pt(2)-N(7B)	177.8(7)	N(22)-Pt(2)-N(3C)	91.0(7)	N(3C)-Pt(2)-N(7B)	89.0(7)
C(2B)-N(1B)-C(6B)	122(2)	N(1B)-C(2B)-N(2B)	114(2)	N(1B)-C(2B)-N(3B)	128(2)
N(2B)-C(2B)-N(3B)	118(2)	C(2B)-N(3B)-C(4B)	110(2)	N(3B)-C(4B)-C(5B)	128(2)
N(3B)-C(4B)-N(9B)	124(2)	C(4B)-C(5B)-C(6B)	120(2)	C(5B)-C(6B)-N(1B)	111(2)
C(5B)-C(6B)-O(6B)	130(2)	O(6B)-C(6B)-N(1B)	119(2)	C(6B)-C(5B)-N(7B)	133(2)
C(5B)-N(7B)-C(8B)	109(2)	C(5B)-N(7B)-Pt(2)	126(1)	Pt(2)-N(7B)-C(8B)	124(1)
N(7B)-C(8B)-N(9B)	107(2)	C(8B)-N(9B)-C(4B)	109(2)	C(8B)-N(9B)-C(9B)	124(2)
C(4B)-N(9B)-C(9B)	127(2)	N(9B)-C(9B)-C(10B)	111(2)	C(5B)-C(4B)-N(9B)	108(2)
C(4B)-C(5B)-N(7B)	106(2)	O(2C)-C(2C)-N(3C)	124(2)	N(1C)-C(2C)-N(3C)	117(2)
C(2C)-N(3C)-C(4C)	121(2)	C(2C)-N(3C)-Pt(2)	115(1)	C(4C)-N(3C)-Pt(2)	124(2)
N(3C)-C(4C)-N(4C)	118(2)	N(3C)-C(4C)-C(5C)	120(2)	N(4C)-C(4C)-C(5C)	121(2)
C(4C)-C(5C)-C(6C)	119(2)	C(5C)-C(6C)-N(1C)	121(3)	C(6C)-N(1C)-C(1C)	123(2)
C(6C)-N(1C)-C(2C)	121(2)	C(2C)-N(1C)-C(1C)	116(2)	N(1C)-C(2C)-O(2C)	119(2)

TABLE 15 (continued)

Atoms	Distance	Atoms	Distance
N(1B)[a]-O(2A)	2.84(2)	N(1)-O(2C)[a]	2.82(2)
O(6B)[b]-N(11)	2.87(2)	O(6)-N(21)[b]	2.86(2)
O(6B)[b]-N(12)	3.13(2)	O(6)-N(22)[b]	3.05(2)
N(11)-O(22)[c]	3.10(2)	N(21)-O(31)	3.41(4)
N(11)-O(44)	3.15(5)	N(21)-O(34)	3.06(3)
N(12)-O(22)[c]	3.23(3)	N(22)[c]-O(14)[c]	3.11(3)
N(12)-O(23)[c]	3.20(3)	N(22)-O(44)[a]	3.06(6)
N(12)-O(13)[c]	2.90(4)		
N(12)[d]-O(41)	3.35(3)		

Atoms	Angle	Atoms	Angle
C(6B)[a]-N(1B)[a]-O(2A)	137(1)	C(6)-N(1)-O(2C)[a]	138(1)
C(2B)[a]-N(1B)[a]-O(2A)	101(1)	C(2)-N(1)-O(2C)[a]	99(1)
C(2A)-O(2A)-N(1B)[a]	141(1)	C(2C)[a]-O(2C)[a]-N(1)	141(1)
C(6B)[b]-O(6B)[b]-N(11)	162(1)	C(6B)[b]-O(6B)[b]-N(12)	115(1)
Pt(1)-N(11)-O(6B)[b]	107.9(7)	Pt(1)-N(12)-O(6B)[b]	99.3(6)
N(11)-O(6B)[b]-N(12)	58.6(5)	N(21)[b]-O(6)-N(22)[b]	59.4(6)
O(6)-N(21)[b]-Pt(2)[b]	106.6(7)	O(6)-N(22)[b]-Pt(2)[b]	100.1(7)
C(6)-O(6)-N(21)[b]	165(1)	C(6)-O(6)-N(22)[b]	122(1)
Pt(1)-N(12)-O(13)[c]	113(1)	Pt(1)-N(11)-O(44)	118(1)
O(13)[c]-Cl(1)[c]-O(14)[c]	113(2)	N(11)-O(44)-N(22)[b]	83(1)
Pt(2)[c]-N(22)[c]-O(14)[c]	113.7(8)	O(44)-N(22)[b]-Pt(2)[b]	120(1)
Pt(2)[b]-N(22)[b]-O(44)	120(1)	N(11)-O(44)-Cl(4)	146(3)
O(14)-N(22)-O(44)[a]	112(1)	N(22)[b]-O(44)-Cl(4)	131(3)
O(44)-Cl(4)-O(41)	95(3)	Cl(4)[b]-O(41)[b]-N(12)	102(1)
O(41)[b]-N(12)-Pt(1)	149.5(9)	Pt(2)-N(21)-O(34)	94.7(8)
Pt(1)-N(11)-O(22)[c]	91.9(7)	N(21)-O(34)-Cl(3)	111(1)
Pt(1)-N(12)-O(22)[c]	88.4(7)	Cl(2)[c]-O(22)[c]-N(11)	107(1)
Pt(1)-N(12)-O(23)[c]	88.3(6)	O(22)[c]-N(11)-O(44)	140(1)
N(12)-O(22)[c]-N(11)	55.4(6)	Cl(2)[c]-O(22)[c]-N(12)	98(1)
		Cl(2)[c]-O(23)[c]-N(12)	100(1)

a. Atoms are related to those given in Table 14 by a, x-½, ½-y, z-½; b, x-½, ½-y, ½+z; c, x, y, 1+z; d, x-½, ½-y, z-½

TABLE 16

Least squares planes and dihedral angles between planes for cis-diammine(1-methylcytosine-N3)(9-ethylquanine-N7)platinum(II) diperchlorate.

Plane	Atom	Distance from best plane (Å)
1	N(1)C(2)N(3)C(4)C(5)C(6)N(7) C(8)N(9)N(2)*O(6)*C(9)*C(10)* Pt(1)*	no convergence
2	N(1A)C(2A)N(3A)C(4A)C(5A) C(6A)C(1A)*O(2A)*N(4A)*Pt(1)*	N(1A),0.01;C(2A),-0.01;N(3A),0.01;C(4A), 0.0;C(5A),0.0;C(6A),-0.01;C(1A),-0.03; O(2A),0.08;N(4A),-0.02;Pt(1),-0.26.
3	N(11)N(12)N(7)N(3A)Pt(1)*	N(11),0.01;N(12),-0.01;N(7),0.01; N(3A),-0.01;Pt(1),-0.02.
4	N(1B)C(2B)N(3B)C(4B)C(5B) C(6B)N(7B)C(8B)N(9B)N(2B)* O(6B)*C(9B)*C(10B)*Pt(2)*	N(1B),0.03;C(2B),0.06;N(3B),-0.04;C(4B), 0.0;C(5B),0.01;C(6B),-0.08;N(7B),0.04; C(8B),0.01;N(9B),-0.03;N(2B),0.17;O(6B), -0.20;C(9B),-0.04;C(10B),-1.42;Pt(2),0.24.
5	N(1C)C(2C)N(3C)C(4C)C(5C) C(6C)C(1C)*O(2C)*N(4C)*Pt(2)*	N(1C),0.01;C(2C),-0.03;N(3C),0.02;C(4C), 0.01;C(5C),-0.03;C(6C) 0.02;C(1C),0.08; O(2C),-0.07;N(4C),0.0;Pt(2);0.24.
6	N(21)N(22)N(7B)N(3C)Pt*(2)	N(21),0.0;N(22),0.0;N(7B),0.0;N(3C),0.0; Pt(2),0.04.

Dihedral angle for planes are,

2-5	5.9°	4-5	77.7°
2-3	87.2°	4-6	88.2°
		5-6	83.8°

Errors in atom positions about 0.03 Å. Rms deviation for Plane 2, 0.009Å; Plane 3, 0.011Å; Plane 4, 0.043Å; Plane 5, 0.024Å; Plane 6, 0.0Å.

cis-$[Pt(NH_3)_2(1\text{-MeCyt-N3})(9\text{-EtGua-N7})]^{2+}$ is illustrated in Figure 10. The structure is normal. The coordinations around the two independent platinum atoms are square planar with only marginal distortion around Pt(1). The angles of the square plane are all close to 90°. The bond lengths around the platinum atoms are normal, i.e., Pt-NH_3 distances range from 2.05(1) to 2.07(1) Å and average 2.06(1) Å. These values agree well with those Pt-NH_3 distances reported in Table 8, p. 56. The Pt-N(3) distances are normal (see Table 8) and the Pt-N(7) distances, 2.01(2), 2.01(1), agree well with the Pt-N distance in the trans imidazole complex, trans-$[Pt(N_2C_4H_6)_2(NH_3)_2]Cl_2 \cdot 2H_2O$, 2.01(2) Å. Pt-N(7) distances reported for analogous compounds are 1.97(2) (for $[Pten(Guo)_2]^{2+}$),[57] and 1.99(1), 2.02(1) (for [cis-$Pt(NH_3)_2(Guo)_2]^{2+}$).[58] The dihedral angle between the cytosine and guanine rings is 78° compared to 70° and 74°[58] for the guanine rings in cis-$[Pt(NH_3)_2(Guo)_2]^{2+}$ and 77° for the cytosine rings in cis-$[(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2]^{2+}$ (see Sect. 2.7.2). The large angle prevents interactions of the exocyclic oxygen atoms of guanine and cytosine with the ammine molecules bound to the platinum atom. A peculiar feature of the $[Pt(NH_3)_2(1\text{-MeCyt-N3})(9\text{-EtGua-N7})]^{2+}$ cation is that the exocyclic oxygens, O(6) of guanine and O(2) of cytosine are arranged head-to-head (O(6)-O(2) distances are 3.28(2) and 3.17(2)). A head-to-tail arrangement would allow O(6)

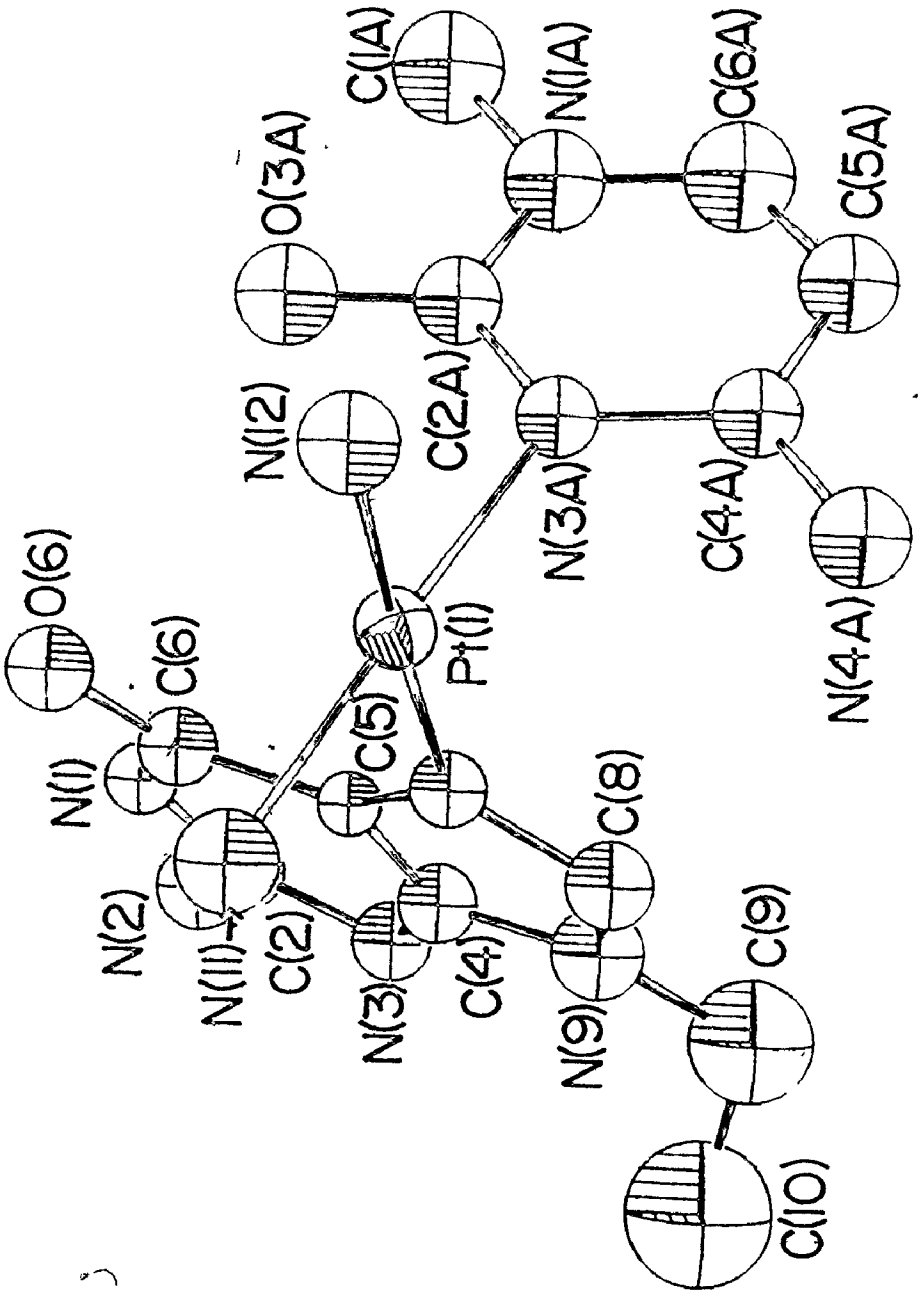


Figure 10

The molecular cation cis-$[Pt(NH_3)_2(C_5H_7N_3O)(C_7H_9N_5O)]^{2+}$ showing the atom numbering of ligands bound to Pt(1).

of guanine to interact with N(4) of cytosine (to form an intramolecular hydrogen bond). This arrangement would also minimize O(6)-O(2) repulsions. It is probable that intermolecular hydrogen bonds with perchlorate help to stabilize the head-to-head configuration. Bond lengths and angles within the 9-ethylguanine molecules do not differ significantly from the average values listed by Voet and Rich.[105] The guanine molecule is essentially planar. Bond lengths and angles within the cytosine ring are discussed in Sect. 2.6, p. 149.

The packing of the title compound within the crystal is shown in Fig. 11. The unit cell is made up of four chains of dimeric units which run along the $\underset{\sim}{c}^*$ axis. Each of the dimeric units is made up of two molecular cations $[Pt(NH_3)_2(1\text{-MeCyt-N3})(9\text{-EtGua-N9})]^{2+}$ (where each cation is associated with one of two crystallographically independent platinum atoms, i.e., Pt(1) and Pt(2)). The two molecular cations within the dimeric unit are held together by two hydrogen bonds, where each bond is formed when N(1)-H of a guanine pairs with O(2) of the cytosine in the opposite cation (e.g., N(1)-O(2) distances are 2.84(2) Å and 2.82(2) Å). The dimeric units are themselves hydrogen bonded together up the $\underset{\sim}{c}^*$ axis when the ammonia molecules (which are bound to Pt(1) and Pt(2)), which are arranged head-to-head, interact with the exocyclic O(6) atoms of guanine molecules in adjacent dimeric units. These hydrogen bonds, N(11)-H...O(6B) and,

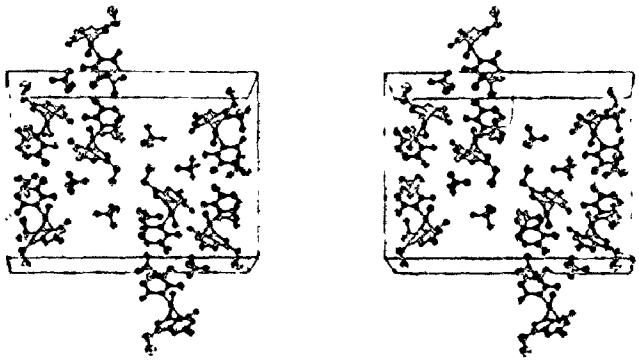


Figure 11. The unit cell contents of cis-$[Pt(NH_3)_2(C_5H_7N_3O)(C_7H_9N_5O)](ClO_4)_2$. $\underset{\sim}{a}$ and $\underset{\sim}{b}$ are parallel to the side and bottom of the page, respectively. The view is down $\underset{\sim}{c}^*$.

N(21)-H...O(6) are relatively strong (N(11)-O(6B) and N(21)-O(6) distances are 2.87(2) and 2.86(2) Å, respectively). The chains of dimeric units are held together in the direction of the a axis by a small amount of π-π overlap between cytosine molecules and also by two of the perchlorate ions which weakly hydrogen bond to the ammonia molecules bound to platinum. The Cl(4) perchlorate ion bridges three molecular cations through the ammonia molecules: O(41) of the perchlorate ion hydrogen bonds to N(12) of Pt(1), O(44) of the same perchlorate ion hydrogen bonds to N(11) of the symmetry related molecule of Pt(1) and to N(22) of Pt(2). As well, O(13) of a second perchlorate ion hydrogen bonds to N(12) of Pt(1) and O(14) of the same perchlorate ion hydrogen bonds to N(22) of Pt(2). The other two perchlorate ions weakly interact with ammonia molecules of the molecular cations but do not bridge: the oxygen atoms of Cl(2) (O(22) and O(23)) weakly hydrogen bond with N(11) and N(12) of Pt(1) while O(34) of Cl(3) binds to N(21) of Pt(2). The forces holding the chains together in the b direction appear to be ionic. No hydrogen bonding was observed.

2.3.3 The Crystal and Molecular Structure of trans-diammine di(1-methylcytosine-N3)platinum(II) dinitrate[108]

Introduction

Because trans-$Pt(NH_3)_2Cl_2$ does not show anticancer activity, there have been almost no structural studies on the interaction of trans-ammine complexes with the corres-

ponding organic compounds, even though in vitro chemical and biochemical studies suggest very similar behaviour to the corresponding cis-complexes.[10,11,35] This is surprising because there must be some biochemical factor dependent on the structure which causes the physiological differences. In vivo tests on DNA cross-linking show that there is a discernible difference in behaviour of cis and trans-Pt-$(NH_3)_2Cl_2$.[35]

When attempts were made to synthesize cis-$Pt(NH_3)_2$-$(1\text{-MeCyt})_2^{2+}$ to study the stereochemical requirements of this moiety, one of the major products of the reaction of cis-$Pt(NH_3)_2(NO_3)_2$ with two equivalents of 1-methylcytosine was indeed cis-$Pt(NH_3)_2(1\text{-MeCyt})_2^{2+}$.

Another product in 5% yield was trans-$Pt(NH_3)_2(1\text{-MeCyt})_2^{2+}$ which is also of stereochemical interest. It is structurally related to trans-$Pt(NH_3)_2Cl_2$, but was thought at first to be prepared from cis-$Pt(NH_3)_2Cl_2$. It was later suggested that it results from impurities of trans-$Pt(NH_3)_2Cl_2$ in the starting material (< 5%). See Sect. 2.7.2, p. 155 for details of synthesis.

Analysis: Calcd. for $C_{10}H_{20}N_{10}O_8Pt$: C 19.9, H 3.4, N 23.2, Pt 32.3; Found: C 20.1, H 3.5, N 22.9, Pt 32.2.

Discussion

Crystal data and other numbers related to data collection and structure refinement are summarized in

Table 17. The atom parameters from the final refinement are listed in Table 18 and the corresponding moduli of F_o and F_c are listed in reference 179. Selected bond lengths and angles are given in Table 19 and the molecular cation, trans-$[Pt(NH_3)_2(C_5H_7N_3O)_2]^{2+}$ is illustrated in Figure 12. The structure is normal. The coordination about the platinum atom is square planar and constrained by the inversion centre.

Although the Pt-NH_3 distance appears slightly longer than the average of values found in other structures reported in Table 8, p. 56 (2.07(1) Å vs. 2.054(10) Å) and Pt-N(3) distance appears slightly shorter than average (2.023(8) Å vs. 2.038(15) Å), they are not significantly different from the average values. The angles around the platinum atom are normal. The dihedral angle between the pyrimidine rings and square plane of the four ligand atoms is 78.2°. This large angle means that O(2) is 3.36(1) Å from N(2), so if there is any intramolecular hydrogen bonding, it will be very weak. The 1-methylcytosine rings are planar (within the errors). Bond lengths and angles within the ring are discussed in Sect. 2.6, p. 149.

The packing of the title molecule within the crystal is shown in Figure 13. The cytosine rings of molecules at the origin are interleaved with those of molecules centred at 1/2,1/2,0. The nitrate ions are

TABLE 17

Compound	$C_{10}H_{20}N_{10}O_8Pt$
F.W.	603.42
Crystal size	Cylinder, r, 0.062 mm, l, 0.25 mm
Crystal colour	colourless
ρ_{calc}	2.24 g cm^{-3}
ρ_{obs}	2.22(2) g cm^{-3}
Systematic absences	0k0, k = 2n + 1 h0l, l = 2n + 1
Space group	$P2_1/c$ (No. 14)
Unit cell parameters	a = 6.834 (2) b = 10.315(2), β = 107.90(2) c = 13.349(3)
Volume	395.5(4)
Z	2
Crystal mount axis	roughly along a
Linear absorption coefficient	83 cm^{-1}
Transmission coefficient limits	2.26 to 2.29
Max 2θ; quadrant	45°, h, k, ± l
Standard reflections	(1) 3,3,-3 (2) 1,-2,-2
Overall e.s.d.	(1) 2.06% (2) 2.33%
Temperature	22°C
No. of independent reflections	1687
No. with $I > 3\sigma(I)$	1055
$3\sigma(I) > I > \sigma(I)$ where $F_c > F_o$	73
$3\sigma(I) > I > \sigma(I)$ where $F_c < F_o$	180
$I < \sigma(I)$, (rejected)	379

Continued.....

TABLE 17 (Continued)

Compound	$C_{10}H_{20}N_{10}O_8Pt$
Final R_1	0.0346
Final R_2	0.0410
Final shift in e.s.d. Max.	0.006
Ave.	0.0003
g (secondary extinction)	3.49×10^{-7}
Final difference map	
Highest peak; location	1.09 e/Å^3; 0.40, 0.05, 0.42
Lowest valley; location	-0.89 e/Å^3; 0.40, 0.40, 0.20
Weighting	$\frac{1}{\omega} = (9.947 - 0.232\|F_o\| + 0.00238\|F_o\|^2)$

TABLE 18

Atom parameters and temperature factors ($Å^2$) for trans-diamminedi(1-methylcytosine-N3)platinum(II) dinitrate ($\times 10^3$) *

	x	y	z	U
Pt	0.0	0.0	0.0	
N(2)	117(1)	27.3(8)	-123.4(6)	34(2)
N(1)	431(1)	273.2(7)	174.3(6)	25(2)
C(1)	649(2)	264(1)	238.6(8)	37(2)
C(2)	343(10)	162.1(9)	120.5(7)	27(2)
O(2)	443(1)	65.7(8)	120.7(6)	38(2)
N(3)	130(1)	168.6(8)	65.8(6)	26(3)
C(4)	25(1)	278.6(9)	64.3(7)	28(2)
N(4)	-181(1)	278(1)	12.4(7)	41(2)
C(5)	116(2)	392(1)	114.8(8)	36(2)
C(6)	325(2)	386(1)	173.4(8)	70(3)
N(10)	264(1)	144(1)	365.8(8)	43(2)
O(11)	89(2)	174(1)	318.5(8)	66(2)
O(12)	317(3)	30(2)	367(1)	133(6)
O(13)	386(1)	229(1)	414.1(8)	60(3)

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

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	25.0(3)	25.5(3)	22.4(3)	-7.5(3)	4.2(2)	-5.2(3)

* Estimated standard deviation from the least squares programs are given in parentheses.

TABLE 19

Selected interatomic distances (Å) and angles (deg.) for trans-diamminedi(cytosinato-N3)platinum(II) dinitrate

Atoms	Distance	Atoms	Distance	Atoms	Distance
Pt-N(2)	2.067(10)	Pt-N(3)	2.023(8)	N(1)-C(1)	1.48(1)
N(1)-C(2)	1.39(1)	C(2)-O(2)	1.21(1)	C(2)-N(3)	1.42(1)
N(3)-C(4)	1.34(1)	C(4)-N(4)	1.37(1)	C(4)-C(5)	1.40(1)
C(5)-C(6)	1.41(1)	C(6)-N(1)	1.37(1)	N(10)-O(11)	1.21(1)
N(10)-O(12)	1.22(2)	N(10)-O(13)	1.25(1)		

Possible hydrogen bond distances

N(2)-O(11)[a]	3.30(1)	N(2)-O(11)[b]	3.16(1)	N(2)-O(13)[b]	3.06(1)
N(2)-O(2)[c]	3.15(1)	N(4)-O(13)[c]	2.85(1)		

Atoms	Angle	Atoms	Angle	Atoms	Angle
N(2)-Pt-N(2)	180.0(4)	N(2)-Pt-N(3)	90.3(3)	N(2)-Pt-N(3)	89.7(3)
N(3)-Pt-N(3)	180.0(5)	Pt-N(3)-C(2)	115.4(6)	Pt-N(3)-C(4)	123.9(6)
C(1)-N(1)-C(2)	117.0(8)	C(1)-N(1)-C(6)	119.7(8)	C(6)-N(1)-C(2)	123.3(8)
N(1)-C(2)-O(2)	121.3(8)	N(1)-C(2)-N(3)	116.4(8)	O(2)-C(2)-N(3)	122.3(8)
C(2)-N(3)-C(4)	120.6(8)	N(3)-C(4)-N(4)	117.8(9)	N(3)-C(4)-C(5)	123.0(8)
N(4)-C(4)-C(5)	119.2(9)	C(4)-C(5)-C(6)	117.(1)	C(5)-C(6)-N(1)	119.6(9)

Possible hydrogen bond angles.

Pt-N(2)-O(11)[a]	111.8(4)	N(10)[a]-O(11)[a]-N(2)	111.2(8)	Pt-N(2)-O(11)[b]	108.7(4)
N(10)[b]-O(11)[b]-N(2)	98.7(7)	Pt-N(2)-O(13)[b]	110.1(4)	N(10)[b]-O(13)[b]-N(2)	102.8(7)
Pt-N(2)-O(2)[c]	123.7(3)	C(2)[c]-O(2)[c]	142.4(7)	C(4)-N(4)-O(13)[d]	176.9(8)
N(10)[d]-O(13)[d]-N(4)	130.8(8)	O(11)[a]-N(2)-O(11)[b]	116.0(4)	O(11)[a]-N(2)-O(13)[b]	137.4(4)
O(11)[a]-N(2)-O(2)	89.6(3)	O(11)[b]-N(2)-O(13)[b]	39.8(3)	O(11)-N(2)-O(2)	106.5(4)
O(13)[b]-N(2)-O(2)	73.8(3)				

a. Atoms are related to those given in Table 18 by a, -x, -y, -z; b, x, ½ - y, z - ½; c, 1 - x, -y, -z; d, x - 1, ½ - y, z - ½.

TABLE 20

Least squares planes and dihedral angles between planes for trans-diammminedi(1-methylcytosine-N3)platinum(II) dinitrate

Plane	Atoms	Distance from best plane (Å)
1	N(1)C(2)N(3)C(4)C(5)C(6)C(1)* O(2)*N(4)*Pt*	N(1),-0.01; C(2),0.02; N(3), -0.01; C(4),-0.01; C(5), 0.02; C(6),-0.01; C(1),-0.10; O(2),0.07; N(4),-0.10; Pt,-016.
2	$N(2)N(2)^{1}PtN(3)N(3)^{1}$	-

Dihedral angle for planes 1 and 2 is 78.2°.

Errors in atom positions about 0.01 Å. Rms deviation for Plane 1 is 0.015 Å.

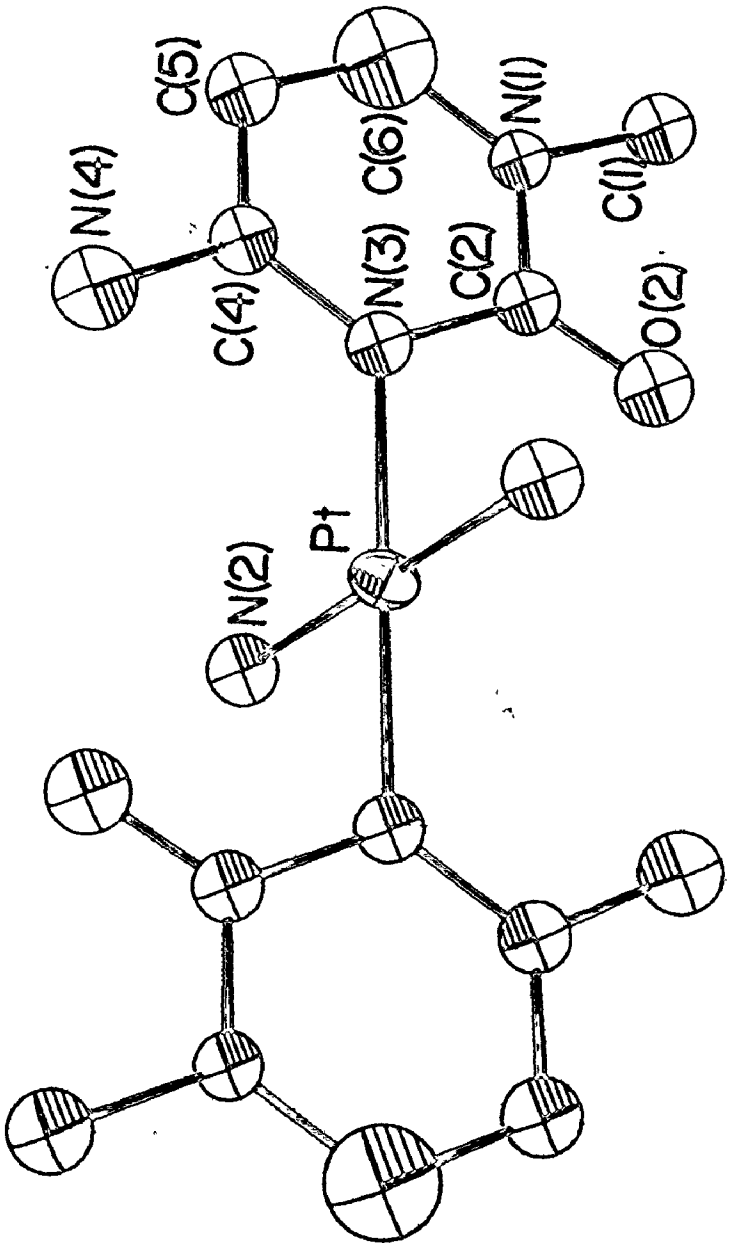


Figure 12

The molecular cation <u>trans</u>-$[Pt(NH_3)_2(C_5H_7N_3O)_2]^+$ showing the atom numbering.

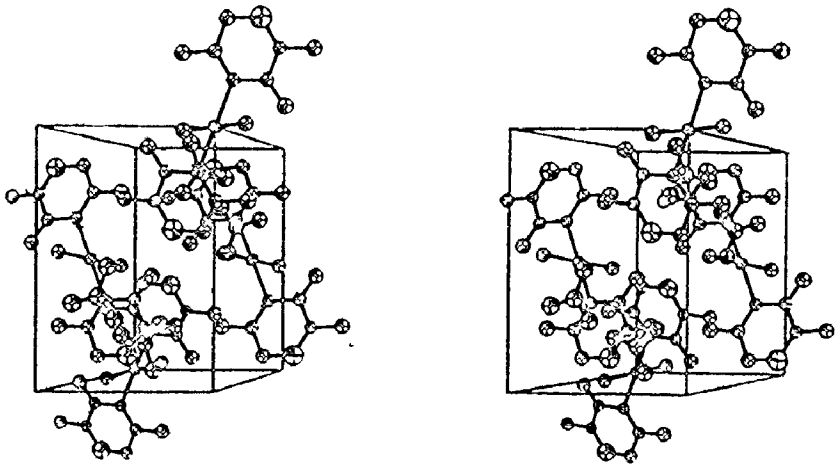


Figure 13

The unit cell contents of <u>trans</u>-$[Pt(NH_3)_2(C_5H_7N_3O)_2](NO_3)_2$. $\underset{\sim}{b}$ and $\underset{\sim}{c}$ are parallel to the side and bottom of the page, respectively. The view is down $\underset{\sim}{a}^*$.

intercalated between adjacent cytosine rings in the $\underset{\sim}{a}$ direction, giving cytosine-nitrate-cytosine-nitrate stacks at roughly y = 1/4, z = 1/4 and y = -1/4, z = -1/4. This maximizes the π-π interactions between the nitrate ions and the pyrimidine rings. Because of the large dihedral angle between the cytosine ring and the ligand atom square plane, the ammonia groups bound to the platinum atom are in a position to hydrogen bond to the nitrate groups above and below the cytosine ring. This results in hydrogen bonding up the $\underset{\sim}{a}$ direction along the stacks and also results in cross bonding in the $\underset{\sim}{b}$ direction. In the $\underset{\sim}{c}$ direction, there are two types of hydrogen bonding: between N(4) of cytosine and O(13) of a nitrate ion; and, between N(2) bound to platinum and O(2) of cytosine in the nearest centrosymmetrically related molecule along $\underset{\sim}{c}$.

2.3.4 Discussion

Cramer and Dahlstrom[58] have discussed the mode of anticancer activity of cis-$Pt(NH_3)_2Cl_2$ in light of the model compound cis-$[Pt(NH_3)_2(Guo\text{-}N7)_2]^{2+}$ (formed when cis-$Pt(NH_3)_2Cl_2$ was reacted with Guo in 2:1 ratio). They suggested that a severe distortion would be caused in DNA by cis-$Pt(NH_3)_2Cl_2$ binding at adjacent guanine molecules. This results, in part, from the short Pt-N(7) bond lengths (as compared to Pt-Cl) and also because of the large dihedral angle (about 70-75° as compared to 0° in DNA) required by cis

binding at platinum. A similar large distortion caused by the large dihedral angle would also result in DNA if a platinum complex bound to N(7) of guanine and N(3) of cytosine as in cis-$[Pt(NH_3)_2(1\text{-MeCyt-N3})(9\text{-EtGua-N7})]^{2+}$. Such binding, however, is unlikely to occur. The N(7) site of guanine is an exposed site in DNA. Hence, platinum complexes would probably bind here first. For a platinum complex to bind to N(3) of an adjacent cytosine in the same DNA strand, the whole Pt-guanine moiety would have to rotate about the guanine-ribose C-N bond. This is unlikely to occur because other bases are stacked above and below the guanine molecule hindering its rotation. The trans compound can obviously not intrastrand crosslink and only binds monofunctionally at each strand.

With respect to interstrand crosslinking, the cis compound (again because of the large dihedral angles) when crosslinked to the complementary base or to another base on the complementary DNA strand, would cause marked disruption in the hydrogen bonding above and below the site of the crosslink. The trans compound, because of the large bite distance (the N(3)-N(3)' distance is 4.05 Å) will probably not crosslink complementary base pairs (average N-N and N-O distances of hydrogen bonded G-C and A-T pairs is 2.87(4) Å). Trans-$Pt(NH_3)_2Cl_2$ can crosslink bases (on complementary strands) which are separated from each other. This will again cause a marked disruption in hydrogen bonding above and below the crosslink.

2.4 CHARACTERIZATION OF STARTING MATERIALS

2.4.1 Introduction

In preparing mixed base compounds such as $[Pt(NH_3)_2$-(9-ethylguanine)(1-methylcytosine)$](ClO_4)_2$ described in Sect. 2.3.2, it was necessary to synthesize first a monobase compound $[(H_3N)_2PtCl(1\text{-MeCyt})]NO_3$. Crystallographic characterization of this starting material was undertaken and an interesting variation in packing showed up. The compound exists in two different crystal forms with different space groups.

2.4.2 The Crystal and Molecular Structure of chloro-cis-diammine(1-methylcytosine-N3)platinum(II) nitrate[109]

Preparation (by B. Lippert)

A Space group $P2_1/c$

Cis-$[PtCl(NH_3)_2(C_5H_7N_3O)]Cl\cdot H_2O$, which was prepared by reacting equimolar amounts of cis-$Pt(NH_3)_2Cl_2$ and 1-methylcytosine in water (0.39 g, 10 mL), was reacted with one equivalent of $AgNO_3$ (0.12 g, 10 mL) and AgCl was filtered off. The title compound crystallized as $P2_1/c$ (yield 95%) from solution at 22°C. Crystals suitable for crystallographic work were prepared by recrystallization from H_2O at 22°C.

Analysis: Calcd. for $C_5H_{13}ClN_6O_4Pt$: C 13.20, H 2.91, N 18.61, Pt 43.18, O 14.17; Found: C 13.44, H 3.02, N 18.67, Pt 43.63, O 14.89.

B Space group C2/c

Cis-$Pt(NH_3)_2Cl_2$ (0.5 g) was reacted with one equi-

valent of $AgNO_3$ in water (0.28 g, 10 mL) and AgCl was filtered off. One equivalent of 1-methylcytosine in water (0.21 g, 10 mL) was added. After 24 h at 45°C, the reaction mixture was concentrated to a small volume (~ 5 mL) by evaporation and cooled to 0°C. A precipitate of the title compound, C2/c, formed as the main product within 12 days. Cis-$Pt(NH_3)_2Cl_2$ was removed by treating the precipitate with dimethylformamide (3 x 10 mL). When the C2/c product is recrystallized from hot H_2O, the main product is $P2_1/c$ with C2/c as a minor product. Crystals were separated by hand.

Analysis: Calcd. for $C_5H_{13}ClN_6O_4Pt$: C 13.3, H 2.9, N 18.6, Pt 43.2; Found: C 13.4, H 2.9, N 18.0, Pt 43.1.

Solution of the Structure

Precession photographs of zero and first layers for compound B showed that the crystal was monoclinic with systematic absences hkl, h + k = 2n + 1, h0l, l = 2n + 1 suggesting either space group Cc (No. 9) or C2/c (No. 15). The latter was assumed and confirmed by the successful refinement of the structure.

Discussion

Crystal data and other numbers related to data collection and structure refinement are summarized in Tables 21A and 21B. The atom parameters from the final refinement are listed in Tables 22A and 22B and the corresponding moduli of F_o and F_c are listed in reference

TABLE 21A

Compound	$C_5H_{13}ClN_6O_4Pt$
F.W.	451.74
Crystal size	Cylinder, r, 0.075 mm, l, 0.40 mm
Crystal colour	colourless
ρ_{calc}	2.45 g cm^{-3}
ρ_{obs}	2.47(2) g cm^{-3}
Systematic absences	0k0, k = 2n + 1 h0l, l = 2n + 1
Space group	$P2_1/c$ (No. 14)
Unit cell parameters	a = 8.143(2) Å b = 6.899(1) Å, β = 91.27(2)° c = 21.434(3) Å
Volume	1222.2(9) $Å^3$
Z	4
Crystal mount axis	roughly along a
Linear absorption coefficient	123.0 cm^{-1}
Transmission coefficient limits	4.03-4.33
Max 2θ; quadrant	55°, h, k, ± l
Standrad reflections	(1) 1, 0, 6 (2) 2, -1, 6
Overall e.s.d.	(1) 1.16% (2) 1.12%
Temperature	22°C
No. of independent reflections	3018
No. with $I > 3\sigma(I)$	2168
$3\sigma(I) > I > \sigma(I)$ where $F_c > F_o$	135
$3\sigma(I) > I > \sigma(I)$ where $F_c < F_o$	187
$I < \sigma(I)$, (rejected)	528

Continued.....

TABLE 21A (Continued)

Compound	$C_5H_{13}ClN_6O_4Pt$
Final R_1	0.0349
Final R_2	0.0396
Final shift in e.s.d. Max.	0.035
Avg.	0.006
g (secondary extinction)	2.23×10^{-7}
Final difference map	
Highest peak; location	1.35 e/Å^3; 0.40,-0.08, 0.16
Lowest valley; location	-1.11 e/Å^3; 0.20, 0.10, 0.31
Weighting	$\frac{1}{\omega} = (10.7-0.154\|F_o\| + 0.00105\|F_o\|^2)$

TABLE 2)B

Compound	$C_5H_{13}ClN_6O_4Pt$
F.W.	451.74
Crystal size	Polyhedron with faces: {010}, 0.10 mm apart; 110 and $\bar{1}\bar{1}0$, 0.11 mm apart, $1\bar{1}0$ and $\bar{1}10$, 0.10 mm apart
Crystal colour	colourless
ρ_{calc}	2.45 g cm^{-3}
ρ_{obs}	2.47(2) g cm^{-3}
Systematic absences	hkl, h + k = 2n + 1 h0l, l = 2n + 1
Space group	C2/c (No. 15)
Unit cell parameters	a = 13.155(6) Å b = 9.754(5) Å, β = 99.70(3)° c = 19.097(7) Å
Volume	2415(2)
Z	8
Crystal mount axis	roughly along c
Linear absorption coefficient	123.0 cm^{-1}
Transmission coefficient limits	1.93-3.96
Max 2θ; quadrant	45°; h, k, ± l
Standard reflections	(1) 3,1,7 (2) 0,0,6 (3) 2,0,4
Overall e.s.d.	(1) 1.96% (2) 1.93% (3) 2.08%
Temperature	22°C
No. of independent reflections	1700
No. with $I > 3\sigma(I)$	1344
$3\sigma(I) > I > \sigma(I)$ where $F_c > F_o$	61
$3\sigma(I) > I > \sigma(I)$ where $F_c < F_o$	81
$I < \sigma(I)$, rejected	214

Continued.....

TABLE 21B (Continued)

Compound	$C_5H_{13}ClN_6O_4Pt$
Final R_1	0.0467
Final R_2	0.057
Final shift in e.s.d. Max.	0.057
Ave.	0.006
g (secondary extinction)	7.32×10^{-8}
Final difference map	
Highest peak; location	1.47 e/Å^3; 0.20, 0.30, 0.26
Lowest valley; location	-1.85 e/Å^3; 0.15, 0.12, 0.27
Weighting	$\frac{1}{w} = (34.6-0.293\|F_o\| + 0.00339\|F_o\|^2)$

TABLE 22A

Atom parameters and temperature factors ($Å^2$) for chloro-cis-diammine(1-methylcytosine-N3)platinum(II) nitrate

Space group: $P2_1/c$ ($\times 10^3$) *

	x	y	z	U
Pt	182.07(3)	230.01(4)	315.68(1)	
Cl	286.6(3)	-75.8(3)	331.9(1)	
N(7)	336.2(9)	267(1)	242.5(3)	37(1)
N(8)	81(1)	502(1)	299.8(4)	44(2)
N(1)	-213.7(9)	114(1)	434.6(3)	38(2)
C(1)	-379(1)	35(1)	426.1(5)	51(2)
C(2)	-112(1)	121(1)	384.4(4)	33(2)
O(2)	-160.2(8)	57(1)	332.8(3)	45(1)
N(3)	39.6(8)	203.0(9)	391.4(3)	30(1)
C(4)	94(1)	267(1)	447.8(4)	34(2)
N(4)	243(1)	344(1)	452.8(4)	43(2)
C(5)	- 9(1)	258(1)	499.8(4)	41(2)
C(6)	-161(1)	181(1)	491.5(4)	42(2)
N(9)	364.2(9)	11(1)	112.1(4)	41(2)
O(10)	422(1)	12(1)	59.3(4)	63(2)
O(11)	221(1)	68(1)	119.0(4)	60(2)
O(12)	452(1)	-42(1)	156.6(4)	72(2)

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

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	25.8(1)	30.2(2)	27.2(2)	-2.3(1)	-1.08(9)	-1.9(1)
Cl	47(1)	34(1)	64(1)	-6.0(9)	1(1)	1(1)

* Estimated standard deviation from the least squares programs are given in parentheses.

TABLE 22B

Atom parameters and temperature factors ($\AA^2$) for chloro-*cis*-diammine(1-methylcytosine-N3)platinum(II) nitrate

Space group: C2/c ($\times 10^3$) *

	x	y	z	U
Pt	141.85(4)	226.08(5)	266.48(2)	
Cl	150.9(3)	442.5(4)	314.8(2)	
N(7)	82.6(9)	312(1)	171.0(6)	39(3)
N(8)	124.4(8)	34(1)	222.4(6)	37(3)
N(1)	203.0(9)	55(1)	473.6(6)	45(3)
C(1)	139(1)	0.0(2)	523.4(9)	61(5)
C(2)	152(1)	100(1)	408.4(7)	35(3)
O(2)	59.1(7)	98(1)	394.6(5)	46(2)
N(3)	213.2(8)	146(1)	361.9(6)	36(3)
C(4)	316(1)	150(1)	377.3(7)	36(3)
N(4)	371.7(9)	193(1)	330.1(6)	43(3)
C(5)	366(1)	104(2)	445.3(8)	46(4)
C(6)	307(1)	57(2)	491.5(9)	55(4)
N(9)	636(1)	266(1)	371.7(8)	49(3)
O(11)	592(1)	303(2)	315(1)	68(3)
O(10)	386(1)	212(1)	411.4(7)	104(5)
O(12)	729(2)	284(2)	389(1)	112(6)

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

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	32.8(4)	34.8(5)	24.5(4)	-0.5(2)	6.3(2)	2.9(2)
Cl	55(2)	39(2)	49(2)	-6(2)	7(2)	-1(2)

* Estimated standard deviations from the least squares programs are given in parentheses.

179. The cation of the $P2_1/c$ structure, cis-$[PtCl(NH_3)_2(C_5H_7N_3O)]^+$, is illustrated in Fig. 14 and selected interatomic distances and angles are given in Table 23. The two molecular cations are very similar and only the angles Cl-Pt-N(8), N(8)-Pt-N(3) and Cl-Pt-N(7), differ by more than 3σ ($\sigma = (\sigma_1^2 + \sigma_2^2)^{1/2}$). The plane of the cytosine ring is almost at 90° to the square plane of the ligand ($P2_1/c$, 88°, C2/c, 84°) and there is no intramolecular hydrogen bonding between O(2) or N(4) with the cis, N(8), ammonia group. Such an interaction was observed for similar complexes of thymine and uracil[110] and for N(4) with Cl in trans-$PtCl_2(NH_3)$(1-methylcytosine) as discussed in Sect. 2.5.2. The two ammonia molecules, N(3) of 1-methylcytosine and the chlorine atom form a rough square plane around the platinum atom although there is a slight distortion towards a tetrahedral arrangement. In both structures, N(7) and N(3) lie slightly above the best plane through the four atoms while N(8) and Cl lie slightly below the plane. The platinum atom lies in the best plane through the other four atoms (see Table 24). The bond lengths and angles around the platinum atom are normal (see Table 8, p. 56, for comparison of bond lengths), and agree well with values found in other similar compounds reported in this work. The 1-methylcytosine rings are planar (within the errors). Bond lengths and angles within the ring are discussed in Sect. 2.6, p. 149.

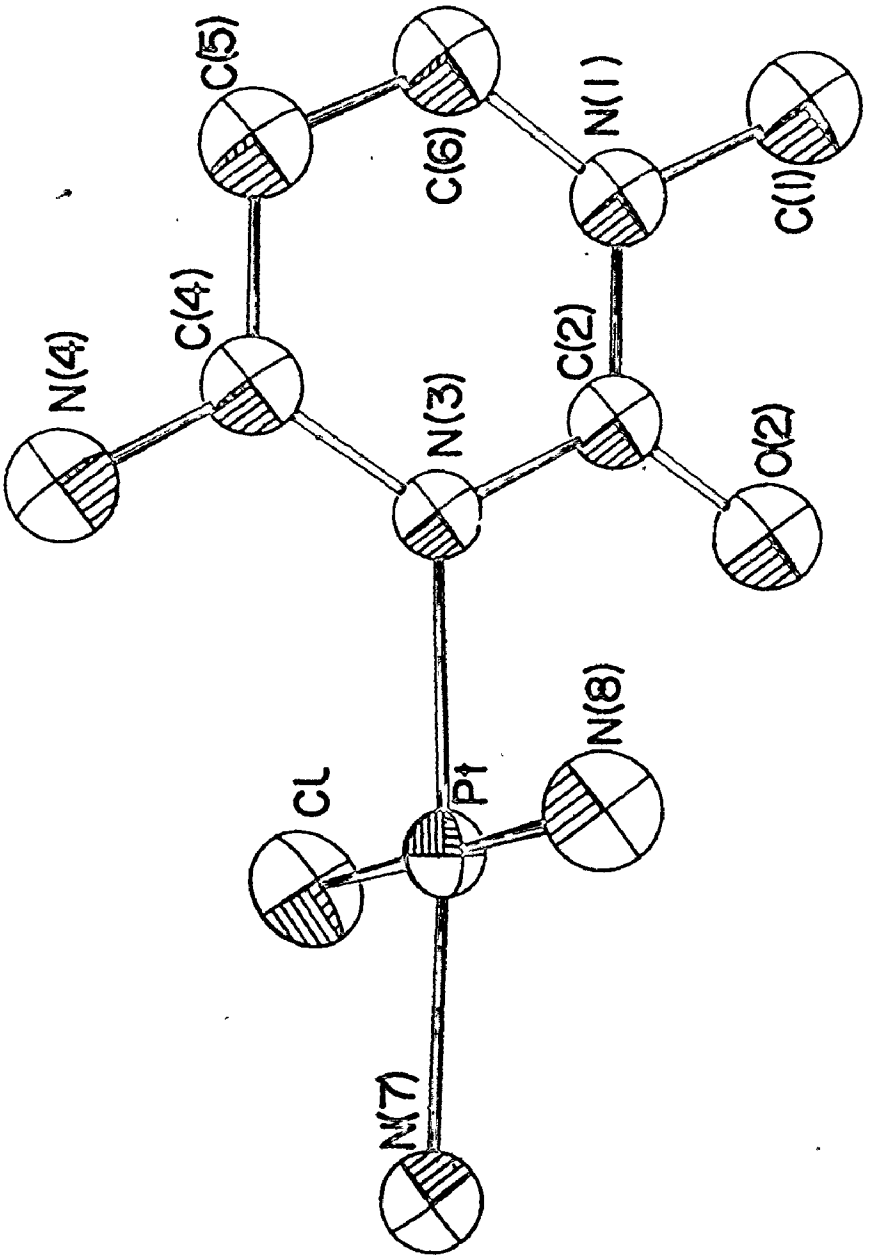


Figure 14

The molecular cation cis-$[PtCl(NH_3)_2(C_5H_7N_3O)]^+$ ($P2_1/c$ structure) showing the atom numbering.

TABLE 23

Selected interatomic distance (Å) and angles (deg.) for chloro-cis-diammine(1-methylcytosine-N3)platinum(II) nitrate $P2_1/c$, A, C2/c, B.

Atoms	Distance A	Distance B	Atoms	Distance A	Distance B	Atoms	Distance A	Distance B
Pt-Cl	2.299(2)	2.300(4)	Pt-N(7)	2.047(7)	2.04(1)	Pt-N(8)	2.053(8)	2.05(1)
Pt-N(3)	2.026(6)	2.06(1)	N(1)-C(1)	1.46(1)	1.48(2)	N(1)-C(2)	1.37(1)	1.38(2)
C(2)-O(2)	1.24(1)	1.21(2)	C(2)-N(3)	1.37(1)	1.37(1)	N(3)-C(4)	1.35(1)	1.33(2)
C(4)-N(4)	1.33(1)	1.32(2)	C(4)-C(5)	1.41(1)	1.43(2)	C(5)-C(6)	1.35(1)	1.35(2)
C(6)-N(1)	1.36(1)	1.36(2)	N(9)-O(10)	1.24(1)	1.20(2)	N(9)-O(11)	1.24(1)	1.21(2)
N(9)-O(12)	1.24(1)	1.22(2)	O(10)-O(10)	2.87(1)	3.15(2)	N(8)-O(2)	2.96(1)	3.07(1)

Possible hydrogen bond distances

N(8)-Cl[a]	3.44(1)	N(7)-O(11)	3.11(1)	N(7)-O(12)	2.98(1)	
N(7)-O(2)[b]	2.93(1)	N(7)-O(12)[c]	3.04(1)	N(8)-O(11)[b]	3.08(1)	
N(4)-O(10)[d]	2.86(1)	N(4)-O(10)[c]	2.98(1)			
B N(8)-Cl[e]	3.28(1)	N(7)-Cl[f]	3.38(1)	N(7)-O(2)[f]	2.93(2)	
N(8)-O(10)[g]	2.93(2)	N(4)-O(10)[h]	3.08(2)	N(4)-O(11)	2.99(2)	
N(4)-O(10)	3.15(2)	N(7)-O(12)[h]	2.91(3)			

Atoms	Angle A	Angle B	Atoms	Angle A	Angle B	Atoms	Angle A	Angle B
Cl-Pt-N(7)	89.9(2)	88.2(4)	Cl-Pt-N(8)	177.8(2)	176.6(3)	Cl-Pt-N(3)	90.6(2)	90.3(3)
N(7)-Pt-N(8)	90.7(3)	90.5(5)	N(7)-Pt-N(3)	176.4(3)	175.2(4)	N(8)-Pt-N(3)	88.9(3)	91.2(4)
Pt-N(3)-C(12)	118.8(5)	118.1(8)	Pt-N(3)-C(4)	120.2(5)	118.7(9)	C(1)-N(1)-C(2)	119.0(7)	117(1)
C(1)-N(1)-C(6)	120.7(8)	120(1)	C(6)-N(1)-C(2)	120.3(7)	122(1)	N(1)-C(2)-O(2)	120.1(7)	120(1)
N(1)-C(2)-N(3)	119.1(7)	116(1)	O(2)-C(2)-N(3)	120.8(8)	123(1)	C(2)-N(3)-C(4)	121.0(7)	123(1)
N(3)-C(4)-N(4)	119.1(7)	121(1)	N(3)-C(4)-C(5)	119.9(7)	119(1)	N(4)-C(4)-C(5)	121.0(8)	119(1)
C(4)-C(5)-C(6)	118.2(8)	118(1)	O(10)-N(9)-O(11)	119.1(8)	118(1)	O(11)-N(9)-O(12)	121.9(9)	121(2)
O(10)-N(9)-O(12)	118.9(8)	121(2)	Pt-N(8)-O(2)	100.8(3)	97.5(4)	C(2)-O(2)-N(8)	146.2(6)	144(1)

(cont'd)

TABLE 23 (cont'd)

Possible hydrogen bond angles

A	Pt^{a}-Cl^{a}-N(8)	125.1(2)	Pt-N(8)-Cl^{a}	122.9(3)	Pt-N(7)-O(11)	114.8(3)
	N(9)-O(11)-N(7)	88.6(6)	Pt-N(7)-O(12)	126.2(4)	N(9)-O(12)-O(7)	94.5(6)
	Pt-N(7)-$O(2)^{b}$	102.0(3)	$C(2)^{b}$-$O(2)^{b}$-N(7)	150.7(6)	Pt-N(7)-$O(12)^{c}$	81.8(3)
	$N(9)^{c}$-$O(12)^{c}$-N(7)	171.6(7)	Pt-N(8)-$O(11)^{b}$	111.7(4)	$N(9)^{b}$-$O(11)^{b}$-N(8)	141.3(6)
	C(4)-N(4)-$O(10)^{d}$	130.8(6)	$N(9)^{d}$-$O(10)^{d}$-N(4)	122.3(6)	C(4)-N(4)-$O(10)^{c}$	170.3(6)
	$N(9)^{c}$-$O(10)^{c}$-N(4)	116.5(6)	$O(10)^{c}$-N(4)-$O(10)^{d}$	58.9(3)	$N(4)^{i}$-O(10)-$N(4)^{j}$	121.1(4)
	O(11)-N(7)-O(12)	41.6(3)	O(11)-N(7)-$O(2)^{b}$	72.4(3)	O(11)-N(7)-$O(12)^{c}$	162.5(4)
	O(12)-N(7)-$O(2)^{b}$	107.9(3)	O(12)-N(7)-$O(12)^{c}$	124.5(3)	$O(2)^{b}$-N(7)-$O(12)^{c}$	111.1(3)
	O(2)-N(8)-$O(11)^{b}$	135.7(3)	N(7)-O(12)-$N(7)^{j}$	93.0(3)	O(2)-N(8)-Cl^{a}	87.6(2)
	$O(11)^{b}$-N(8)-Cl^{a}	98.3(3)	N(7)-O(11)-$N(8)^{k}$	79.4(3)		
B	Pt-N(8)-Cl^{e}	107.1(4)	Pt^{e}-Cl^{e}-N(8)	98.6(2)	Pt-N(7)-Cl^{f}	85.9(3)
	Pt^{f}-Cl^{f}-N(7)	72.5(2)	Pt-N(7)-$O(2)^{f}$	102.2(5)	$C(2)^{f}$-$O(2)^{f}$-N(7)	129(1)
	Pt-N(8)-$O(10)^{g}$	118.2(6)	$N(9)^{g}$-$O(10)^{g}$-N(8)	138(1)	C(4)-N(4)-$O(10)^{h}$	155.7(9)
	$N(9)^{h}$-$O(10)^{h}$-N(4)	97(1)	C(4)-N(4)-O(11)	104.4(8)	N(9)-O(11)-N(4)	106(1)
	C(4)-N(4)-O(10)	142.8(9)	N(9)-O(10)-N(4)	126(1)	$O(10)^{h}$-N(4)-O(11)	99.8(6)
	$O(10)^{h}$-N(4)-O(10)	60.8(5)	O(11)-N(14)-O(10)	39.2(5)	N(4)-O(10)-$N(4)^{h}$	104.5(6)
	Pt-N(7)-$O(12)^{h}$	95.3(6)	$N(9)^{h}$-$O(12)^{h}$-N(7)	142(4)	Cl^{e}-N(8)-O(2)	121.7(4)
	Cl^{e}-N(8)-$O(10)^{g}$	98.6(5)	O(2)-N(8)-$O(10)^{g}$	114.8(5)	Cl^{f}-N(7)-$O(2)^{f}$	77.3(3)
	Cl^{f}-N(7)-$O(12)^{h}$	155.7(6)	$O(2)^{f}$-N(7)-$O(12)^{h}$	106.7(6)	$N(7)^{f}$-Cl-$N(8)^{e}$	170.1(3)

a. Atoms are related to those given in Tables 22A and 22B by

a, x, 1 + y, z; b, -x, ½ + y, ½ - z; c, 1 - x, ½ + y, ½ - z; d, x, ½ - y, ½ + z; e, ½ - x, ½ + y, ½ - z; f, -x, y, ½ - z; g, x - ½, y - ½, z; h, 1 - x, y, ½ - z; i, x, ½ - y, z - ½; j, 1 - x, y - ½, ½ - z; k, -x, y - ½, ½ - z.

TABLE 24

Least squares planes through part of the molecules chloro-cis-diammine (1-methylcytosine-N3)platinum(II) nitrate, $P2_1/c$ and C2/c

Plane	Atoms in Plane	Distance of atom from plane (Å)
$P2_1/c$		
1	N(1)C(2)N(3)C(4)C(5)C(6)C(1)* O(2)*N(4)*Pt*	N(1)0.01;C(2)-0.02;N(3)0.02;C(4)-0.01; C(5)0.00;C(6)0.00;C(1)0.04;O(2)-0.04; N(4)0.01;Pt 0.12.
2	N(7)N(8)N(3)Cl Pt*	N(7)0.05;N(8)-0.05;N(3)0.05;Cl -0.05; Pt -0.01.
3	O(10)9(11)O(12)N(9)*	N(9)-0.01.
4	1**	
5	2**	
6	3**	
C2/c		
7	N(1)C(2)N(3)C(4)C(5)C(6)C(1)* O(2)*N(4)*Pt*	N(1)0.00;C(2)0.00;N(3)0.00;C(4)0.00; C(5)0.00;C(6)0.00;C(1)-0.05;O(2)0.02; N(4)-0.03;Pt 0.13.
8	N(7)N(8)N(3)Cl Pt*	N(7)0.07;N(8)-0.71;N(3)0.07;Cl-0.07; Pt -0.01.
9	O(10)O(11)O(12)N(9)*	N(9)0.00.
10	7***	
11	8***	
12	9***	

Interplanar angles

1-2,4-5	88.1°	2-5	46.2°	7-11,8-10	73.3°
1-3,4-6	45.6°	2-6,3-5	86.5°	7-12,9-10	48.9°
1-4	50.5°	3-6	41.0°	8-9,11-12	76.3°
1-5,2-4	42.0°	7-8,10-11	84.0°	8-11	11.4°
1-6,3-4	5.9°	7-9,10-12	7.8°	8-12,9-11	65.5°
2-3,5-6	47.6°	7-10	76.3°	9-12	53.9°

Errors in atom positions; for $P2_1/c$,0.01Å; for C2/c,0.02A.

Rms deviation for Plane 1, 0.012Å; Plane 2, 0.058Å; Plane 7, 0.0; Plane 8, 0.081.

The packing of the $P2_1/c$ structure is shown in Fig. 15. The structure contains a large, essentially planar, basic unit made up of two nitrate ions and the cytosine rings of two cations. These units are held together by hydrogen bonding in the $\underset{\sim}{a}$ direction from N(4)-H of the cytosines to O(10) of the nitrate ions. The units are centred about the z = 0 and z = 1/2 planes and are canted with respect to each other. The nitrate ions of one unit lie above and below the cytosine rings on the adjacent units. In the $\underset{\sim}{b}$ direction, the only interaction between units (aside from van der Waals forces) is a hydrogen bond between N(7) of the ammonia group and O(11) of the nitrate ion. There are extensive hydrogen bonding interactions in both the $\underset{\sim}{c}$ and $\underset{\sim}{b}$ directions (at z = 1/4 and 3/4) between the adjacent units. The network of hydrogen bonding is the result of interactions between N(8)-Cl, N(8)-O(11), N(7)-O(2) and N(7)-O(12).

The packing in the C2/c structure is shown in Figure 16. The basic unit of the two nitrate ions hydrogen bonded to the cytosine rings of two cations by N(4)-H...O(10) hydrogen bonds (which was identified in the $P2_1/c$ cell) exists in the C2/c structure. It is no longer planar, but is bent about the nitrate-nitrate axis. The dihedral angle between the two cytosine rings is 76.3°. Because of the bonding and resultant variations in packing, at z = 0 and 1/2, the cytosine rings of adjacent units are now interleaved so that

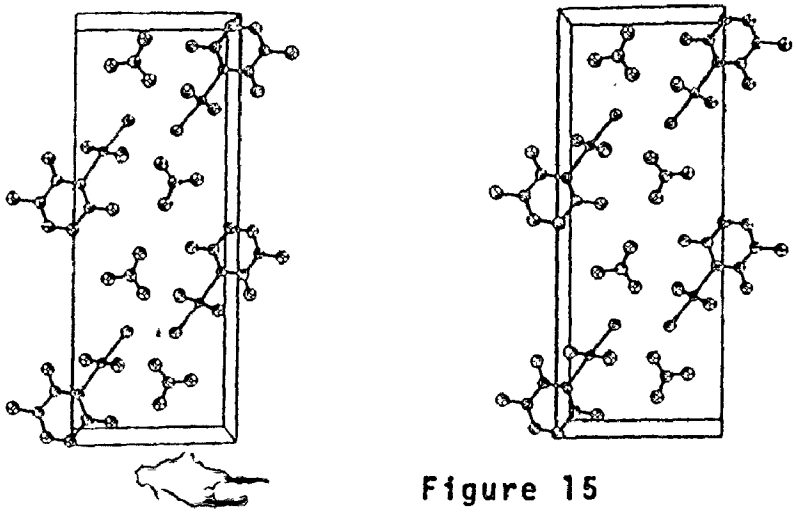


Figure 15

The unit cell contents of cis-$[PtCl(NH_3)_2(C_5H_7N_3O)]NO_3$, $P2_1/c$. $\underset{\sim}{a}$ and $\underset{\sim}{c}$ are parallel to the bottom and side of the page, respectively. The view is down $\underset{\sim}{b}^*$.

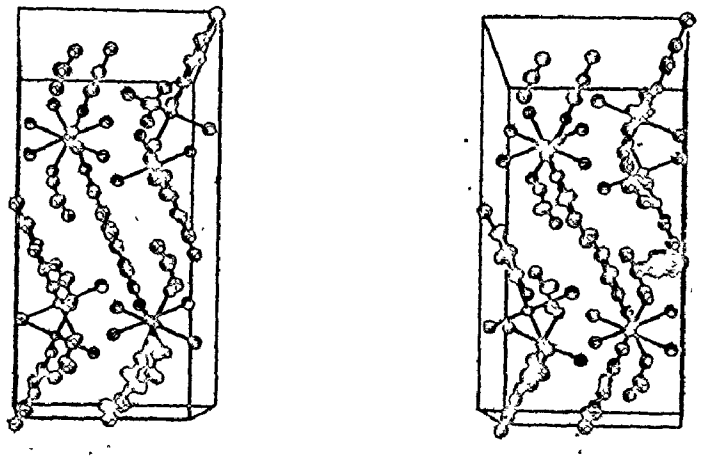


Figure 16

The unit cell contents of cis-$[PtCl(NH_3)_2(C_5H_7N_3O)]NO_3$, $C2/c$. $\underset{\sim}{b}$ and $\underset{\sim}{c}$ are parallel to the bottom and side of the page, respectively. The view is down $\underset{\sim}{a}^*$.

π-π interactions are maximized in the $\underset{\sim}{b}$ direction. Also as a result of the bonding, the units are held together in the $\underset{\sim}{a}$ direction by N(7)-Cl and N(7)-O(2) hydrogen bonding at z = 1/4 and 3/4. As well, since the PtX_4 planes come into close contact, there is N(8)-Cl hydrogen bonding in the $\underset{\sim}{b}$ direction.

2.5 PROBLEMS WITH ISOMERIZATION

2.5.1 Introduction

When cis-$Pt(NH_3)_2Cl_2$ was reacted with an equimolar amount of 1-methylcytosine in aqueous solution, 25°C, trans-$PtCl_2(NH_3)$(1-methylcytosine-N3) precipitated in low (1-2%) yield. This compound was first characterized by Roos et al. in a mass spectroscopic study.[56] They observed formation of this compound (trans-$Pt(NH_3)_2Cl_2$ can be prepared by heating of $[Pt(NH_3)_3Cl]Cl$ to 200°C) only at 250-300°C and implied that they did not expect this reaction to occur at room temperature in aqueous solution. The solution studies reported here show otherwise.

2.5.2 The Crystal and Molecular Structure of trans-dichloro-ammine(1-methylcytosine-N3)platinum(II) hemihydrate[108]

Preparation (by B. Lippert)

The title compound was produced in very low yields (1-2%) when cis-$[(NH_3)_2Pt(1\text{-Mecytosine-N3})Cl]Cl\cdot H_2O$ was prepared by reacting equimolar amounts of cis-$Pt(NH_3)_2Cl_2$ and 1-methylcytosine in aqueous solution at 25°C. It also precipitates (as yellow crystals) at room temperature (22°C) and elevated temperature (50°C) when attempts are made to recrystallize cis-$[(NH_3)_2Pt(1\text{-Mecytosine-N3})Cl]Cl\cdot H_2O$ (colourless) from aqueous saline and acidic solutions: 160 mg of cis-$[PtCl(NH_3)_2(C_5H_7N_3O)]Cl\cdot 1H_2O$ and 200 mg NaCl were dissolved in 5 mL H_2O at 40°C and then kept at room

temperature in an open flask (pH = 5.25). Within 4-6 days well shaped columns of the yellow title compound had formed, pH 5.5. The crystals were filtered, washed with some water and dried in air (first crop 15 mg). The solution was kept at 5 mL volume and every five days, the precipitate was filtered off. After three weeks, a total of 36 mg had been collected (24% yield). The pH of the yellow solution at that time was 7.3. Recrystallization was from water. In an analogous procedure a few drops of 0.2 N HCl were added instead of NaCl (pH = 2.0) and the solution kept at 5 mL volume. Yellow crystals of the title compound were collected every few days. Yield within three weeks was 31%. pH at that time was 2.05. Recrystallization was from water. Analysis: Calcd. for $C_5H_{11}Cl_2N_4O_{15}Pt$: C 14.3, H 2.6, N 13.3, Pt 46.4; Found: C 14.5, H 2.9, N 13.2, Pt 47.4.

Solution of the structure

Precession photographs of zero and first layers showed that the crystal was monoclinic with systematic absences hkl, h + k = 2n + 1, h0l, l = 2n + 1 suggesting either space group Cc (No. 9) or C2/c (No. 15). The latter was assumed and confirmed by the successful refinement of the structure.

Discussion

Crystal data and other numbers related to data collection and structure refinement are summarized in Table 25. The atom parameters from the final refinement

TABLE 25

Compound	$C_5H_{11}Cl_2N_4O_{15}Pt$
F.W.	417.17
Crystal size	Cylinder, r, 0.083 mm, l, 0.40 mm
Crystal colour	pale yellow
ρ_{calc}	2.57 g cm^{-3}
ρ_{obs}	2.55(2) g cm^{-3}
Systematic absences	h k l, h + k = 2n + 1 h0l, l = 2n + 1
Space group	C2/c (No. 15)
Unit cell parameters	a = 14.697(6) b = 6.816(1), β = 112.03(2) c = 23.225(4)
Volume	2157(1)
Z	8
Crystal mount axis	roughly along b
Linear absorption coefficient	141.4 cm^{-1}
Transmission coefficient limits	5.97 to 6.86
Max 2θ; quadrant	50°; h, k, ± l
Standard reflections	(1) -2, 0, -12 (2) -1, -1, -12
Overall e.s.d.	(1) 1.35% (2) 1.36%
Temperature	22°C
No. of independent reflections	2503
No. with $I > 3\sigma(I)$	1795
$3\sigma(I) > I > \sigma(I)$ where $F_c > F_o$	103
$3\sigma(I) > I > \sigma(I)$ where $F_c < F_o$	146
$I < \sigma(I)$ (rejected)	459

Continued.....

TABLE 25 (Continued)

Compound	$C_5H_{11}Cl_2N_4O_{15}Pt$
Final R_1	0.0612
Final R_2	0.0775
Final shift in e.s.d. Max.	0.015
Ave.	0.002
g (secondard extinction)	1.67×10^{-7}
Final difference map	
Highest peak; location	2.99 e/Å^3; 0.15, 0.05, 0.37
Lowest valley; location	-2.74 e/Å^3; 0.20, 0.05, 0.29
Weighting	$\frac{1}{\omega} = (69.34-1.083\|F_o\|+0.00804\|F_o\|^2)$

are listed in Table 26 and the corresponding moduli of F_o and F_c are listed in reference 179. Selected bond lengths and angles are given in Table 27 and the molecule, trans-$PtCl_2(NH_3)(C_5H_7N_3O)$, are illustrated in Fig. 17. In the molecule, the platinum atom is in square planar coordination, with the chlorine atoms trans. As usual, the 1-methylcytosine ring is N(3) bound to the platinum atom. The four nearest neighbour ligand atoms and the platinum atom are planar (within the errors, see Table 28). The bond lengths around the platinum atom are normal (see Table 8, p. 56) and agree well with values found in other similar structures reported in this work. The structure of the title compound is very similar to that of trans-dichloro(dialkylsulfoxide-S)(1-methylcytosine-N3)platinum(II) reported in Sect. 2.2.2 and ref. 83. Equivalent bond distances and angles do not differ significantly from those in the sulfoxide complexes except for the Cl-Pt-N(3) and Cl(1)-Pt-Cl(2) angles. The Cl-Pt-N(3) angles are significantly larger in the title compound (av. 90.8(4)° vs. 87.6(3)° and 88.1(5)°) such that now the chlorine atoms are bent away from the pyrimidine ring (Cl(1)-Pt-Cl(2), 181.6(4) vs. 174.3(1) and 176.1(1)). This is probably because the NH_3 group is much less bulky than the organic sulfoxides and the chloride ammonia repulsion will not be as great as the chloride-sulfoxide repulsion. The dihedral angle between the plane of the pyrimidine ring and the plane of the four ligand

TABLE 26

Atom parameters and temperature factors ($A^{\circ 2}$) for trans-dichloroammine(1-methylcytosine-N3)platinum(II) hemihydrate ($\times 10^3$) *

	x	y	z	U
Pt	217.13(4)	50.79(6)	328.45(2)	
Cl(1)	76.3(3)	- 64.3(6)	336.7(2)	
Cl(2)	355.9(3)	170.4(7)	317.6(2)	
N(2)	136(1)	158(2)	242.2(6)	46(3)
N(1)	389.6(9)	19.2(6)	519(3)	38(2)
C(1)	428(1)	158(2)	470.0(7)	48(3)
C(2)	335(1)	83(2)	461.9(6)	35(3)
O(2)	317.9(7)	257(2)	452.2(4)	41(2)
N(3)	297.4(8)	- 52(1)	414.7(5)	32(2)
C(4)	312(1)	-250(2)	427.1(6)	36(3)
N(4)	272(1)	-374(2)	381.2(6)	46(3)
C(5)	373(1)	-313(2)	486.8(7)	46(3)
C(6)	409(1)	-180(2)	530.6(7)	44(3)
O(1)	0	498(5)	0.250	101(8)

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

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	37.6(3)	26.5(3)	23.9(3)	1.7(2)	9.5(2)	1.9(2)
Cl(1)	43(2)	61(2)	37(2)	-10(2)	9(1)	12(2)
Cl(2)	46(2)	64(2)	66(2)	- 2(2)	25(2)	22(2)

* Estimated standard deviation from the least squares programs are given in parentheses.

TABLE 27

Selected interatomic distances (Å) and angles (deg.) for trans-dichloroammine(1-methylcytosine-N3)platinum(II) hemihydrate

Atoms	Distance	Atoms	Distance	Atoms	Distance
Pt-Cl(1)	2.288(5)	Pt-Cl(2)	2.296(5)	Pt-N(2)	2.04(1)
Pt-N(3)	2.03(1)	N(1)-C(1)	1.45(2)	N(1)-C(2)	1.34(2)
C(2)-O(2)	1.22(2)	C(2)-N(3)	1.38(2)	N(3)-C(4)	1.38(2)
C(4)-N(4)	1.32(2)	C(4)-C(5)	1.41(2)	C(5)-C(6)	1.32(2)
C(6)-N(1)	1.39(2)				

Possible hydrogen bond distances.

N(4)-O(2)[d]	2.94(2)	O(1)-N(2)	3.11(3)	O(1)-N(2)[a]	3.11(3)
O(1)-Cl(2)[b]	3.29(1)	O(1)-Cl(2)[c]	3.29(1)	N(2)-Cl(1)[a]	3.33(1)
Cl(1)-N(4)	3.40(1)				

Atoms	Angle	Atoms	Angle	Atoms	Angle
Cl(1)-Pt-N(2)	89.4(4)	Cl(1)-Pt-Cl(2)	178.4(1)	Cl(1)-Pt-N(3)	90.5(4)
N(2)-Pt-Cl(2)	89.1(5)	N(2)-Pt-N(3)	179.1(6)	Cl(2)-Pt-N(3)	91.1(4)
Pt-N(3)-C(2)	117.6(8)	Pt-N(3)-C(4)	122.1(8)	C(1)-N(1)-C(2)	120(1)
C(1)-N(1)-C(6)	119(1)	C(6)-N(1)-C(2)	121(1)	N(1)-C(2)-O(2)	120(1)
N(1)-C(2)-N(3)	119(1)	O(2)-C(2)-N(3)	121(1)	C(2)-N(3)-C(4)	120(1)
N(3)-C(4)-N(4)	118(1)	N(3)-C(4)-C(5)	120(1)	N(4)-C(4)-C(5)	122(1)
C(4)-C(5)-C(6)	118(1)	C(5)-C(6)-N(1)	122(1)		

Possible hydrogen bond angles.

C(4)-N(4)-O(2)	99.1(9)	C(2)-O(2)-N(4)	158(1)	N(2)-O(1)-N(2)[a]	83.5(9)
N(2)-O(1)-Cl(2)[b]	72.3(3)	N(2)-O(1)-Cl(2)[c]	146.8(8)	Cl(2)[b]-O(1)-Cl(2)[c]	138(1)
Pt-N(2)-O(1)	111.3(6)	Pt[b]-Cl(2)-O(1)	133.1(5)	Pt-N(2)-Cl(1)[a]	117.3(6)
Pt[a]-Cl(1)[a]-N(2)	119.2(3)	Pt-Cl(1)-N(4)	63.2(3)	C(4)-N(4)-Cl(1)	85.2(9)

a-c. Atoms are related to those given in Table 26 by a, $-x, y, \frac{1}{2} - z$; b, $x-\frac{1}{2}, \frac{1}{2} + y, z$; c, $\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z$; d, $x, y-1, z$.

TABLE 28

Least squares planes and dihedral angles between planes for trans-dichloroammine(1-methylcytosine-N3)platinum(II) hemihydrate.

Plane	Atoms	Distance from best plane (Å)
1	N(1)C(2)N(3)C(4)C(5)C(6)C(1)* O(2)*N(4)*Pt*	N(1),-0.02; C(2),0.00; N(3),0.02; C(4),-0.03; C(5),0.01; C(6),0.01; C(1),-0.08; O(2),-0.03; N(4),-0.05; Pt,0.08.
2	N(2)N(3)Cl(I)Cl(2)Pt*	N(2),0.01; N(3),0.01; Cl(1),-0.01; Cl(2),-0.01; Pt,-0.01.

Dihedral angle for planes 1 and 2 is 64.4°.

Errors in atom positions about 0.02 Å. Rms deviation for Plane 1, 0.019Å, Plane 2, 0.011Å.

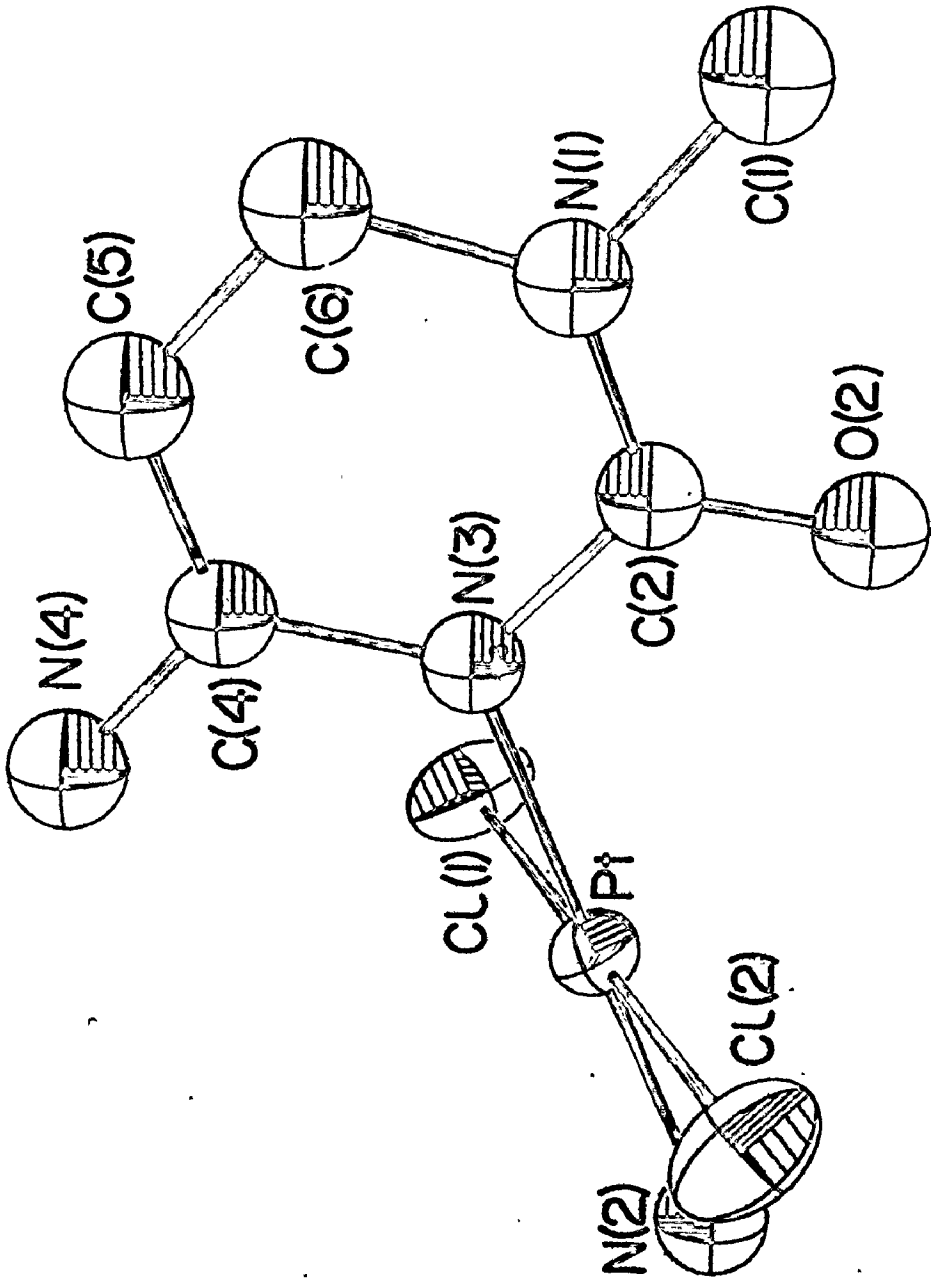


Figure 17

The molecule trans-$PtCl_2(NH_3)(C_5H_7N_3O)$ showing the atom numbering.

atoms is only 64.4° compared to the much larger angles (84.4°, 77.4°) in the sulfoxide complexes. The twist brings N(4) relatively close to Cl(1) (3.48(1) Å) so there is possibly a weak intramolecular hydrogen bond. The 1-methylcytosine ring is planar within the errors. Bond lengths and angles within the ring are discussed in Sect. 2.6, p. 149.

The crystal packing is shown in Figure 18. Chains of cytosine rings are formed by cytosine of one molecule hydrogen bonding through N(4)-H to O(2) of another cytosine related by a translation along $\underset{\sim}{b}$. Down $\underset{\sim}{a}$ there are two sets of four of these chains, giving sheets of parallel pyrimidine rings centred at z = 0 and 1/2. Down $\underset{\sim}{a}$, molecules of one chain in the sheet are inverted with respect to those in adjacent chains so that the cytosine rings of molecules in one chain are interleaved with those of molecules in adjacent chains. There are no hydrogen bonds between the cytosine rings in the $\underset{\sim}{a}$ direction and interaction is van der Waals. The interleaving maximizes the π-π interactions between adjacent cytosine rings. Hydrogen bonding in the $\underset{\sim}{a}$ direction does occur at z = 1/4 and 3/4 between O(1) of water molecules and the ammonia groups (N(2) of pairs of molecules). The molecules of each pair are also directly hydrogen bonded through two N(2)-H...Cl(2) bonds. These pairs of molecules are hydrogen bonded to others through Cl-O-Cl interactions in the $\underset{\sim}{b}$ direction.

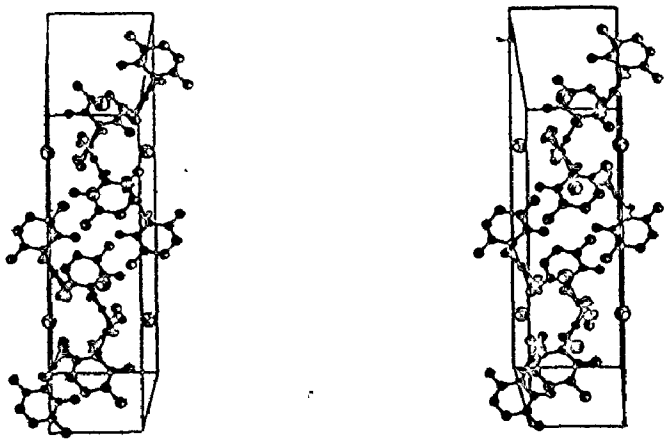
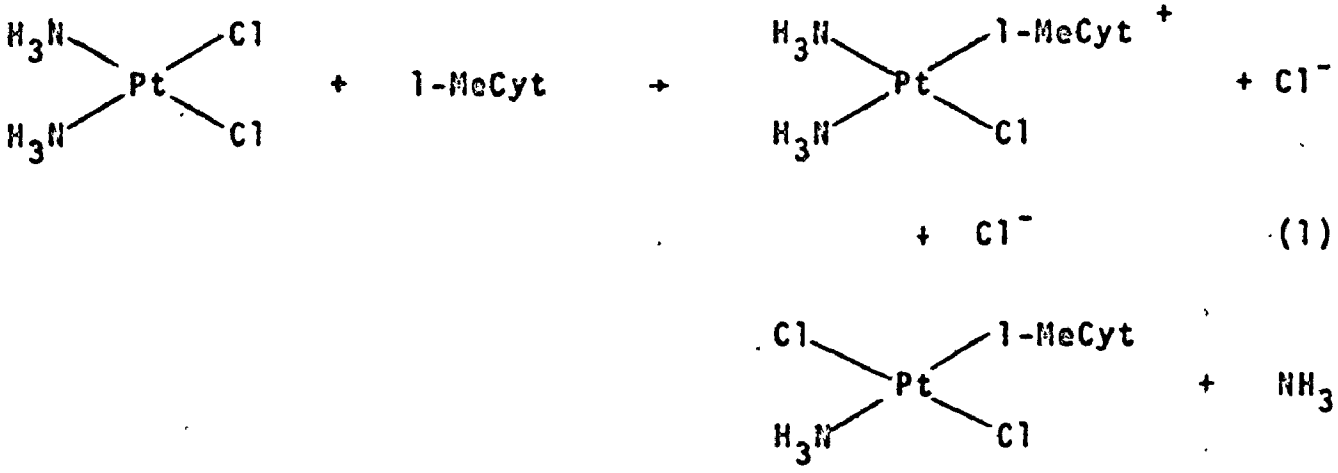


Figure 18

The unit cell contents of <u>trans</u>-$PtCl_2(NH_3)(C_5H_7N_3O)\cdot\frac{1}{2}H_2O$. $\underset{\sim}{b}$ and $\underset{\sim}{c}$ are parallel to the bottom and side of the page, respectively. The view is down $\underset{\sim}{a}^*$.

2.5.3 Discussion

In aqueous solution, the trans compound is thought to result from reaction of the main product cis-$PtCl(NH_3)_2$-(1-methylcytosine-N3)$^+$ with excess Cl^- released into the reaction mixture by the initial displacement reaction. Hence, the apparent isomerization of cis-$Pt(NH_3)_2Cl_2$ to trans-$Pt(NH_3)$(1-MeCyt)Cl_2 can be explained in terms of the two step mechanism illustrated below:



Confirmation of this description is given by recrystallizing cis-$[Pt(NH_3)_2$(1-methylcytosine-N3)Cl]$Cl\cdot H_2O$,[9] from aqueous solution where release of NH_3 can be monitored on binding of Cl^-.[111] Wherland et al.[113] have previously reported obtaining free ammonia from the reactions of cis-$Pt(NH_3)_2Cl_2$ with DNA bases. The displacement of ammine by chloride is not unusual and in fact is a standard method

[9] Compound synthesized and crystals prepared by B. Lippert. X-ray crystal structure solved by R. Faggiani.

for preparing trans-PtL_2X_2 compounds where the trans directing influence of Cl^- causes the second Cl^- to enter trans to the first one:[114]

$$[Pt(NH_3)_4]Cl_2 + 2HCl \rightleftharpoons \text{trans-}[Pt(NH_3)_2Cl_2] + 2NH_4Cl$$

In these reactions, the equilibrium is shifted to favour deammination by HCl. (Note that high yields, 31%, of trans-dichloroammine-(1-methylcytosine-N3)platinum(II), result when the cis compound is recrystallized from HCl.) These results are consistent with:

$$\text{trans-}PtCl_2(DMSO)am + Cl^- \rightleftharpoons PtCl_3(DMSO)^- + am$$

and

$$\text{cis-}PtCl(DMSO)am_2^+ + Cl^- \rightleftharpoons \text{cis-}PtCl_2(DMSO)am + am$$

which can be driven to the right in acidic solution. Although the rate of ammine substitution is independent of pH, the protonation of the released ammine forces the equilibrium to the right.[115]

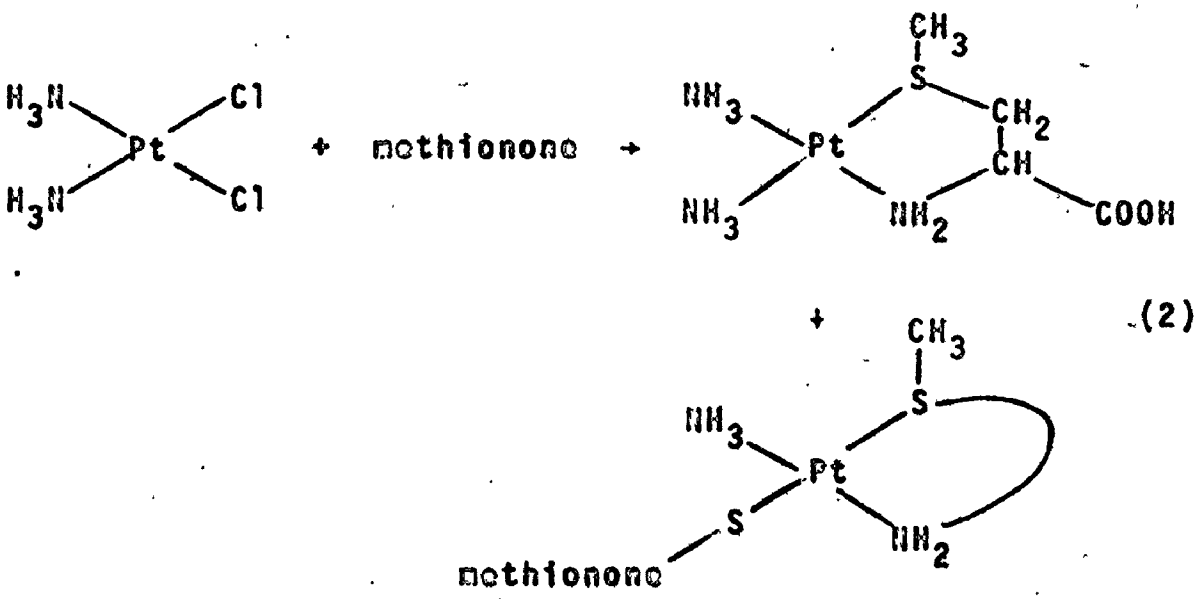
Similar isomerisms have been shown to exist for other platinum compounds, PtL_2X_2 where the interconversion is catalyzed by trace amounts of L or acids:

$$\text{cis-}PtL_2X_2 \underset{-X}{\overset{+L}{\rightleftharpoons}} PtL_3X^+ \underset{-L}{\overset{+X}{\rightleftharpoons}} \text{trans-}PtL_2X_2$$

These reactions are well characterized for L = PR_3, AsR_3 and SbR_3,[117] and X = Cl and I,[118] and equilibrium concentrations of the cis isomer in PtL_2Cl_2 range from 7.5% for

L = PEt_3 to 34.4% for L = $SbEt_3$.

It is interesting that the lability of the ammine groups can be increased when ligands such as sulphur or cyanide are bound trans.[116] Only the ammine group trans to S or CN^- is labilized in the reaction:



(2)

Lippard has observed NH_3 release during formation of "platinum pyrimidine blues" from cis-$Pt(NH_3)_2(OH_2)_2^{2+}$ and uracil and thymine.[112] Since H_2O and OH^- cannot labilize NH_3, it was considered that the pyrimidine ligands were exercising the trans-labilizing effect resulting in the release of NH_3. In light of this possibility, another pathway for the interconversion of cis-$PtCl(NH_3)_2$(1-MeCyt) to trans-$PtCl(NH_3)_2$(1-MeCyt) can be considered. The NH_3 ligand trans to 1-methylcytosine in cis-$PtCl(NH_3)_2$(1-MeCyt) is replaced. This is followed by an isomerization step and by uptake of chloride with formation of the trans pro-

duct. However, when cis-$[PtCl(NH_3)_2(C_5H_7N_3O)]Cl$ was reacted with additional 1-MeCyt in water,[108] major quantities of cis-$[Pt(NH_3)_2(C_5H_7N_3O)_2]Cl_2$ were observed and only a small amount of trans-$[PtCl_2(NH_3)(C_5H_7N_3O)]\cdot\frac{1}{2}H_2O$. This finding indicates that the trans-influence of 1-MeCyt cannot be strong, because then a compound of composition trans-$[PtCl(NH_3)(C_5H_7N_3O)_2]Cl$ should have been obtained in substantial yield.

The isomerization reactions are of questionable relevance to the mechanism of anticancer action of cis-$Pt(NH_3)_2Cl_2$ because they occur relatively slowly and are catalyzed by excess ligand (i.e., cytosine rather than NH_3 in this case) and H^+. According to the mechanism proposed earlier, binding of cytosine to platinum complexes cannot occur until the platinum complex is aquated at low Cl^- concentrations within the cell cytoplasm. The concentration of Cl^- here (4 mM) is low enough that minimal amounts of isomerization will occur.

A possibility suggested by the formation of trans-$(NH_3)PtCl_2$(1-MeCyt) is that platinum complexes could bind to three DNA bases rather than two as originally thought. This kind of simultaneous binding to three bases would be unique for cis-$[PtCl(NH_3)_2(OH_2)]^+$ and possibly cis-$[PtCl(OH)(NH_3)_2]$ and would not be expected for trans-$Pt(NH_3)_2Cl_2$ or any of its aquation products.

2.6 ASSIMILATION OF CRYSTALLOGRAPHIC DATA

2.6.1 Introduction

The binding sites for the structures contained in this work and for all other published platinum complex DNA base, nucleoside and nucleotide structures are summarized in Table 29. The atomic numbering schemes illustrated in Figure 19 for purines and pyrimidines are conventional and used consistently by biochemists and molecular biologists in North America.[39] Exocyclic atoms are numbered according to the ring atom to which they are bound. Hence, the exocyclic oxygen atom bound to C(6) of guanine is O(6). Similarly, the exocyclic nitrogen atom bound to C(4) of cytosine is labelled as N(4).

Nucleosides result from attachment of the bases adenine, cytosine, guanine, uracil and thymine to ribose or deoxyribose molecules, both of which are cyclic sugars. Nucleotides are nucleoside monophosphates, usually 5'. Polynucleotides are formed by linking 5'-nucleotides at the 3'-position of adjacent sugar molecules (phosphodiester bridges) as illustrated in Figure 20 for DNA. Note that the sugar molecules contained in RNA are riboses while those contained in DNA are 2'-deoxyriboses.

All of the structures contained in this work are either methyl blocked at N(1) of the pyrimidines, or, methyl or ethyl blocked at N(9) of the purines. This is done to prevent platinum complexes binding at these sites which, in DNA,

Table 29

Summary of Pt(II) binding sites on DNA bases*

Compound	Site	Reference
cis-$[PtCl(NH_3)_2(1\text{-MeCyt})]NO_3$	Pt-N(3)	Sect. 2.4.2,109
cis-$[PtCl(NH_3)_2(1\text{-MeCyt})]NO_3$	Pt-N(3)	Sect. 2.4.2,109
cis-$[Pt(NH_3)_2(1\text{-MeCyt})(9\text{-EtGua})](ClO_4)_2$	Pt-N(3)	Sect. 2.3.2,107
$[(NH_3)_2Pt(1\text{-MeCyt-H})_2Pt(NH_3)_2](NO_3)_2\cdot 2H_2O$	Pt(1)-N(3),Pt(2)-N(4)	Sect. 2.7.2,138
cis-$[PtCl(NH_3)_2(1\text{-MeCyt})]Cl\cdot H_2O$	Pt-N(3)	140
$[Pt(en)(5'\text{-CMP})]_2\cdot 2H_2O$	Pt-N(3),Pt(2)-O(phos)	135
cis$[Pt(NH_3)_2(1\text{-MeCyt})(9\text{-EtGua})](ClO_4)_{1.5}$	Pt-N(3)	107
cis-$[(NH_3)_2Pt(1\text{-MeCyt})_2](NO_3)_2$x1-MeCyt	Pt-N(3)	140
$(H_5O_2)[(NH_3)_2(NO_2)Pt(1\text{-MeCyt-H})_2\text{-}Pt(NH_3)_2(NO_2)](NO_3)_2$	Pt(1)-N(3),Pt(2)-N(4)	138
trans-$[PtCl_2(Me_2SO)(Cyd)]$	Pt-N(3)	83
trans-$[PtCl_2(i\text{-}Pr_2SO)(1\text{-MeCyt})]$	Pt-N(3)	Sect. 2.2.2, 81
trans-$[PtCl_2(NH_3)(1\text{-MeCyt})]\cdot\frac{1}{2}H_2O$	Pt-N(3)	Sect. 2.5.2,108
trans-$[Pt(NH_3)_2(1\text{-MeCyt})_2](NO_3)_2$	Pt-N(3)	Sect. 2.3.3,108
trans-$PdCl_2(1\text{-MeCyt})_2$	Pd-N(3)	139
cis-$[Pt(NH_3)_2(1\text{-MeCyt})(9\text{-EtGua})](ClO_4)_2$	Pt-N(7)	Sect. 2.3.2,107

Continued.....

Table 29 (Continued)

Compound	Site	Reference
cis-$[Pt(NH_3)_2(Guo)_2]Cl_{3/2}(ClO_4)_{1/2}\cdot 7H_2O$	Pt-N(7)	58
$[Pt(en)(Guo)_2]Cl_{3/2}I_{1/2}\cdot 2H_2O$	Pt-N(7)	57
cis-$[Pt(NH_3)_2$(1-MeCyt)(9-EtGua)$](ClO_4)_{1.5}$	Pt-N(7)	107
$[PtCl_2$(1-$Pr_2SO)]_2$(9-MeAde)$\cdot H_2O$	Pt(1)-N(1),Pt(2)-N(7)	Sect. 2.2.3,103
$PtCl_3$(9-MeAdeH$^+$)	Pt-N(7)	141
$[(NH_3)_2Pt$(1-MeThy-H)$_2Pt(NH_3)_2](NO_3)_2\cdot H_2O$	Pt(1)-N(3),Pt(2)-O(4)	143
$[(NH_3)_2Pt$(1-MeUra-H)$_2Pt(NH_3)_2](NO_3)_2\cdot 3H_2O$	Pt(1)-N(3),Pt(2)-O(4)	142
PtCl(en)(Thy-H)	Pt-N(1)	110
(H_5O_2)Cl[PtCl(en)(Ura-H)]	Pt-N(1)	110

* See also platinum complexes of 5'-IMP in Kistenmacher et al., J. Amer. Chem. Soc., 101, 1143 (1979), ref. 181, and references therein.

Figure 19

The chemical structure and standard atom numbering system of the pentoses and bases.

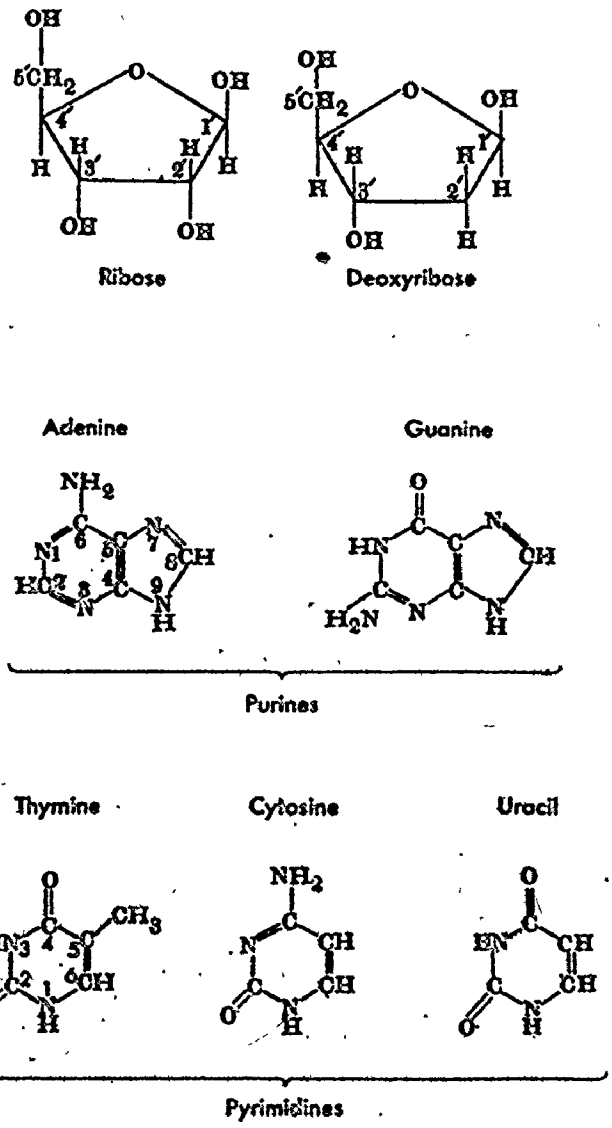


Figure 19 was reproduced from ref. 123, L. Levine, "Biology of the Gene", The C.V. Mosby Co., St. Louis (1969).

Figure 20

Segment of a DNA molecule showing sugar-phosphate backbone.

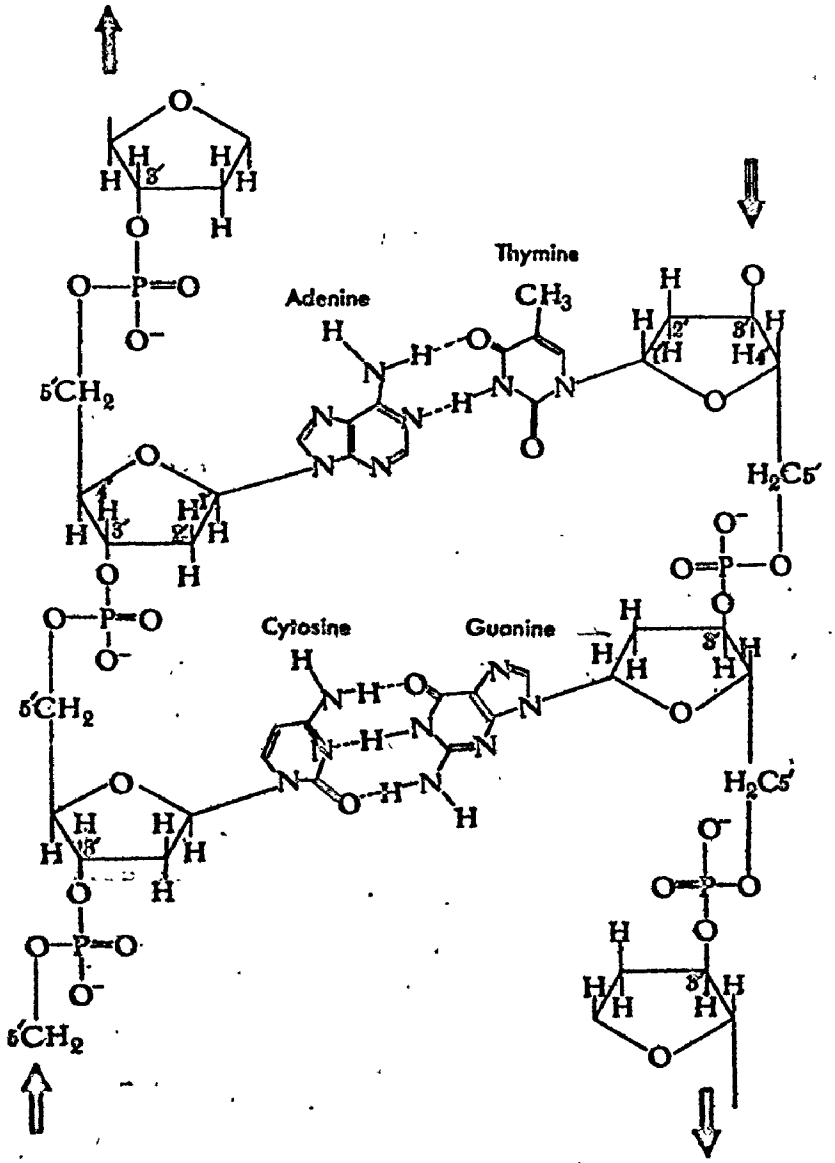


Figure 20 was reproduced from ref. 123, L. Levine, "Biology of the Gene", The C.V. Mosby Co., St. Louis (1969).

are normally blocked by cyclic 2'-deoxyribose sugars. Methylation at these sites is an effective way of blocking the sites without significantly altering the basicity (pK_a) of other binding sites with respect to DNA (see Table 30). As discussed by Harbers et al.[47] the sugar moiety lowers the basicity of pyrimidine and imidazole sites in nucleosides (adding ribose lowers the pK_a by 1.7 units in guanosine as compared to guanine or 1.3 units with respect to dGMP; 0.4 pK_a units comparing Cyt and dCMP, ~ 1 pK_a units comparing Ado and dAMP). Although changes are less when deoxyribose groups are added to the bases (0.3 - 0.5) it would appear that nucleosides especially ribonucleosides, are not good models for binding studies (although they have been used[48,53]). The phosphate residue of nucleotides increases the basicity of binding sites.[47] Perhaps fortuitously, the methylated bases have almost equivalent pK_a's (see Table 30) to those of the deoxyribonucleotide 5'-monophosphates (difference is 0 - 0.05) and are very good models for binding studies. By using methylated bases, the problems of binding platinum complexes to nucleosides with altered basicities are avoided. The formation of irrelevant[40] polymeric species where platinum atoms are bound to phosphate groups is also avoided. The amounts of data needed for crystal structure solutions are lower and the accuracy of bond lengths and angles are considerably better for the lower molecular weight platinum-methylated base compounds.

TABLE 30

pKa's of bases, nucleosides and nucleotides

	Data from ref. 47*		Data from ref. 124
		$N(7)\text{-}H \rightarrow N(7)^- + H^+$	
	Gua	3.3, 3.0[66]	-
	9-MeGua	2.9[66]	-
Guo 1.6	dGuo	2.8	2.5
	dGMP	2.9	2.9
		$N(3)\text{-}H^+ \rightarrow N(3) + H^+$	
	Cyt	4.6	4.58, 4.5
	1-MeCyt	4.55[125], 4.57[126]	-
Cyd 4.2	dCyd	4.3	4.3
	dCMP	4.6	4.4
		$N(3)\text{-}H^+ \rightarrow N(3) + H^+$	
	Ade	4.15	4.2, 4.12
	9-MeAde	-	-
Ado 3.45	dAdo	3.8	3.8
AMP 3.8	dAMP	4.4	6.65
		$N(3)\text{-}H \rightarrow N(3)^- + H^+$	
	Thymine	9.8	9.9
	Thy	9.8	9.79
	dTMP	6.5	-

*unless otherwise specified

2.6.2 Preferential site for Pt(II) binding to cytosine

It could be argued on the basis of published work that purely monodentate binding by metals other than platinum at N(3) of cytosine is rare[40] and that the metal cytosine bonding is stabilized by secondary interactions. In the majority of published examples, an additional stabilizing interaction with oxygen donor atoms either from the cytosine ring,[127-134] or in nucleotide complexes with phosphate,[134-137] has been observed.

Oxygen coordination alone has also been found in the solid state[128] and in solution.[129] This is not consistent, however, with the six monoplatinated cytosine structures reported in this work[81,107-109] and the five platinum (and one palladium[139]) cytosine structures recently published[83] (or to be published[107,140]), where only monodentate binding by platinum complexes occurs at N(3) (see Table 29). In three cases, an additional interaction occurs. In the two N(3)-N(4) cytosine bridged compounds[138] which will be described in Section 2.7.1, the exocyclic amine group is also involved in binding to platinum atoms. Solution nmr studies showed, however, that the initial interaction of platinum complexes is at N(3) of cytosine. In the third structure, $[Pt(en)\text{-}(5'\text{-CMP})]_2 \cdot 2H_2O$,[130] two platinum atoms are bridged by two 5'-CMP molecules through N(3) of cytosine and oxygen of the phosphate group. No (phosphate) oxygen atom platinum atom interactions have, however, been detected in solution studies.[9]

Similarly, no interactions of platinum compounds with ribose positions have been observed in solution[53] or crystallographic studies.

Examination of Table 29 reveals that platinum complexes bind at the imidazole type site, N(7), of the purines, guanine and adenine, in all of the six structures listed.[57,58,103,107,141] In one of the two adenine structures, a second platinum complex binds at the pyrimidine N(1) site ([i-$Pr_2SOPtCl_3$]:[9-me-adenine] is 2:1).[103] When equimolar amounts of platinum complex and adenine are reacted, only binding at N(7) of adenine occurs.[142] On the basis of this information, one can deduce that platinum complexes bind preferentially at N(7) of purines. This is consistent with chemical and physical studies.

It is more difficult to assess a preferred site or mode of binding of platinum complexes to uracil or thymine on the basis of the limited data available (2 structures which will be discussed in Chapter 3 and 2 structures published in ref. 110). For the first two structures, the bridging behaviour of the uracilato[142] and thyminato[143] ligands is similar to that observed for the cytosinato ligand in $[(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2](NO_3)_2 \cdot 2H_2O$ and it appears that the mechanism for the formation of these compounds may be related. In the other two structures, a $Pt(en)Cl^+$ moiety binds to the non-methylated sites N(1) of the uracil and thymine bases (which in RNA and DNA are blocked by ribose groups).

2.6.3 The effect of Pt(II) on the structure of cytosine

Bond lengths and angles for all structures reported in this thesis are tabulated and averaged in Appendices 2 and 3. Comparison of the bond lengths within the platinated 1-methylcytosine rings (contained in this work) with those reported by Rich and Voet[102] for neutral and protonated cytosine molecules (Appendix 4) shows there are no significant differences (see Table 31). Comparison of bond angles, however, suggests that platinated 1-methylcytosine rings are more like various neutral cytosine molecules rather than the protonated species (see Appendix 5, Table 31 and Fig. 21). Thus, there are significant differences between the averaged angles N(1)-C(2)-N(3), C(2)-N(3)-C(4) and N(1)-C(2)-O(2) in platinated cytosine molecules 118(1), 121(1), 120.5(5) and those average values for protonated cytosine molecules 113.7(4), 125(1) and 124.2(4). These differences are reported at a 99% confidence, i.e., that there is a 99% chance of their being different. Differences at this level of confidence are considered significant. To relax the level of confidence to 95%, the C(5)-C(6)-N(1) angles (121.0(9), 123.1(6)) are different. At 95% confidence, the difference is possibly significant. The N(3)-C(4)-C(5) angles (121(1), 118.4(1)) become different at 90% confidence. This can be best interpreted as just a hint of a difference.

No significant differences exist between any angles in platinated and neutral cytosine molecules, even at the

Table 31

Differences in bond lengths and angles between 1-methylcytosine metallated (Pt) at N(3) and neutral (Δx_{12}) or protonated (Δx_{13}) molecules

Bond Lengths (Å)

	N(1)-C(2)	C(2)-N(3)	N(3)-C(4)	C(4)-C(5)	C(5)-C(6)	C(6)-N(1)	C(2)-O(2)	C(4)-N(4)	N(1)-C(1)
Δx_{12}	.021	.026	.007	.021	.001	.007	.015	.009	.001
$\lambda\sigma_{12}$	.044	.048	.040	.035	.081	.033	.055	.054	.059
Δx_{13}	.024	.008	.002	.001	0.000	.012	.018	.014	.013
$\lambda\sigma_{13}$	.037	.050	.040	.031	.066	.033	.030	.039	.025

Bond Angles (°)

	6-1-2	1-2-3	2-3-4	3-4-5	4-5-6	5-6-1	1-2-O(2)	3-2-O(2)	3-4-N(4)	5-4-N(4)	2-1-C(1)	6-1-C(1)
Δx_{12}	0.3	0.7	0.4	0.6	0.7	0.2	1.6	1.0	0.6	0.1	0.2	1.4
$\lambda\sigma_{12}$	3.3	3.6	3.6	4.4	4.0	2.4	2.5	2.5	4.0	2.5	3.6	1.2
Δx_{13}	0.6	4.2	4.4	2.5	0.1	2.1	3.7	0.5	1.3	1.1	0.8	0.1
$\lambda\sigma_{13}$	2.4	2.7	3.3	2.9	1.8	2.1	1.2	2.0	2.7	2.3	2.8	1.5
$\lambda\sigma_{13}$'				2.48		1.8						
$\lambda\sigma_{13}$"		3.5	4.3				1.6					

Two independent parameters $x_1 \pm \sigma_1$ and $x_2 \pm \sigma_2$ are statistically different if $\Delta x_{12} > \lambda\sigma_{12}$ where $\Delta x_{12} = |x_1 - x_2|$, $\sigma_{12} = \sqrt{\sigma_1^2 + \sigma_2^2}$ and λ is described below. There is a 95% chance that two bond lengths or angles are different if $\Delta x > 1.96\sigma$.

Continued.....

Table 31 (Continued)

Values for λ are obtained from:

p	λ	p	λ
0.30	1.04	0.05	1.96
0.20	1.28	0.01	2.58
0.10	1.65	0.001	3.29

where p is the probability of finding a normally distributed variable more than $\sigma\lambda$ from its true value. All $\sigma\lambda$ values are calculated for 95% level of confidence (except $\sigma\lambda_{13'}$ calculated at 90% and $\sigma\lambda_{13''}$ at 99%). Numbers are derived from data in Appendices 4 and 5.

relaxed 95% confidence. The differences are shown in Fig. 21 for platinated and protonated cytosine molecules. As can be seen, the internal angle at N(3) when protonated (or methylated) is 4° larger than the platinated or neutral cytosine molecules. The internal angles adjacent to the N(3) atom decrease by about 2° to 4° each and the C(5)-C(6)-N(1) angle opposite N(3) increases by about 2° to preserve the planarity of the ring. The increase in the C(2)-N(3)-C(4) angle on protonation probably results from the inductive withdrawal of electron charge from the ring by the proton. The platinum complex, although an electrophile, has a much smaller effect on the molecular structure of the cytosine ring than the proton. The bond lengths and angles in the platinated compounds are in relatively good agreement with those predicted by Spencer[144] and favour the Spencer model over that of Pauling[145] where there are significant differences.

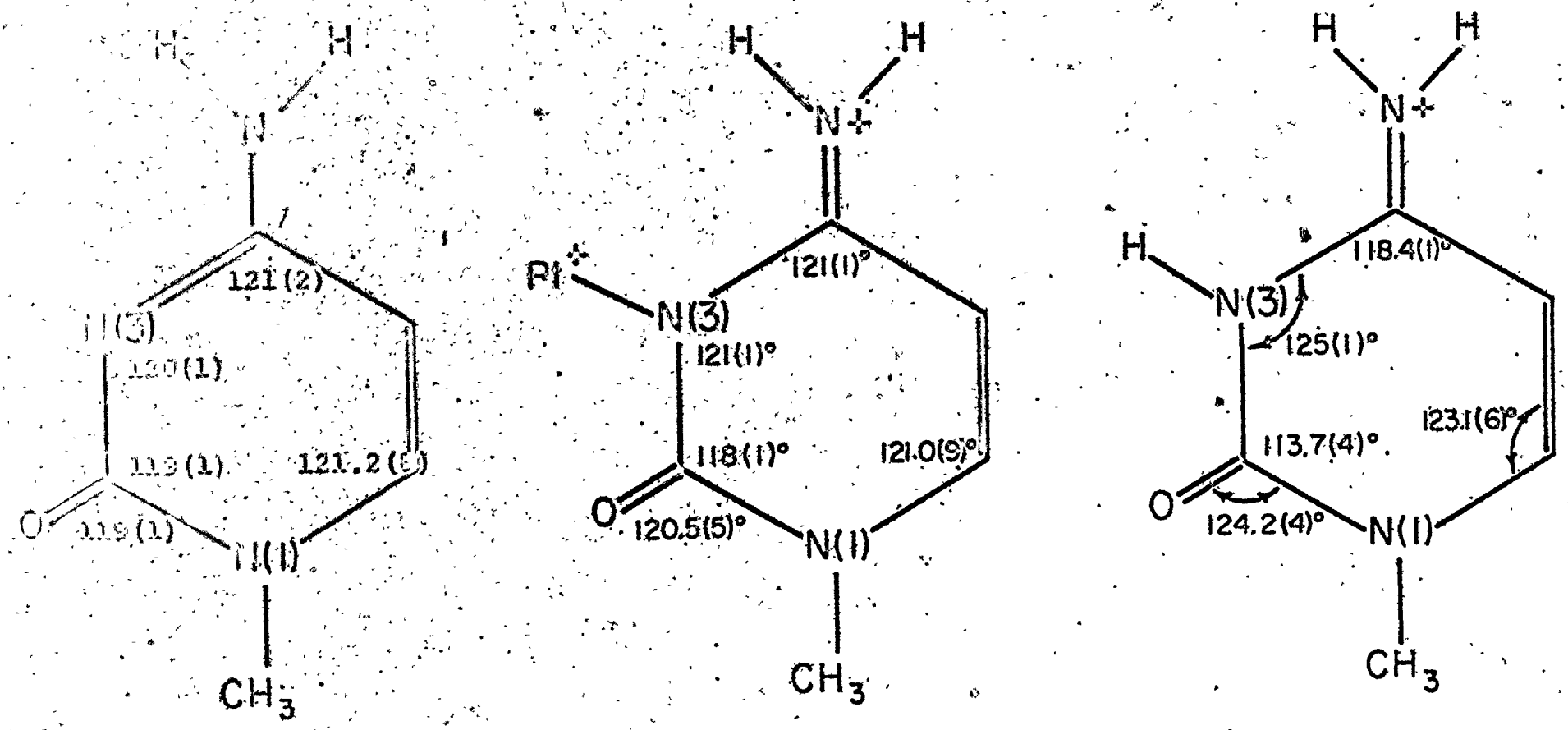


Figure 21

Averaged angles for platinated and protonated cytosines. Angles for neutral cytosine molecule do not differ significantly from platinated molecule but are shown for comparison.

2.7 CYTOSINE AS A MULTI-SITE LIGAND

2.7.1 Introduction

A minor product of the reaction of cis-$Pt(NH_3)_2Cl_2$ with two equivalents of 1-methylcytosine was [cis-$(NH_3)_2Pt$-$(C_5H_6N_3O)_2Pt(NH_3)_2](NO_3)_2$. The molecular structure of this compound suggests another mode of bonding of cis-$Pt(NH_3)_2Cl_2$ to DNA bases which could produce the primary cytotoxic lesion in DNA (see Chapter 3, p. 184). In this compound, the exocyclic amine group is involved in binding to the platinum atom.

2.7.2 The crystal and molecular structure of di(μ-cytosinato-N3,N4)-bis(cis-diammineplatinum(II))dinitrate dihydrate[138]

Preparation (by B. Lippert)

The title compound was prepared in two ways:

(1) in very low yield (2%) when cis-$[Pt(NH_3)_2(OH_2)_2](NO_3)_2$ (an aqueous solution of cis-$Pt(NH_3)_2(NO_3)_2$)[145] was reacted with two equivalents of 1-methylcytosine (0.04 M based on Pt, 20 h at 40°C in a stoppered flask). The resulting solution of pH ∿ 5 was adjusted to pH = 6.0 with aqueous 2N NaOH and concentrated to 1/7 volume by rotary evaporation. The solution was kept in an open beaker and allowed to evaporate slowly at room temperature and at 0°C for 3 days.

The main crystalline products of the reaction were precipitated by fractional recrystallization from solution because of the differing product solubilities in H_2O. Trans-$[(NH_3)_2Pt(1\text{-MeCyt})_2](NO_3)_2$, the title compound of Section 2.3.3; p. 97, is very insoluble in H_2O and precipitates first in 2-5% yield. Cis-$[Pt(NH_3)_2(C_5H_7N_3O)_2]$-$(NO_3)_2\cdot(C_5H_7N_3O)$ and, cis-$[Pt(NH_3)_2(C_5H_6N_3O)]_2(NO_3)_2$, the title compound, A, are moderately soluble in H_2O and precipitate next in yields of 15% to 2%, respectively. The main product of the reaction, cis-$[Pt(NH_3)_2(C_5H_7N_3O)_2](NO_3)_2\cdot H_2O$ (60% yield) is highly water-soluble and does not precipitate until the reaction mixture is almost dry. The formation of

trans-$[Pt(NH_3)_2(C_5H_7N_3O)_2](NO_3)_2$ is believed to be caused by the presence of an impurity of trans-$Pt(NH_3)_2Cl_2$ in the bulk starting material cis-$Pt(NH_3)_2Cl_2$.

(2) when 0.005 mole of $[(NH_3)_2Pt(OH)]_2(NO_3)_2$,[25] and 0.01 mole of 1-methylcytosine were stirred in 150 mL H_2O in a stoppered flask at 70°C for a few minutes until the two compounds had dissolved. The pH of the solution was 6.8 when cooled to room temperature. The solution was then put in a 36°C waterbath in a stoppered flask. Within two days, the solution became brownish and the pH rose to 8.7. Some black precipitate (~ 3 mg) was filtered off, the solution brought to pH 6 with 2N HNO_3, concentrated in a rotary evaporator to 40 mL volume and kept at room temperature in a stoppered flask. After cooling to 0°C, 210 mg of the starting platinum compound was filtered off. The pH of the filtrate was then 6.5 and was brought back to 6.0 with diluted HNO_3. Within two days at room temperature (open beaker), crystals of the title compound A and the starting platinum compound had formed. They were filtered off, separated by means of dimethylformamide, DMF (A dissolves forming a yellow solution, the Pt starting compound remains undissolved) and, after evaporation of DMF to dryness, A was recrystallized from H_2O. The first crop of A was 110 mg. The filtrate of the reaction mixture had a pH of 6.25 and was brought back to 6.0. Upon gradual concentration of the solution

and keeping the pH at 6.0 over a period of 2-3 weeks, additional crops of A could be obtained. Total yield of A, 450 mg. Recrystallization from H_2O gave well-shaped transparent crystals of up to 1.5 mm length.

When the reaction mixture was taken to dryness, a large quantity of cis-$[(NH_3)_2Pt(1\text{-MeCyt})_2](NO_3)_2 \cdot xH_2O$ was obtained (colourless, transparent crystals after recrystallization, highly water soluble) as well as an undefined, presumably amorphous, brown material.

Analysis: Calcd. for $C_{10}H_{28}N_{12}O_{10}Pt_2$: C, 13.9; H, 3.3; N, 19.4; O, 18.5; Pt, 45.0%. Found: C, 13.9; H, 3.3; N, 19.4; O, 18.6; Pt, 44.5%.

Discussion

Crystal data and other numbers related to data collection and structure refinement are summarized in Table 32. The atom parameters from the final refinement are listed in Table 33 and the corresponding moduli of F_o and F_c are listed in reference 179. Selected bond lengths and angles are given in Table 34 and the molecular cation $(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2^{2+}$ is illustrated in Fig. 22. The cation is dimeric. The two platinum atoms are bridged by two 1-methylcytosinato ligands through N(3) and the deprotonated exocyclic N(4) atoms. These bridging ligands are arranged head-to-tail. The two ammine groups are cis on each platinum atom and the square planes of ligand atoms about each platinum atom lie roughly on top of each other.

Comparison of $[(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2](NO_3)_2 \cdot 2H_2O$, A, with cytosine molecules bound through N(3) to only one platinum atom (Appendix 2 shows that the bond distances within the cytosine rings do not differ significantly. Differences are not detectable because of the large errors in bond lengths. Although the differences in angles of cytosine in the title compound and monoplatinated cytosine (from Appendix 3) are also not significant (again because of large errors), there appear to be marked distortions caused by the second platinum atom binding at N(4) (see comparison in Table 35). The N(3)-C(4)-N(4) angle is about 4° larger in A. Compensating

TABLE 32

Compound	$C_{10}H_{28}N_{12}O_{10}Pt_2$
F.W.	866.59
Crystal size	Sphere of radius .05 mm
Crystal colour	colourless
ρ_{calc}	2.44 g cm^{-3}
ρ_{obs}	2.41(1) g cm^{-3}
Systematic absences	0k0, k = 2n + 1 h0l, l = 2n + 1
Space group	$P2_1/c$ (No. 14)
Unit cell parameters	a = 9.887(3) Å, b = 17.191(5) Å, β = 116.40(2)° c = 15.532(4) Å
Volume	2365(1) $Å^3$
Z	4
Crystal mount axis	roughly along bc diagonal
Linear absorption coefficient	125.3 cm^{-1}
Transmission coefficient limits	2.35 - 2.39
Max 2θ; quadrant	45°; h k ± l
Standard reflections	(1) 0, -4, 1 (2) -1, -3, 1
Overall e.s.d.	(1) 2.01% (2) 2.03%
Temperature	22°C
No. of independent reflections	3248
No. with $I > 3\sigma(I)$	1631
$3\sigma(I) > I > \sigma(I)$, $F_c > F_o$	272
$3\sigma(I) > I > \sigma(I)$, $F_c < F_o$	513
and $I < \sigma(I)$, (rejected)	832

Continued.....

TABLE 32 (Continued)

Compound	$C_{10}H_{28}N_{12}O_{10}Pt_2$
Final R_1	.0739
Final R_2	.0953
Final shift in e.s.d. Max.	.042
Ave.	.003
g (secondard extinction)	2.10×10^{-8}
Final difference map	
Highest peak, location	1.29 e/Å^3; 0.05, 0.20, 0.28
Lowest valley, location	-1.17 e/Å^3; 0.27, 0.13, 0.12
Weighting	$\frac{1}{\omega} = [\sigma(F)^2 + (.069\|F_o\|)^2]$

TABLE 33

Atom parameters and temperature factors ($A^{\circ 2}$) for di(μ-cytosinato-N3,N4)bis(cis-diammineplatinum(II)) dinitrate dihydrate (x 10^3)

	x	y	z	U
Pt(1)	174.5(1)	204.58(7)	288.37(8)	
Pt(2)	232.2(1)	212.36(7)	115.83(8)	
N(11)	- 22(3)	268(2)	234(2)	46(8)
N(12)	293(3)	298(2)	377(2)	45(8)
N(21)	411(4)	286(2)	169(2)	55(8)
N(22)	103(3)	301(1)	28(2)	44(7)
N(1)	573(3)	88(1)	482(2)	40(7)
C(1)	652(5)	83(2)	589(3)	53(11)
C(2)	437(4)	123(2)	439(2)	39(8)
O(2)	379(3)	147(1)	496(2)	50(6)
N(3)	373(3)	144(1)	346(2)	22(6)
C(4)	428(4)	113(2)	287(2)	33(8)
N(4)	373(3)	128(1)	195(2)	24(6)
C(5)	555(4)	60(2)	332(2)	36(8)
C(6)	630(4)	53(2)	424(2)	41(8)
N(1A)	-139(3)	82(1)	-77(2)	28(6)
C(1A)	-221(4)	74(2)	-181(2)	32(8)
C(2A)	- 13(3)	126(2)	-33(2)	32(7)
O(2A)	31(2)	161(1)	-86(2)	39(6)
N(3A)	50(3)	138(1)	62(2)	26(6)
C(4A)	3(3)	99(1)	119(2)	16(6)
N(4A)	52(3)	112(2)	205(2)	38(7)
C(5A)	-118(4)	43(2)	76(2)	41(9)
C(6A)	-101(4)	37(2)	-26(2)	33(8)
N(7)	320(5)	775(2)	25(3)	82(12)
O(71)	401(4)	796(2)	104(2)	89(10)
O(72)	215(4)	730(2)	6(2)	82(9)

Continued.....

TABLE 33 (Continued)

	x	y	z	U
O(73)	343(5)	793(2)	-51(3)	114(13)
N(8)	139(9)	458(4)	202(5)	127(21)
O(81)	28(12)	445(6)	158(7)	291(51)
O(82)	113(6)	537(4)	208(4)	163(19)
O(83)	237(8)	424(4)	219(4)	190(27)
OH(1)	248(5)	704(2)	206(3)	118(14)
OH(2)	473(4)	563(2)	424(3)	103(12)

Anisotropic Temperature Factors U_{ij} ($\times 10^3$)*

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt(1)	35.6(9)	32.0(8)	21.0(7)	-0.8(6)	15.7(6)	-4.3(6)
Pt(2)	39.9(9)	30.3(7)	18.6(7)	-7.2(6)	14.9(6)	-0.3(6)

* Estimated standard deviation from the least squares programs are given in parentheses.

TABLE 34

Selected interatomic distances (Å) and angles (deg.) in di(μ-1-methylcytosinato-N3,N4)bis(cis-diammineplatinum(II)) dinitrate dihydrate, A, and di(μ-1-methylcytosinato-N3,N4) bis(nitro-cis-diammineplatinum(III))dinitrate dihydrate, B.

Atoms	Distance		Atoms	Distance	
	A	B		A	B
Pt(1)-Pt(2)	2.981(2)	2.584(1)	Pt(1)-N(11)	2.06(3)	2.07(2)
Pt(1)-N(12)	2.11(3)	2.05(2)	Pt(2)-N(21)	2.03(3)	2.08(2)
Pt(2)-N(22)	2.06(3)	2.07(2)	Pt(1)-N(3)	2.04(2)	2.00(2)
Pt(1)-N(4A)	2.06(3)	2.00(2)	Pt(2)-N(3A)	2.06(3)	2.06(2)
Pt(2)-N(4)	2.01(2)	2.02(2)	Pt(1)-N(5)	-	2.12(3)
N(1)-C(1)	1.50(1)	1.49(4)	N(1A)-C(1A)	1.46(4)	1.57(4)
N(1)-C(2)	1.34(5)	1.34(3)	N(1A)-C(2A)	1.36(4)	1.35(3)
C(2)-O(2)	1.32(6)	1.17(3)	C(2A)-O(2A)	1.25(5)	1.23(4)
C(2)-N(3)	1.34(4)	1.46(4)	C(2A)-N(3A)	1.35(4)	1.41(4)
N(3)-C(4)	1.38(5)	1.37(3)	N(3A)-C(4A)	1.35(5)	1.38(4)
C(4)-N(4)	1.31(4)	1.29(4)	C(4A)-N(4A)	1.23(4)	1.28(3)
C(4)-C(5)	1.45(5)	1.45(4)	C(4A)-C(5A)	1.44(4)	1.50(3)
C(5)-C(6)	1.29(5)	1.37(5)	C(5A)-C(6A)	1.42(5)	1.26(5)
C(6)-N(1)	1.40(6)	1.38(4)	C(6A)-N(1A)	1.36(5)	1.37(4)
Pt(2)-N(6)	-	2.13(2)	N(5)-O(51)	-	1.24(3)
N(51)-O(52)	-	1.21(3)	N(6)-O(61)	-	1.27(3)
N(6)-O(62)	-	1.20(3)	N(7)-O(71)	1.18(5)	1.35(5)
N(7)-O(72)	1.22(6)	1.05(6)	N(7)-O(73)	1.34(8)	1.17(5)
N(8)-O(81)	1.02(12)	1.23(3)	N(8)-O(82)	1.07(11)	1.30(4)
N(8)-O(83)	1.35(10)	1.21(2)			

Possible hydrogen bonding distances.

	Atoms	Distance	Atoms	Distance	Atoms	Distance
A	N(11)-N(4A)	2.87(4)	N(11)-O(2A)[a]	2.86(4)	N(11)-OH(1)[b]	2.98(7)
	N(12)-O(2)	3.07(4)	N(12)-O(2A)[a]	2.97(5)	N(12)-O(83)	3.13(8)
	N(12)-O(71)[c]	2.90(6)	N(21)-O(2)[d]	2.81(5)	N(21)-N(4)	2.80(4)
	N(21)-O(83)	3.21(9)	N(21)-O(71)[c]	3.18(5)	N(22)-O(2)[d]	3.11(5)
	N(22)-O(2A)	2.88(4)	N(22)-O(72)[e]	3.01(5)	N(4)-OH(2)[c]	3.09(6)
	N(4A)-O(82)[b]	2.99(8)	O(72)-OH(1)	3.04(6)	O(73)-OH(2)[f]	2.90(6)
	O(82)-OH(1)	3.10(8)	O(71)-OH(1)	3.08(7)	OH(2)-OH(2)[g]	3.06(6)
B	O(2)-N(12)	2.86(3)	O(2)-N(12)[j]	2.85(3)	O(2A)-N(22)	2.95(3)
	O(2A)-OH(2)[p]	2.83(5)	N(22)-OH(1)[j]	3.09(4)	N(22)-O(83)[k]	3.02(2)
	N(22)-O(83)[l]	2.95(4)	N(4A)-O(61)[k]	3.21(3)	N(22)-O(81)[l]	3.25(3)
	N(21)-O(52)[o]	3.04(3)	N(12)-O(2)[j]	2.86(3)	N(12)-O(52)[j]	3.28(2)
	N(12)-OH(1)[j]	3.24(4)	N(12)-O(72)[m]	2.99(6)	N(11)-OH(1)[j]	2.84(4)
	N(11)-O(82)[k]	2.93(3)	N(11)-O(83)[k]	3.18(4)	N(11)-O(81)[h]	2.99(3)
	N(21)-O(72)[m]	2.82(5)	N(21)-O(73)[g]	3.11(5)	N(21)-O(51)[o]	2.88(3)

TABLE 34 (Cont'd)

Atoms	Angle A	Angle B	Atoms	Angle A	Angle B
Pt(2)-Pt(1)-N(11)	98(1)	97.7(7)	Pt(1)-Pt(2)-N(2)	98(1)	93.2(7)
Pt(2)-Pt(1)-N(12)	106(1)	100.1(7)	Pt(1)-Pt(2)-N(22)	109(1)	99.7(7)
Pt(2)-Pt(1)-N(3)	83.8(8)	83.6(7)	Pt(1)-Pt(2)-N(3A)	81.5(8)	85.0(6)
Pt(2)-Pt(1)-N(4A)	77(1)	82.2(7)	Pt(1)-Pt(2)-N(4)	77(1)	83.0(6)
Pt(2)-Pt(1)-N(5)	-	171.0(5)	Pt(1)-Pt(2)-N(6)	-	172.9(5)
N(11)-Pt(1)-N(12)	91(1)	90.2(7)	N(21)-Pt(2)-N(22)	89(1)	89.2(7)
N(11)-Pt(1)-N(3)	178(1)	177.6(8)	N(21)-Pt(2)-N(3A)	179(1)	177.8(9)
N(11)-Pt(1)-N(4A)	88(1)	87.9(7)	N(21)-Pt(2)-N(4)	88(1)	90.5(7)
N(11)-Pt(1)-N(5)	-	86.2(9)	N(21)-Pt(2)-N(6)	-	86.8(8)
N(12)-Pt(1)-N(3)	87(1)	91.6(7)	N(22)-Pt(2)-N(3A)	91(1)	92.4(7)
N(12)-Pt(1)-N(4A)	177(2)	177.2(8)	N(22)-Pt(2)-N(4)	174(1)	177.2(9)
N(12)-Pt(1)-N(5)	-	88.0(9)	N(22)-Pt(2)-N(6)	-	87.4(8)
N(3)-Pt(1)-N(4A)	94(1)	90.3(7)	N(3A)-Pt(2)-N(4)	93(1)	88.1(6)
N(3)-Pt(1)-N(5)	-	92.2(8)	N(3A)-Pt(2)-N(6)	-	94.8(7)
N(4A)-Pt(1)-N(5)	-	89.8(9)	N(4)-Pt(2)-N(6)	-	89.8(8)
Pt(1)-N(3)-C(2)	122(3)	119(1)	Pt(2)-N(3A)-C(2A)	116(2)	120(2)
Pt(1)-N(3)-C(4)	120(2)	120(2)	Pt(2)-N(3A)-C(4A)	123(2)	119(2)
Pt(1)-N(4A)-C(4A)	131(3)	126(2)	Pt(2)-N(4)-C(4)	131(2)	123(2)
Pt(1)-N(5)-O(51)	-	120(2)	Pt(2)-N(6)-O(6)	-	120(1)
Pt(1)-N(5)-O(52)	-	120(2)	Pt(2)-N(6)-O(62)	-	121(2)
O(51)-N(5)-O(52)	-	119(2)	O(61)-N(6)-O(62)	-	118(2)
C(1)-N(1)-C(2)	119(4)	117(2)	C(1A)-N(1A)-C(2A)	123(3)	114(2)
C(1)-N(1)-C(6)	122(3)	121(2)	C(1A)-N(1A)-C(6A)	115(3)	124(2)
C(6)-N(1)-C(2)	118(3)	122(2)	C(6A)-N(1A)-C(2A)	122(3)	122(2)
N(1)-C(2)-O(2)	117(3)	123(3)	N(1A)-C(2A)-O(2A)	117(3)	124(3)
N(1)-C(2)-N(3)	123(4)	118(2)	N(1A)-C(2A)-N(3A)	121(4)	116(3)
O(2)-C(2)-N(3)	119(3)	119(2)	O(2A)-C(2A)-N(3A)	122(3)	120(2)
C(2)-N(3)-C(4)	118(3)	120(2)	C(2A)-N(3A)-C(4A)	121(3)	122(2)
N(3)-C(4)-N(4)	124(3)	118(2)	N(3A)-C(4A)-N(4A)	123(3)	118(2)
N(3)-C(4)-C(5)	117(3)	119(3)	N(3A)-C(4A)-C(5A)	119(3)	118(3)
N(4)-C(4)-C(5)	120(4)	122(2)	N(4A)-C(4A)-C(5A)	118(3)	124(3)
C(4)-C(5)-C(6)	121(4)	117(3)	C(4A)-C(5A)-C(6A)	119(4)	115(3)
C(5)-C(6)-N(1)	119(3)	122(2)	C(5A)-C(6A)-N(1A)	118(3)	127(2)
O(71)-N(7)-O(72)	125(6)	118(4)	O(71)-N(7)-O(73)	123(5)	92(3)
O(72)-N(7)-O(73)	112(4)	150(4)	O(81)-N(8)-O(82)	102(8)	120(2)
O(81)-N(8)-O(83)	129(10)	122(3)	O(82)-N(8)-O(83)	127(8)	118(2)

Possible hydrogen bond angles

	Atoms	Angle	Atoms	Angle	Atoms	Angle
A	Pt(1)-N(11)-N(4A)	45.9(8)	C(4A)-N(4A)-N(11)	110(2)	Pt(1)-N(11)-O(2A)[a]	96(1)
	C(2a)[a]-O(2A)[a]-N(11)	152(2)	Pt(1)-N(11)-OH(1)[b]	112(1)	N(4A)-N(11)-O(2A)[a]	127(1)
	N(4A)-N(11)-OH(1)[b]	89(1)	O(2A)[a]-N(11)-OH(1)[b]	72(1)	Pt(1)-N(12)-O(2)	70.9(9)
	C(2)-O(2)-N(12)	87(2)	Pt(1)-N(12)-O(2A)[a]	91(1)	C(2A)[a]-O(2A)[a]-N(12)	146(2)
	Pt(1)-N(12)-O(83)	99(2)	N(8)-O(83)-N(12)	114(7)	Pt(1)-N(12)-O(71)[c]	108(2)
	N(7)[c]-O(71)[c]-N(12)	108(4)	O(2)-N(12)-O(2A)[a]	97(1)	O(2)-N(12)-O(83)	163(2)
	O(2)-N(12)-O(71)[c]	86(1)	O(2A)[a]-N(12)-O(83)	97(2)	O(2A)[a]-N(12)-O(71)[c]	160(1)
	O(83)-N(12)-O(71)[c]	84(2)	Pt(2)-N(21)-O(2)[d]	99(1)	C(2)[d]-O(2)[d]-N(21)	151(2)
	Pt(2)-N(21)-N(4)	45.9(8)	C(4)-N(4)-N(21)	109(2)	Pt(2)-N(21)-O(83)	96(2)
	N(8)-O(83)-N(21)	151(6)	Pt(2)-N(21)-O(71)[c]	118(2)	N(7)[c]-O(71)[c]-N(21)	157(3)

TABLE 34 (Cont'd)

	Atoms	Angle	Atoms	Angle	Atoms	Angle
	O(2)^{d}-N(21)-N(4)	125(1)	O(2)^{d}-N(21)-O(83)	95(2)	O(2)^{d}-N(21)-O(71)^{c}	143(1)
	N(4)-N(21)-O(83)	124(2)	N(4)-N(21)-O(71)^{c}	87(1)	O(83)-N(21)-O(71)^{c}	79(2)
	Pt(2)-N(22)-O(2)^{d}	90(1)	C(2)^{d}-O(2)^{d}-N(22)	151(2)	Pt(2)-N(22)-O(2A)	73(1)
	C(2A)-O(2A)-N(22)	94(2)	Pt-N(22)-O(72)^{e}	106(1)	N(7)^{e}-O(72)^{e}-N(22)	150(3)
	O(2)^{d}-N(22)-O(2A)	98(1)	O(2)^{d}-N(22)-O(72)^{e}	162(1)	O(2A)-N(22)-O(72)^{e}	78(1)
	C(4)-N(4)-OH(2)^{c}	120(2)	C(4A)-N(4A)-O(82)^{b}	113(2)	N(8)^{b}-O(82)b-N(4A)	121(6)
	N(7)-O(72)-OH(1)	98(3)	N(7)-O(73)-OH(2)^{f}	154(3)	N(8)-O(82)-OH(1)	153(6)
	N(7)-O(71)-OH(1)	96(3)	N(21)-N(4)-OH(2)^{c}	98(1)	N(11)-N(4A)-O(82)^{b}	95(2)
	N(11)-OH(1)^{b}-O(71)^{b}	125(2)	N(11)-OH(1)^{b}-O(72)^{b}	121(2)	N(11)-OH(1)^{b}-O(82)	91(2)
	O(71)-OH(1)-O(72)	41(1)	O(71)-OH(1)-O(82)	139(2)	O(72)-OH(1)-O(82)	106(2)
	O(73)^{h}-OH(2)-OH(2)^{g}	116(2)	O(73)^{h}-OH(2)-N(4)^{2}	98(2)	OH(2)^{g}-OH(2)-N(4)^{i}	139(2)
B	Pt(1)-N(12)-O(2)	78.1(7)	C(2)-O(2)-N(12)	101(2)	Pt(1)-N(12)-O(2)	130(1)
	C(2)^{j}-O(2)^{j}-N(12)	167(2)	Pt(2)-N(22)-O(2A)	75.2(7)	C(2A)-O(2A)-N(22)	97(2)
	C(2A)-O(2A)-OH(2)^{p}	150(2)	Pt(2)-N(22)-OH(1)^{j}	116(1)	Pt(2)-N(22)-O(83)^{k}	112(1)
	N(8)^{k}-O(83)^{k}-N(22)	140(2)	Pt(2)-N(22)-O(83)^{l}	139(1)	N(8)^{l}-O(83)^{l}-N(22)	107(2)
	C(4A)-N(4A)-O(61)^{k}	107(1)	N(6)^{k}-O(61)^{k}-N(4A)	114(1)	Pt(2)-N(22)-O(81)^{l}	127(1)
	N(22)-O(81)^{l}-N(8)^{l}	91(2)	Pt(1)-N(12)-O(2)	78.1(7)	N(12)-O(2)-C(2)	101(2)
	Pt(1)-N(12)-O(2)	130(1)	C(2)^{j}-O(2)^{j}-N(12)	167(2)	Pt(1)-N(12)-O(52)^{j}	137(1)
	N(12)-O(52)-N(5)^{j}	104(1)	Pt(1)-N(12)-OH(1)^{j}	94.6(8)	Pt(1)-N(12)-O(72)^{m}	120(1)
	N(7)^{m}-O(72)^{m}-N(12)	137(4)	Pt(1)-N(11)-OH(1)^{j}	107.1(8)	Pt(1)-N(11)-O(82)^{k}	119(1)
	N(11)-O(82)^{k}-N(8)^{k}	104(1)	Pt(1)-N(11)-O(83)^{k}	124(1)	N(11)-O(83)^{k}-N(8)^{k}	95(2)
	Pt(1)-N(11)-O(81)^{n}	135(1)	N(11)-O(81)^{n}-N(8)^{n}	107(2)	Pt(2)-N(21)-O(72)^{m}	112(1)
	N(21)-O(72)^{m}-N(7)^{m}	146(3)	Pt(2)-N(21)-O(73)^{g}	116(1)	N(21)-O(73)^{g}-N(7)^{g}	101(3)
	Pt(2)-N(21)-O(51)^{o}	111(1)	N(21)-O(51)^{o}-N(5)^{o}	101(1)	Pt(2)-N(21)-O(52)^{o}	129(1)
	N(21)-O(52)^{o}-N(5)^{o}	95(1)				

a-i. Atoms are related to those in Table 33 by the relationships.

a, x, ½ - y, ½ + z;	b, -x, y - ½, ½ - z;	c, 1 - x, y - ½, ½ - z;
d x, ½ - y, z - ½;	e, -x, 1 - y, -z;	f, x, 1.5 - y, z - ½;
g, 1 - x, 1 - y, 1 - z;	h, x, 1.5 - y, ½ + z;	i, 1 - x, ½ + y, ½ - z;
j, -x, -y, 1 - z;	k, x - 1, y, z;	l, 1 - x, -y, -z;
m, x, y - 1, z;	n, -x, -y, -z;	o, 1 + x, y, z;
p, x, y, z - 1;	q, -x, 1 - y, 1 - z;	r, x, y, 1 + z.

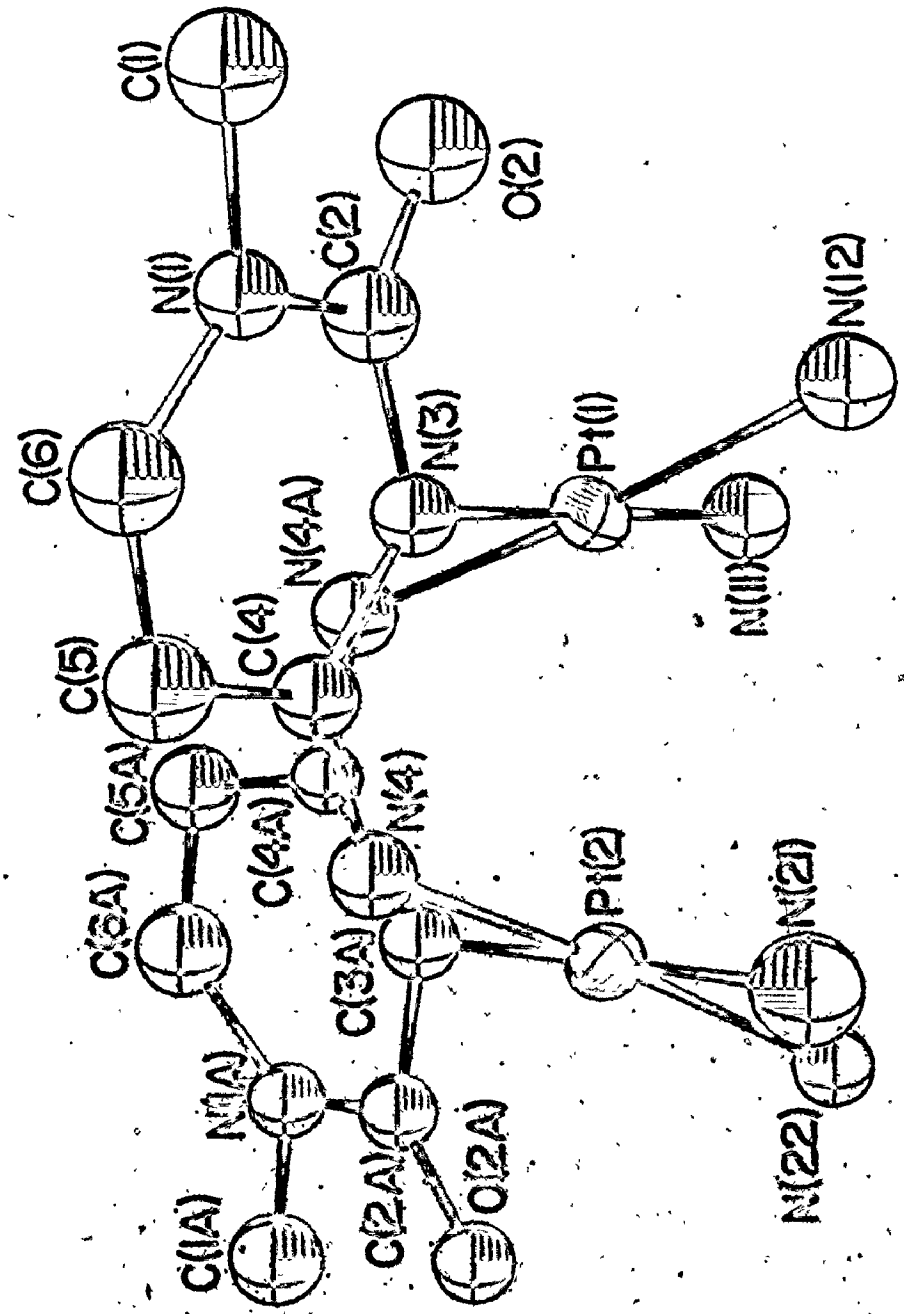


Figure 22

The molecular cation $[(NH_3)_2Pt(C_5H_6NO)_2Pt(NH_3)_2]^{2+}$ showing the atom numbering.

TABLE 35

Selected cytosine bond angles (deg.) for A, B and monoplatinated cytosines

Angle	A[a]	Pt-(1-MeCyt-N3)[b]	B[c]
N(3)-C(4)-N(4)	123(3)	119(1)	118(2)
N(4)-C(4)-C(5)	119(4)	120(1)	123(2)
N(3)-C(4)-C(5)	118(3)	121(1)	118(3)
C(5)-C(6)-N(1)	118(3)	121(1)	124(2)
N(1)-C(2)-O(2)	117(3)	120.5(5)	123(3)
N(1)-C(2)-N(3)	122(4)	118(1)	117(2)
C(4)-C(5)-C(6)	120(4)	117.7(5)	116(3)

a - data is from Table 34 (average of two reported values)

b - data is extracted from Appendix 3

c - data from ref. 138 (average of two reported values)

changes occur in angles N(4)-C(4)-C(5), N(3)-C(4)-C(5), C(5)-C(6)-N(1) and N(1)-C(2)-O(2) (which decrease by 1°, 3°, 3° and 3°, respectively) and in angles N(1)-C(2)-N(3) and C(4)-C(5)-C(6) (which increase by 4° and 2°, respectively).

The title compound, A, is very much like platinum(II)-1-methylthyminato,[143] platinum(II)-1-methyluracilato,[142] and platinum(IIS)[h]-1-methylcytosinato,[138] B, (see Figure 23) which has recently been reported. The major differences in the cations lie in the change in platinum atom-platinum atom distances from 2.981(2), 2.954(2),[142] and 2.974(1)[143] for the Pt(II) complexes to 2.584(1) for the Pt(IIS) complex. As the platinum atom-platinum atom distance decreases (i.e., as the Pt(II) dimer is oxidized to the Pt(IIS) dimer), the N(3)-C(4)-N(4) angle also decreases by about 5° to 118(2)°, essentially the same angle found in monoplatinated cytosine (119(1), see Appendix 3 and Table 35). Other angular changes occur in the bridging framework (see Table 36) as the Pt-Pt distance is shortened: C(4)-N(4)-Pt(2) decreases by about 5° as does Pt-N(3)-C(4) (4°) while Pt(1)-Pt(2)-N(4) and Pt(2)-Pt(1)-N(3) increase by 5° and 2°, respectively. These angular changes are expected for a shortening of the Pt-Pt distance. What is interesting, though, are the angular changes (described above) which occur <u>within</u> the cytosine rings. These changes might be caused by <u>inductive</u> effects resulting from the oxidation

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[h] The Roman numeral representation for $\frac{1}{2}$ is the letter S (semis).

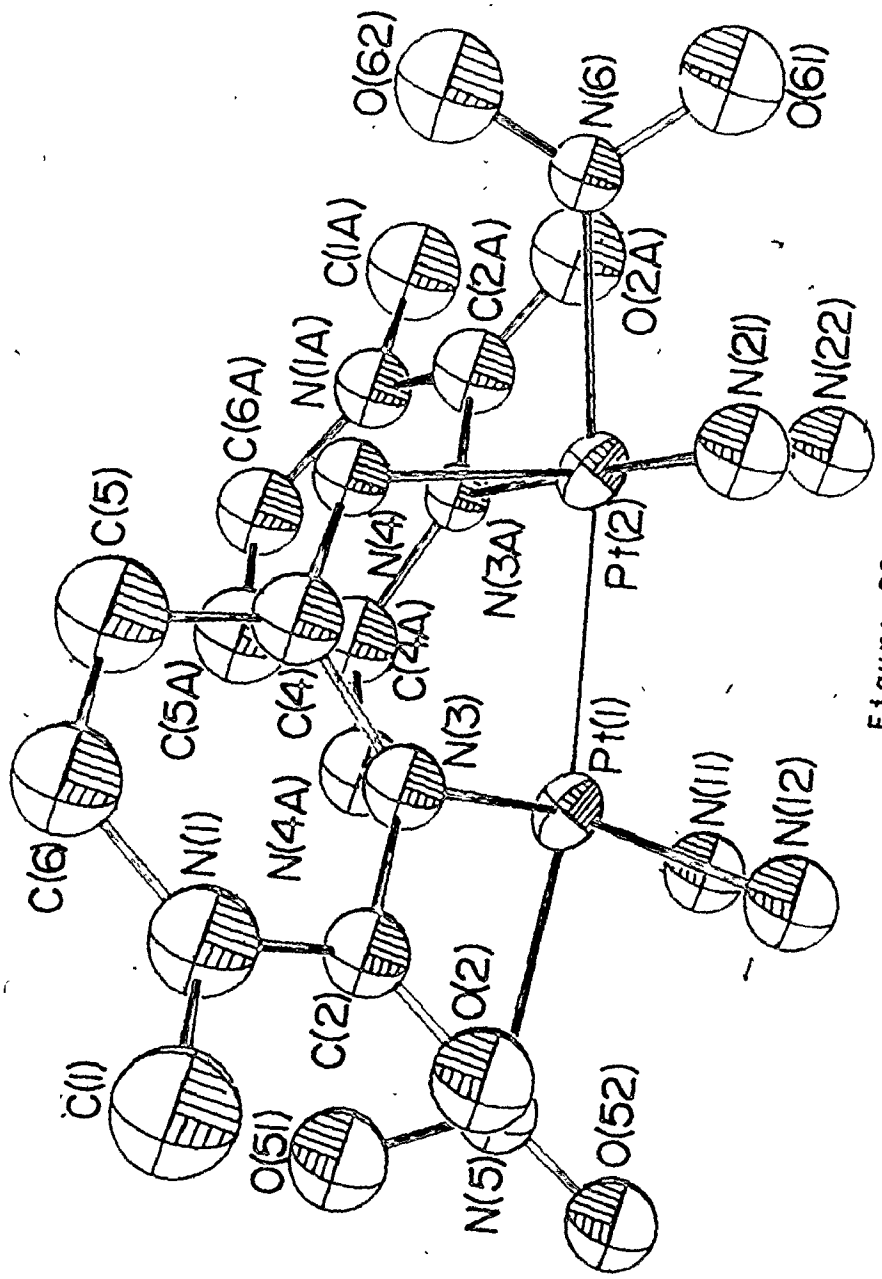


Figure 23

The molecular cation $[O_2N(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2NO_2]^+$. showing the atom numbering. Reproduced from ref. 138.

TABLE 36

Comparison of bond lengths and angles within the bridging framework of a series of dimeric platinum-pyrimidine complexes

	Distance (Å)				
	Pt-Pt	Pt-N3	N3-C4	C4-O4(N4)	Pt-O4(N4)
Pt(II)-1-methylthymine[143]	2.974(1)	2.064(8) 2.014(9)	1.30(2) 1.35(2)	1.26(2) 1.29(1)	2.037(7) 2.013(7)
Pt(II)-1-methyluracil[142]	2.954(2)	2.041(13) 2.046(15)	1.37(3) 1.34(3)	1.28(4) 1.25(4)	2.026(18) 2.060(16)
Pt(II)-1-methylcytosine	2.981(2)	2.04(2) 2.06(3)	1.38(5) 1.31(4)	1.31(4) 1.23(4)	2.01(2) 2.06(3)
Average	2.970	2.04	1.34	1.27	2.03
Pt-(IIS)-1-methylcytosine[138]	2.584(1)	2.00(2) 2.06(2)	1.37(3) 1.29(4)	1.29(4) 1.28(3)	2.02(2) 2.00(2)
Average		2.03	1.33	1.285	2.01

	Angle (deg.)				
	Pt-Pt-N3	Pt-N3-C4	N3-C4-O4(N4)	C4-O4(N4)-Pt	O4-Pt-Pt
Pt(II)-1-methylthymine	79.6(3) 81.6(3)	125.1(8) 124.9(7)	123(1) 121(1)	129.5(8) 130.6(8)	78.7(3) 77.4(3)
Pt(II)-1-methyluracil	82.4(7) 82.6(8)	122(2) 121(2)	122(2) 125(2)	129(1) 127(1)	77.1(6) 76.6(6)
Pt(II)-1-methylcytosine	83.8(8) 81.5(8)	120(2) 123(2)	124(3) 123(3)	131(2) 131(3)	77(1) 77(1)
Average	81.9	123	123	130	77.3
Pt(IIS)-1-methylcytosine	83.6(7) 85.0(6)	120(2) 119(2)	118(2) 118(2)	123(2) 126(2)	83.0(6) 82.2(7)
Average	84.3	119.5	118	124.5	82.6

of Pt(II) to Pt(IIS) rather than by changes in the bridging framework. The angular changes occurring within the cytosine ring (when Pt in A is oxidized to form B) are essentially equal and opposite to the effects caused when a second platinum atom binds at N(4) of a monoplatinated cytosine to form A: the angles N(4)-C(4)-C(5), C(5)-C(6)-N(1) and N(1)-C(2)-O(2) decrease by 3°, 3° and 3.5°, respectively (relative to monoplatinated cytosine) and angles N(1)-C(2)-N(3) and C(4)-C(5)-C(6) increase by 1° and 2°, respectively. Since the bite distance of N(3)-C(4)-N(4) is the same in B and in monoplatinated cytosine , it can be argued that the internal angular distortions are not caused by steric effects, but by inductive effects. These can be explained in the following way: in the next section, an nmr study will be described which shows that when a platinum complex binds at N(3) of cytosine, it inductively withdraws electron density from the ring. The inductive effects, though, are only 60-70% of those caused by protonation at N(3). This implies, of course, that protons can localize electron density better than platinum complexes. When a second platinum complex binds at N(4) of cytosine by displacing a proton, it cannot localize the charge as well. Therefore, electron density is delocalized into the cytosine ring causing distortions in the internal angles. Lippert showed that there was a considerable <u>upfield</u> shift (0.57 ppm)[138] in the C(6) proton resonance

of A relative to monoplatinated cytosine molecules, verifying this postulate. When A is oxidized to B, electron density is withdrawn from the ring. The oxidized platinum atom, now a better electrophile than the proton, causes a marked distortion in the opposite direction as illustrated in Table 35.

The results in Table 37 show that the exocyclic atoms are quite significantly out of the plane of the pyrimidine rings (for both A and B, but especially for B). For the platinum atoms bound to N(3) and N(4) of cytosine in B, this distortion is caused by the axial NO_2 groups. (Major changes in the twist angles of the various groups must occur so that the NO_2 groups can bind as shown by the best least squares planes data in Table 37.) Thus, the dihedral angle between the square planes is reduced to 21° for B from 34° for A and there is an increasing rotation of the two square planes from the eclipsed position from 16° for A to 25° for B. The dihedral angle between the two pyrimidine planes remains about the same in the two complexes (A 77°, B 77°), but the pyrimidine rings are twisted much more from the N(3)-Pt-Pt and N(4)-Pt-Pt planes in B (N(3), 34.6°; 38.5°; N(4), 31.4°, 33.2°) compared to A (N(3), 16.1°, 17.5°; N(4), 21.0°, 23.5°). As can be seen in Figure 23, this is to reduce the contact between the exocyclic O(2) atom and the nitrogen atom of the nitro groups.

The geometries about the platinum atoms are square planar with some small distortion towards tetrahedra.

TABLE 37

Least squares planes through di(μ-1-methylcytosinato-N3,N4)bis(cis-diammineplatinum(II)) dinitrate dihydrate, A, and pentahydrodioxonium di(μ-1-methylcytosinato N3,N4) bis(nitro-cis-diammineplatinum(IIS) dinitrate B.

Plane	Distance of atoms from plane (Å)	
	A	B
1. N(11)N(12)N(3)N(4A)Pt(1)*	N(11), 0.02; N(12), -0.02; N(3), 0.02; N(4A), -0.02; Pt(1), 0.03.	N(11), 0.00; N(12), 0.00; N(3), 0.00; N(4), 0.00; Pt(1), 0.15.
2. N(21)N(22)N(3A)N(4)Pt(2)*	N(21), -0.05; N(22), 0.04; N(3A), -0.04; N(4), 0.05; Pt(2), -0.04.	N(21), -0.04; N(22), 0.04; N(3A), -0.04; N(4), 0.04; Pt(2), -0.01.
3. N(1)C(2)N(3)C(4)C(5)C(6)Pt(1)* C(1)*O(2)*N(4)*Pt(2)*	N(1), 0.07; C(2), -0.10; N(3), 0.04; C(4), 0.05; C(5), -0.08; C(6), 0.03; Pt(1), -0.09; C(1), 0.20; O(2), -0.22; N(4), 0.16; Pt(2), 0.73.	N(1), 0.06; C(2), 0.00; N(3), -0.07; C(4), 0.08; C(5), -0.02; C(6), -0.05; Pt(1), -0.70; C(1), 0.32; O(2), 0.14; N(4), 0.20; Pt(2), 0.55.
4. N(1A)C(2A)N(3A)C(4A)C(5A)C(6A), Pt(2)* C(1A)*O(2A)*N(4A)*Pt(1)*	N(1A), -0.05; C(2A), 0.06; N(3A), -0.02; C(4A), -0.03; C(5A), 0.04; C(6A), 0.00; Pt(2), 0.04; C(1A), -0.12; O(2A), 0.09; N(4A), -0.19; Pt(1), -0.86.	N(1A), -0.03; C(2A), -0.02; N(3A), 0.06; C(4A), -0.05; C(5A), -0.01; C(6A), 0.05; Pt(2), 0.37; C(1A), -0.33; O(2A), -0.06; N(4A), -0.17; Pt(1), -0.78.
5. N(5)O(51)O(52)Pt(1)*	-	Pt(1), -0.30
6. N(6)O(61)O(62)Pt(2)*	-	Pt(2), 0.30
7. N(7)*O(71)O(72)O(73)	N(7), 0.21	N(7), 0.01
8. N(8)*O(81)O(82)O(83)	N(8), 0.11	N(8), 0.01

*Atoms given no weight in determining the best plane; other atoms are given unit weight. Errors in atom positions about 0.02 Å except for the nitrate groups for A ∿ 0.05 Å.

Other planes are 9, Pt(1)Pt(2)N(11); 10, Pt(1)Pt(2)N(12); 11, Pt(1)Pt(2)N(3); 12, Pt(1)Pt(2)N(4A); 13, Pt(2)Pt(1)N(21); 14, Pt(2)Pt(1)N(22); 15, Pt(2)Pt(1)N(3A); 16, Pt(2)Pt(1)N(4).

(cont'd)

TABLE 37 (cont'd) Interplanar Angles (deg.)

Planes	Angle		Planes	Angle		Planes	Angle	
	A	B		A	B		A	B
1-2	34.2	20.6	4-12	23.5	33.2	6-15	-	70.4
11-16	15.8	25.9	4-15	17.5	28.5	6-16	-	20.6
12-15	15.0	25.4	3-7	87.1	76.1	5-9	-	52.1
9-14	16.8	25.8	3-8	72.1	81.1	5-10	-	41.7
10-13	15.5	22.2	4-7	18.4	81.0	5-11	-	52.5
3-4	77.3	77.2	4-8	82.4	23.6	5-12	-	37.4
3-11	16.1	34.6	6-13	-	71.5			
3-16	21.0	31.4	6-14	-	20.4			

As noted previously (see Table 8, p. 56), the $Pt-NH_3$ distances for ammonia groups (*trans* to N(3) of cytosine) range from 2.04(1) to 2.06(2) Å and have an average of 2.05(1) Å. The $Pt-NH_3$ distances *trans* to N(3) in the title compound agree well with these values, 2.03(3) Å and 2.06(3) Å (average 2.045 Å). *Trans* to the deprotonated N(4), however, the $Pt-NH_3$ bond lengths range from 2.05(2) - 2.11(3) Å (for the title compound and $(H_5O_2)[(NH_3)_2(NO_2)-Pt(C_5H_6N_3O)_2Pt(NO_2)(NH_3)_2](NO_3)_2$ [138]) and the average value is 2.07(3) Å. Although the difference in Pt-N distance is not significant, the deprotonated N(4) appears to have a stronger *trans* influence than N(3).

The packing of the bridged molecules are shown in Figures 24 and 25. Hydrogen bonding is a major factor in holding the crystals together. With respect to the $[(NH_3)Pt(C_5H_6N_3O)_2Pt(NH_3)_2](NO_3)_2 \cdot 2H_2O$ structure the molecules are arranged so that Pt(1)-Pt(2) is roughly along $\underset{\sim}{c}$. The molecules are then stacked into chains along $\underset{\sim}{c}$ so that the ammonia groups of one molecule are hydrogen bonded to O(2) of cytosine rings in an adjacent molecule: N(11)-O(2A), N(12)-O(2A), N(21)-O(2) and N(22)-O(2). One chain is centred at about y = 1/4, while the other is at y = 3/4. The chains are linked together in the $\underset{\sim}{b}$ direction, primarily through the N(8) nitrate group of which O(83) is bonded to N(21) and N(12) in one molecule and N(4A) in cytosine of an adjacent chain. O(82) is also bonded through OH(1) to

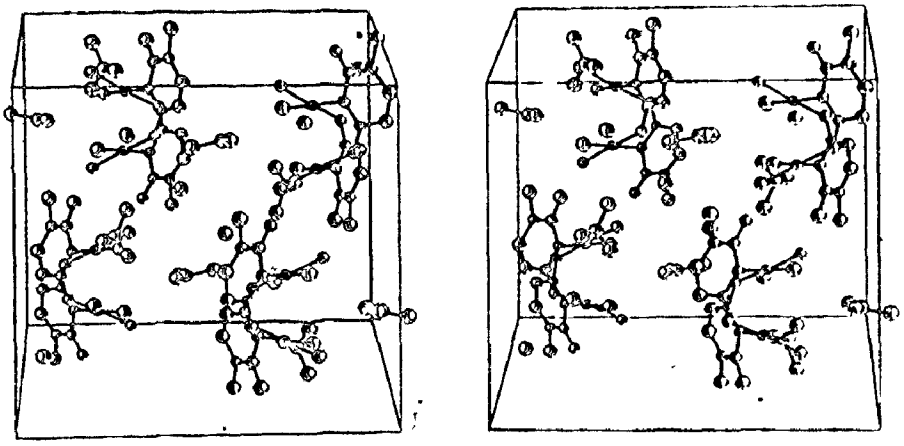


Figure 24

The unit cell contents of $[(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2]$-$(NO_3)_2 \cdot 2H_2O$. $\underset{\sim}{b}$ and $\underset{\sim}{c}$ are parallel to the bottom and sides of the page, respectively and the view is down $\underset{\sim}{a}^*$.

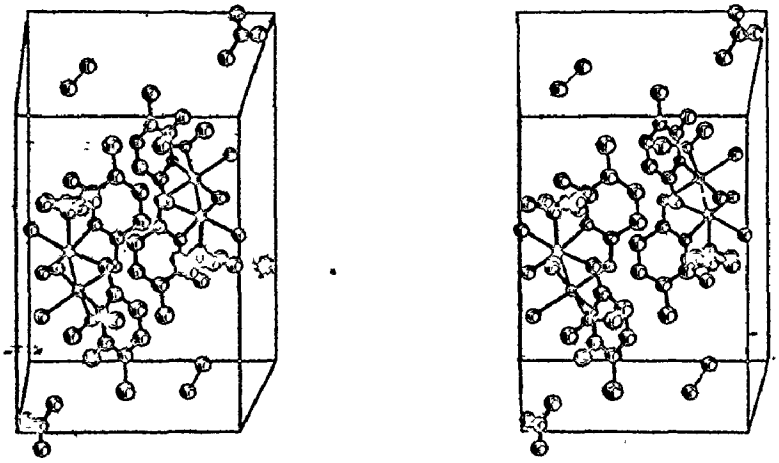


Figure 25

The unit cell contents of $(N_5O_2)[NO_2(NH_3)_2Pt(C_5H_6N_3O_2)_2$-$Pt(NH_3)_2(NO_2)](NO_3)_2$. $\underset{\sim}{b}$ and $\underset{\sim}{c}$ are parallel to the bottom and sides of the page, respectively and the view is down $\underset{\sim}{a}^*$. Reproduced from ref. 138.

O(71) and O(72) of the N(7) nitrate group. The N(7) nitrate ion is stacked parallel to the planes of the cytosine rings in adjacent chains along $\underset{\sim}{b}$ but is only in contact with one of them. In the $\underset{\sim}{a}$ direction, there are primarily C-H, H-C contacts between the cytosine rings and there are few short-range hydrogen bonding links. Some long range NH_3-NO_3-H_2O hydrogen bond interactions occur.

The formation of chains of ligand bridged dimers (along $\underset{\sim}{c}$ as discussed for $[(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2]$-$(NO_3)_2\cdot 2H_2O$ is not unique and occurs in the uracilato and thyminato bridged dimers $[(NH_3)_2Pt(C_5H_5N_2O_2)_2Pt(NH_3)_2]$-$(NO_3)_2\cdot 3H_2O$ and $[(NH_3)_2Pt(C_5H_7N_2O_2)_2Pt(NH_3)_2](NO_3)_2\cdot H_2O$. In both the uracilato and thyminato structure, the chains are essentially along the c axes. In the $(H_5O_2)[NO_2$-$(NH_3)_2Pt(C_5H_6N_3O_2)_2Pt(NH_3)_2(NO_2)](NO_3)_2$ structure, the chains are again along $\underset{\sim}{c}$ (Fig. 25).

2.7.3 Inductive effects caused by cytosine: an NMR study

The title compound is surprising in that cytosine must be deprotonated at C-NH_2 before a platinum complex can bind. Reasons for this are discussed below. The exocyclic NH_2 group can be best represented by:

The bond order for the C-N bond, based on the known bond length[105] and the Pauling bond length-bond order relationship,[146] is 1.6 and thus resonance forms which include the above structure must make an important contribution to the total structure. The NH_2 group will at best be a hindered rotor and in the preferred position will be coplanar with the pyrimidine ring. Least squares plane calculations for the exocyclic N atoms of neutral cytosine molecules show that the exocyclic N atoms deviate marginally from the plane of the ring (average is 0.04 Å where rms deviation from planarity of atoms used to calculate planes averages 0.01 Å, see Table 37, p. 173). The sp^2 hybridized[12] moiety does not present a bonding orbital to a platinum complex and such an orbital becomes available only upon deprotonation.

The pK_a of the free cytosine base is 12.4,[120] and since the pH of the reaction solution was slightly acidic, Pt was thought to effect a pK_a shift in cytosine for the NH_2 protons. Since N(3) is the primary binding

site for platinum complexes (see p. 147), it was considered that the platinum complexes acted inductively to withdraw electron density from NH_2 after binding to N(3), causing a major change in the pK_a of the NH_2 group moving it close to 7. This was expected to cause deprotonation at NH_2 at pH 7 and then binding of the second platinum atom (see more detailed discussion on p. 198).

Such inductive effects by electrophilic platinum complexes could presumably cause changes in the bond angles and lengths of cytosine similar to those caused by the proton. To verify this hypothesis, bond lengths and angles found in neutral cytosine rings and rings protonated at N(3) were compared to those for 1-methylcytosine rings bound to Pt at N(3) (this work, see Section 2.6.3, Appendix.5, and Table 31). Although electrophiles, platinum complexes were shown to have a much smaller effect on the molecular structure of the cytosine ring than protons.

Since the inductive effects of platinum complex binding to cytosine were not large enough to be detected using crystallographic data, a more sensitive probe of such effects was used. The position of the proton resonance in the ^1H-nmr spectrum can be related to the pK of the group to which the proton is attached.[147,148] To show the change in pK of the NH_2 protons of 1-methylcytosine on platinum atom coordination, the nmr spectra were recorded for 1-methylcytosine and a mixture of 1-methylcytosine

and K_2PtCl_4 using dimethylsulphoxide as the solvent in both cases (see p. 45 for details). The spectra are illustrated in Figure 26. As can be seen, the NH_2 resonance of 1-methylcytosine at 6.95 ppm (δ scale) is shifted downfield (by 1.75 and 1.33 ppm) and split into two components on binding to the platinum complex. The splitting of the NH_2 signals suggests that the two protons are now no longer magnetically equivalent, because of increased hindered rotation on metal binding. N(3) was verified as the binding site for platinum complexes because Pt coupling, which is frequently observed when N(3) is the coordination site,[48] occurs in the H(5) peak. The downfield shifts of 1.33 and 1.75 ppm are in the right direction for a decrease in pK_a and are greater than has been observed previously for zinc[69] ($\sim$ 1 ppm) or mercury[149] ($\sim$ 1.3 and 1.6 ppm) coordination but not as great as that caused by addition of a proton[70] to N(3) (1.85 and 3.00 ppm). This is consistent with the crystallographic effects observed earlier (Section 2.6.3, p.149).

Simpson,[150] in a uv spectroscopic study on the complexation of mercury(II) complexes with cytidine, found that besides the marked decrease in pK of the NH_2 group on mercuration at N(3), there was evidence of a pH independent deprotonation of the NH_2 group involving CH_3HgOH. It seems that a similar metal-hydroxide assisted deprotonation may

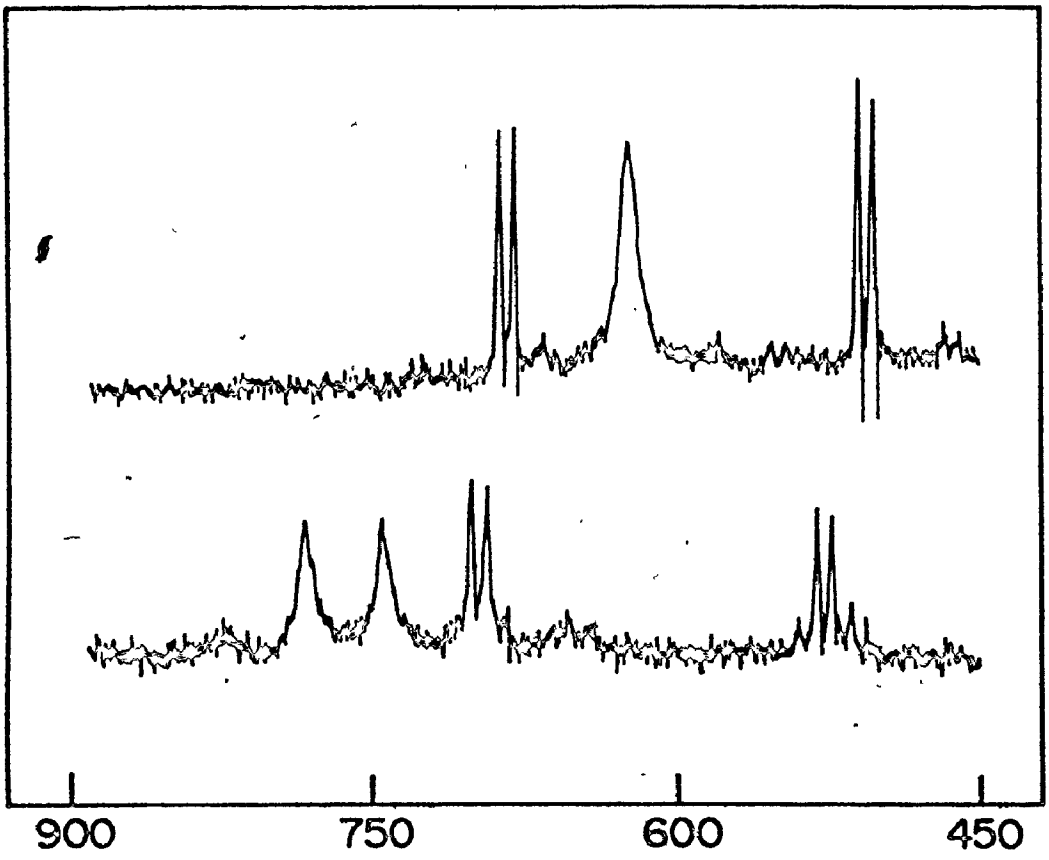


Figure 26

Portions of the proton nmr spectra of:

upper - 1-methylcytosine in dimethylsulphoxide;

lower - 1-methylcytosine and K_2PtCl_4 in dimethyl-sulphoxide.

be taking place as well as the lowering of the pK of the NH_2 group. Metal assisted deprotonation of amines in weakly basic, neutral or slightly acidic solution, although not common, has been reported before, e.g., for gold,[151] copper[152] and platinum(IV) complexes.[153-155] Similar reactions for platinum complexes in non-aqueous solvents have also been reported.[156] The deprotonation which is effected results in ligand bridged formation. The mechanism for formation of the ligand bridged dimers will be discussed in more detail in the Discussion, Chapter 3.

Other inductive effects have been reported previously (or have been measured recently) for DNA bases. Mansy et al. studied platinum complex, 5'-GMP interactions using H^1-nmr (binding sites were verified with ir and Raman spectroscopy). They found that the pK_a of N(1)-H shifted (to become more acidic) by 2.8 units when cis-$Pt(NH_3)_2Cl_2$ bound at N(7) of 5'-GMP[41] (or 1.6 units when cis-$Pt(NH_3)_2(OH_2)_2$ binds at N(7) of inosine[54]). This compares with the value of 1.4 ppm (in the H^1-nmr spectra) measured by B. Lippert[111] for $Pt(NH_3)_2(OH_2)_2^{2+}$ binding to N(7) of 9-methylguanine. An increased acidity in N(1)-H ($\Delta pK_a \approx 2.6$)[66] occurs for methylation at N(7) of 9-methylguanine. So delocalized are the bases (e.g., the resonance stabilization energy calculated for guanine is 60 kcal $mole^{-1}$) that synergistic binding effects can be observed: Mansy and Tobias[67] studied the binding of $CH_3Hg(II)^+$ with inosine

at pH = 8.5. Binding by CH_3Hg^+ occurs quantitatively at N(1)-H of inosine by displacing the proton. Since CH_3Hg^+ cannot localize charge as well as the proton, extensive delocalization of electron density occurs resulting in an increased basicity of N(7). A second CH_3Hg^+ cation was shown to bind at this enhanced site. Binding at N(7) does not occur at pH = 8.5 with 1-methylinosine.

Such enhancement of basicity for a second metal ion has been reported by Ford et al.[157] The proton basicity of pyrazine (1,4-$C_4H_4N_2$) was increased when $Ru(NH_3)_5^{2+}$ bound at N(1), i.e., pK_a increased from 0.6 to 2.5. In fact, $[((NH_3)_5Ru)_2(C_4H_4N_2)]^{4+}$ was readily synthesized. Creutz and Taube[158] deduced that there was a charge transfer from Ru to pyrazine when the first $Ru(NH_3)_5^{2+}$ moiety bound.

The inductive effects which can be induced in DNA bases are of major importance in describing the biological effects of electrophiles. The biological implications of these effects are discussed in Chapter 3.

CHAPTER 3

DISCUSSION

CHAPTER 3

DISCUSSION

3.1 HYDROLYSIS PRODUCTS OF PLATINUM (HYDROXOBRIDGED PLATINUM COMPOUNDS)

Biochemical and physical evidence suggests that the cis-platinum drugs act to cause some primary lesion in cellular DNA by binding to the DNA bases. The structural work contained in this thesis was undertaken to examine the nature of the binding reactions of platinum complexes with the bases. It was considered important to verify to which bases it was possible to bind platinum complexes, and which sites on the bases were most likely to be bound. The X-ray structural results of this work (and those of others) are summarized in Table 29, p. 141 and show that platinum complexes bind to all of the DNA bases plus uracil under mild reaction conditions.

Platinum complexes bind preferentially (see Sect. 2.6.2) at the imidazole sites of adenine and guanine, N(7), and at the tertiary amine site of cytosine, N(3). Binding has also been shown to occur less frequently at: the tertiary amine site of adenine, N(1); deprotonated ring nitrogen sites, N(3) of thymine and uracil; and, at the exocyclic atoms, N(4) of cytosine (after deprotonation), and O(4) of uracil and thymine. Binding at the exocyclic atoms occurs only in ligand bridged platinum dimers of the type [cis-$(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2]^{2+}$

where, in this case, cytosine acts as a bidentate-N(3),N(4) ligand (as illustrated in Figure 22, p.166). Since the structure of these bridged compounds suggests a unique mode of binding of cis-$Pt(NH_3)_2Cl_2$ to the DNA bases, it was considered important to characterize their formation.

The [cis-$(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2](NO_3)_2 \cdot 2H_2O$ dimer was produced (see preparation, p.155) when an aqueous solution of $Pt(NH_3)_2(NO_3)_2$ was reacted with two equivalents of 1-methylcytosine for 20 h at 40°C. The three other ligand bridged dimers (in which a similar mode of binding was observed) are listed in Table 29, p.166. They were also characterized in our X-ray labs during the course of this work.

The first of these $[(NH_3)_2Pt(C_6H_7N_2O_2)_2Pt(NH_3)_2](NO_3)_2 \cdot H_2O$,[143] was formed by reacting an aqueous solution of $Pt(NH_3)_2(NO_3)_2$ (prepared by stirring $Pt(NH_3)_2Cl_2$ with silver nitrate) with an equimolar amount of 1-methylthymine. The pH was adjusted to 6.5 with sodium hydroxide and the solution allowed to sit for 1 week at 37°C. The cationic product is dimeric. The two platinum atoms are bridged by the 1-methylthyminato ligands (through N(3) and O(4)) which are arranged head-to-tail. The two ammine groups are cis on each platinum atom and the square planes of ligand atoms about each platinum atom lie roughly on top of each other.

The second of these compounds, $[(NH_3)_2Pt(C_5H_5N_2O_2)_2Pt(NH_3)_2](NO_3)_2 \cdot 3H_2O$,[142] was formed by reacting $Pt(NH_3)_2(NO_3)_2$

with 1-methyluracil under the same conditions as described above. The uracilato structure is identical to the thyminato structure, except uracilato anions which are N(3)-O(4) bound, form the bridges.

The third structure, cytosinato-N3,N4 bridged, is illustrated in Figure 23, p.169. It precipitated from the same reaction mixture as [cis-$(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2$]-$(NO_3)_2\cdot 2H_2O$, which was reported earlier (see preparation, p.155). The structures are similar except that (H_5O_2)-$[(O_2N)(NH_3)_2Pt(C_5H_6N_3O_2)_2Pt(NH_3)_2(NO_2)](NO_3)_2$[138] has two axial nitro groups, one N bonded to each of the two platinum atoms, i.e., above the square plane of the top platinum atom and below the square plane of the bottom platinum atom. The oxidation states of the platinum atoms in this molecule are different as a result of the bound nitro groups.

The mechanism for formation of these ligand bridged dimers was thought to be based on a more sterically demanding platinum moiety than any of the hydrolysis intermediates cis-$Pt(NH_3)_2(OH_2)_2^{2+}$, cis-$Pt(NH_3)_2(OH_2)Cl^+$, or cis-$Pt(NH_3)_2$-$(OH_2)(OH)^+$, which were normally considered to be the reactive species of platinum. Such a sterically demanding moiety was characterized when attempts were made to isolate hydrolysis intermediates of platinum.

Faggiani et al. found that by treating cis-$Pt(NH_3)_2Cl_2$ in aqueous solution with various silver salts at controlled pH conditions (pH $\sim$ 6.5 maintained by sodium hydroxide) a number of

unusual hydrolysis products could be generated.[25-27] The hydrolysis products were hydroxo bridged dimers, trimers and tetramers that can only be formed by cis platinum compounds. They are formed under mild reaction conditions and are stable even under slightly acidic conditions. Maximum concentrations of hydroxo bridged dimers in saturated aqueous solutions at room temperature were shown to be 0.034 M.

Chikuma et al. subsequently studied the kinetics of the dimerization reaction in freshly prepared aqueous solutions of $Pt(NH_3)_2(NO_3)_2$ using ^{195}Pt nmr.[33] They proposed a mechanism for dimer formation, but more importantly, defined clearly how the equilibrium concentrations of hydroxo bridged dimers varied as the pH of the solutions and as the concentration of the initial diaquo complex. They found that for solutions that were approximately 0.05 M in platinum and for the pH range 4-9, the predominant species were not the diaquo complexes but were the hydroxo bridged dimers and trimers which they had characterized earlier. In fact, the concentration of diaquo species in these solutions becomes negligible. Chikuma et al. concluded that the hydroxo bridged dimers and trimers were important in describing products of reactions of platinum complexes with the DNA bases, particularly for reactions done in vitro where the pH is adjusted to simulate body conditions (~ pH 7.4).

The use of hydrolyzed platinum species as reactants

with DNA bases to form model compounds is in itself a simulation of what is expected to occur *in vivo*. In animal and clinical tests, the platinum drug is administered as the dichloride, $Pt(NH_3)_2Cl_2$. Hydrolysis is postulated to occur in the cells at low $[Cl^-]$ as discussed previously. Since $Pt(NH_3)_2Cl_2$ is very insoluble in water, and since hydrolysis is slow, reactions of $Pt(NH_3)_2Cl_2$ with bases *in vitro* are expedited by reacting hydrolysis products of platinum (usually assumed to be diaquo species) with the bases. The hydrolysis products are prepared by stirring $Pt(NH_3)_2Cl_2$ with silver nitrate and then filtering the silver chloride. Hydrolysis yields solutions of pH ≈ 3.5 (for a typical solution that is 0.04 M in platinum) according to:

$$(NH_3)_2Pt(OH_2)_2^{2+} \rightleftarrows (NH_3)_2Pt(OH_2)(OH)^+ + H^+$$

where $pK_a = 5.56$.[30]

At this pH, 86 mole percent of platinum containing species which exist at equilibrium are diaquo species. As well, though, 12 mole percent of equilibrium species are dimers.[159] (The remaining 2 percent are other hydrolysis products, i.e., monomers and trimers.) Reactions done by mixing equilibrated solutions of $Pt(NH_3)_2(NO_3)_2$ with solutions of DNA bases would be expected to yield products corresponding to the competing reactions:

$$2(H_3N)_2Pt(OH_2)_2^{2+} \xrightarrow{86\%} + \text{base} \rightleftharpoons \text{products}$$

$$2H^+ + [(H_3N)_2Pt(OH)_2Pt(NH_3)_2]^{2+} \xleftarrow{K_d} \xrightarrow{12\%} + \text{base} \rightleftharpoons \text{products}$$

where K_d is fixed by the pH = 3.5 of the solution.

Since the reaction of $Pt(NH_3)_2(NO_3)_2$ with 1-methylcytosine was done without adjusting the pH to 7, the equilibrium ratio of platinum species were approximately as illustrated above (molar ratio is ≈ 7:1). The products [cis-$(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2](NO_3)_2 \cdot 2H_2O$ and $(H_5O_2)[(O_2N)(NH_3)_2Pt(C_5H_6N_3O_2)_2Pt(NH_3)_2(NO_2)](NO_3)_2$ probably resulted (in 2 wt percent and < 2 wt percent, respectively, or < 3 mole percent total) from a reaction of $[(H_3N)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ with 1-methylcytosine. To verify this hypothesis, [cis-$(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2](NO_3)_2$ was resynthesized by reacting dimer of higher purity (to minimize competing reactions) and at higher concentrations with stoichiometric amounts of 1-methylcytosine. The dimer can be maintained in solution as the predominant species by adjusting the pH to within 4-9 (where the concentration of diaquo species is negligible). Since the yield of cytosine bridged dimer was higher (by at least a factor of 4 when the concentration of dimer was increased by 7x), there appears to be a link between the concentration of hydroxo bridged dimers in solution and the mole fraction of ligand bridged compounds formed (see Figure 27). It has not been determined whether the

Figure 27a

Illustration of reactive species (proposed) and products from reactions described in Sect. 2.7.2*

$$\underset{\text{.035 M}}{(H_3N)_2Pt(OH_2)_2^{2+}} + 2\ \text{1-MeCyt} \rightleftarrows \underset{\text{80 wt\%}}{[(H_3N)_2Pt(\text{1-MeCyt})_2]^{2+}}$$

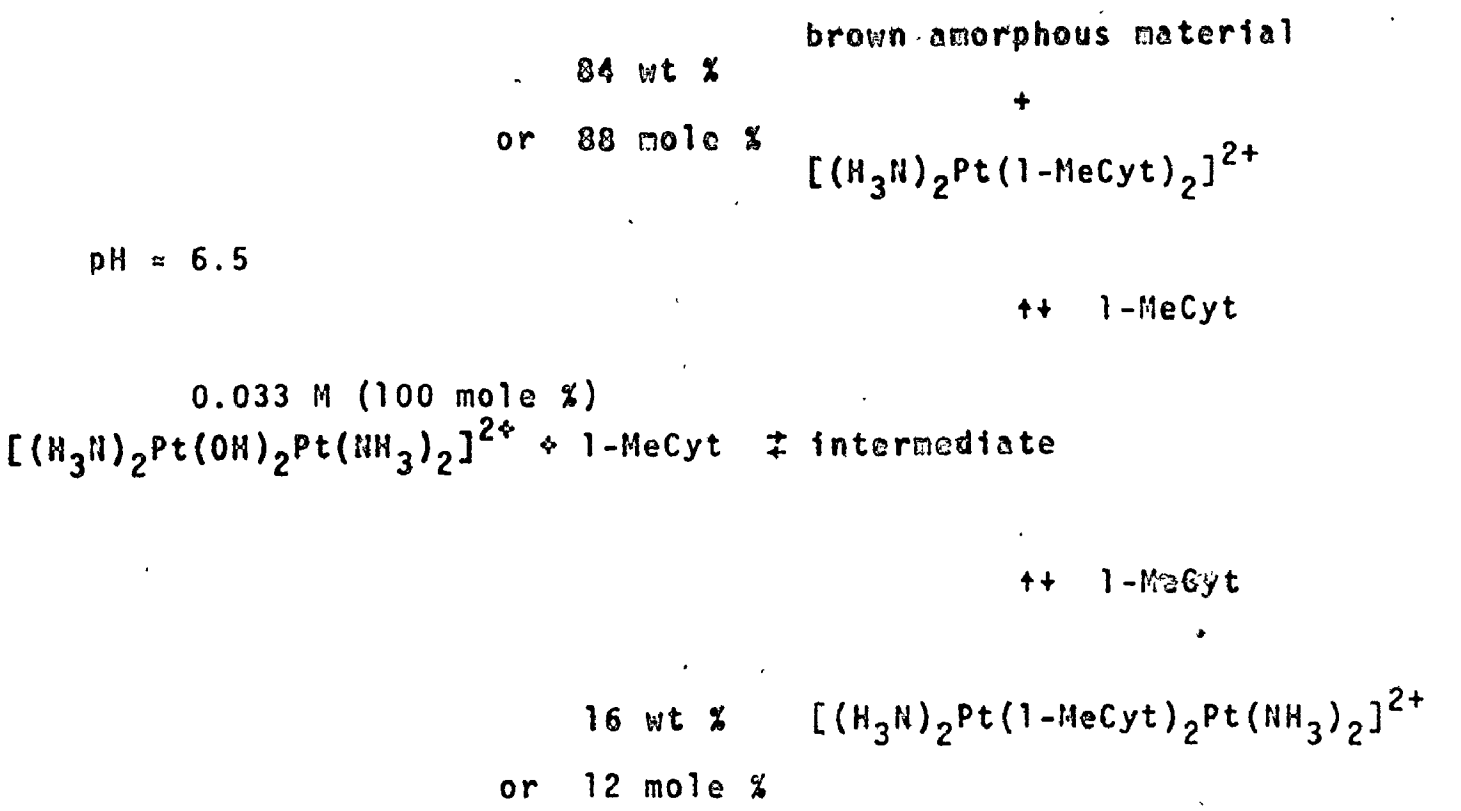
pH ≈ 3.5 ↓↑

$$\underset{\text{.005 M (12 mole\%)}}{[(H_3N)_2Pt(OH)_2Pt(NH_3)_2]^{2+}} + 2\ \text{1-MeCyt} \rightleftarrows \underset{\text{or } < 4\text{ wt\%}}{\overset{< 3\text{ mole \%}}{[(H_3N)_2Pt(\text{1-MeCyt})_2Pt(NH_3)_2]^{2+}}} \rightleftarrows \underset{\text{brown, purple amorphous material}}{\text{16 wt\%}}$$

* Assumptions:

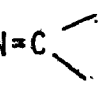
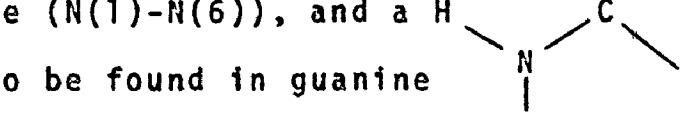
1. [trimer] is negligible since 20% conversion from dimer to trimer takes 2 weeks.[33]
2. at pH ≈ 6.5, the [monomer] is negligible.[33]
3. mole % of products are approximate and based on assumption that all amorphous products have same stoichiometry as $[(H_3N)_2Pt(\text{1-MeCyt})_2](NO_3)_2$

Figure 27b


brown amorphous material
84 wt %
or 88 mole %
+
$[(H_3N)_2Pt(1\text{-MeCyt})_2]^{2+}$
pH ≈ 6.5
++ 1-MeCyt
0.033 M (100 mole %)
$[(H_3N)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ + 1-MeCyt ⇌ intermediate
++ 1-MeCyt
16 wt %
or 12 mole %
$[(H_3N)_2Pt(1\text{-MeCyt})_2Pt(NH_3)_2]^{2+}$

product ratios are determined by kinetic or thermodynamic factors.

The uracilato and thyminato bridged compounds were formed under pH controlled conditions in which the equilibrium fraction of dimer was high and the fraction of diaquo species was negligible. Although the pH was adjusted to 6.4 after the $Pt(NH_3)_2(NO_3)_2$ solution was mixed with uracil or thymine, reactions of platinum complexes with these bases is slow (several days[50]). As well, the half-life period (where $t_{1/2} = \frac{1}{k}$) of the platinum monomers going to hydroxo bridged dimers and trimers is minimized between 6.2 and 7.2. This minimum value for $t_{1/2}$ is 5 min at 25°C, so dimerization would be expected to be complete within ~ 10 min. Since the reaction solution was heated to 37°C, this dimerization would probably occur even more quickly. Binding to uracil and thymine occurs well after dimerization has occurred.

Since an  residue, similar to that found in cytosine, can be found in adenine (N(1)-N(6)), and a  residue found in thymine can also be found in guanine (N(1)-O(6)), it is not unreasonable to propose that reaction of the hydroxo bridged dimer with adenine and guanine should produce similar ligand bridged compounds. This proposed structure for guanine which has been suggested previously by Barton et al.,[160] is illustrated in Figure 28. Verification for such a reaction was provided by Macquet and Theophanides when they reacted cis and trans-$Pt(NH_3)_2Cl_2$

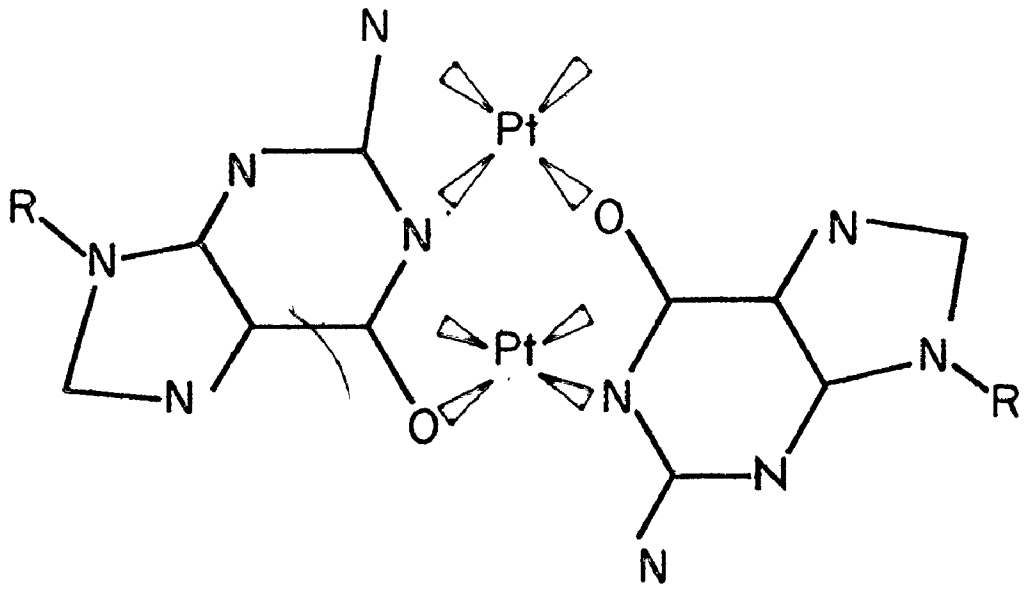


Figure 28

Postulated ligand bridged dimer formed by <u>cis</u>-$Pt(NH_3)_2Cl_2$ and guanine.

with DNA,[161] and found that protons were released. They attributed this to $Pt(NH_3)_2Cl_2$ binding at N(1) of guanine and N(3) of thymine. Also, formation of such a product for guanine would help to rationalize Stone's results which show that the extent of binding of cis-$Pt(NH_3)_2Cl_2$ to DNA can be correlated with the occurrence of GpG sequences.[51] Others[11,51,54,56] have also suggested that platinum complexes bind to pairs of adjacent bases in DNA strands.

Unknowingly, Chu et al.[41] may have studied intermediates of the reactions of $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ with guanine. They have recently described how certain polymeric species (see Figure 3, p. 26) result when "diaquo" species of platinum are reacted with 5'-GMP. The "diaquo" species were prepared[54] by stirring silver perchlorate with cis-$Pt(NH_3)_2Cl_2$ for five hours. After filtering the silver chloride, the solution was evaporated to dryness on a rotovap.[i] As suggested earlier,

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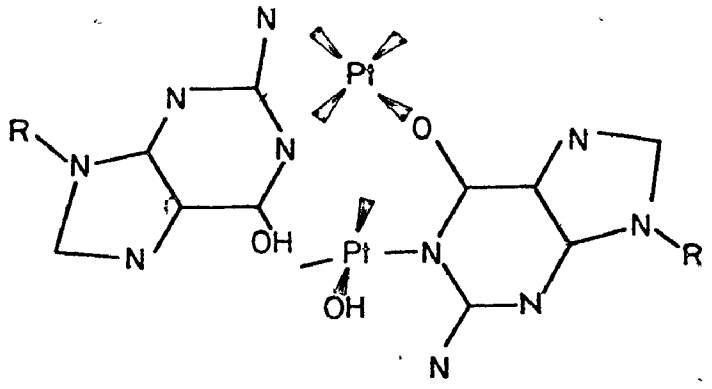
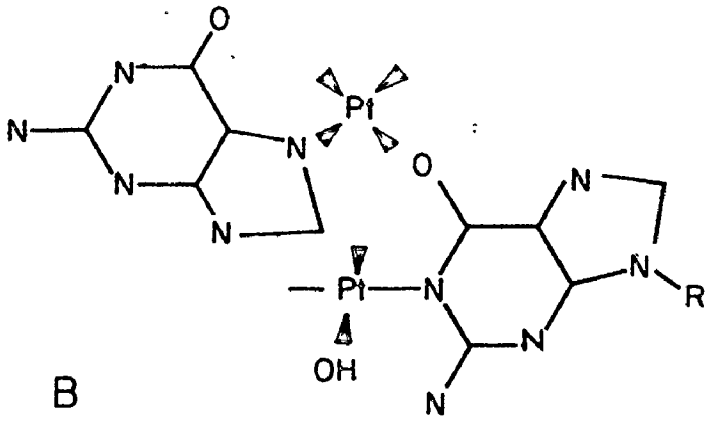
[i] Their own ir evidence,[54] which they have difficulty in explaining, shows that $(NH_3)_2Pt(OH_2)_2(ClO_4)_2$ is probably $[(H_3N)_2Pt(OH)_2Pt(NH_3)_2](ClO_4)_2$ (ir and Raman spectra for $[(H_3N)_2Pt(OH)_2Pt(NH_3)_2](NO_3)_2$ are listed in references 25 and 162). Concentrations of dimer in solution, then, would be higher than the 12% indicated. Lock[163] has recently explained (on the basis of work done by Brown and Shannon)[164] why the diaquo species is unlikely to exist in crystalline form).

products of such preparations are hydrolyzed in aqueous solutions and yield at least 12 percent equilibrium fractions of hydroxo bridged dimers. Since the pH of their solutions were adjusted to 7 before, or just after addition of guanine to the aqueous solutions of platinum, it is probable that mole fractions of $[(H_3N)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ were even higher than this. The identification of the "diaquo" species as the primary reactant involved in polymerization may be incorrect (although monomeric aquo species are probably involved in some form of unidentate binding to guanine at N(7)). The polymers described by Mansy were illustrated previously (Figure 3, p. 26). These proposed structures contain N(1)-N(7) and N(7)-O(6) bridges. They are more complicated than the ligand bridged dimers which were suggested earlier (Fig. 28) and are not consistent with other molecules which have been crystallographically characterized. The assessment that polymerization occurs is based on nmr and ir spectral shifts which suggest that platinum atoms bind at N(7), N(1) and O(6) of the guanine molecule in 5'-GMP. Broadening in the proton nmr resonances of H(8) of the guanine molecule and H(1') of the ribose group also occurs when platinum complexes bind to 5'-GMP. The broadening was detected when the ratio of platinum complex to 5'-GMP increased above 0.5 (maximum ratio used was 1.0). Since this maximum ratio of platinum to GMP is stoichiometric for formation of ligand bridged dimers, the polymers might be better described as: A, intermediates in the formation of ligand bridged

dimers; or, B, intermediates which have misbound to N(7) of excess guanine molecules (which results in quenching of bridge formation reaction). In these structures, as illustrated in Figure 29, binding to N(7), N(1) and O(6) of guanine are invoked to explain the ir, Raman and nmr data. In A and B, guanine bridges two platinum atoms through N(1) and O(6) atoms. Binding to N(7) of guanine occurs as illustrated in compound B.



A



B

Figure 29

Proposed intermediates in the formation of ligand bridged dimers.

3.2 MECHANISMS FOR THE FORMATION OF DNA BASE BRIDGED PLATINUM COMPOUNDS IN AQUEOUS SOLUTION

On the basis of only this structural information and even that physical evidence provided in Chapter 2, it is very difficult to propose a mechanism to describe the reaction of hydroxo bridged dimers with DNA bases to form ligand bridged dimers.

A mechanism involving initial overlap and binding of $[(H_3N)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ with the N(3)-C(4)-N(4) moiety of cytosine as illustrated in Figure 30 has been suggested by Lock *et al.*[143] The initiating step would be a nucleophilic substitution at Pt(1) by N(3) of cytosine. The initiating Pt-N(3) interaction results in a lowering of the pK of the $N(4)H_2$ group. As well, the metal-hydroxide assisted deprotonation (as described previously, p.180) results in a proton transfer to the bridging O-H which is then displaced by N(3) of cytosine.

The deprotonated N(4) substitutes for the second OH (probably also proton assisted) resulting in intermediate B. It is presumed that the reactions described above are concerted. Intermediate B is sterically well disposed (*cis* leaving groups OH and OH_2) to nucleophilic attack by a second cytosine. The second cytosine probably binds to Pt(2) (of intermediate B) as a monodentate ligand (through N(3)) in a simple substitution reaction. The deprotonation induced at N(4) and subsequent proton transfer to the

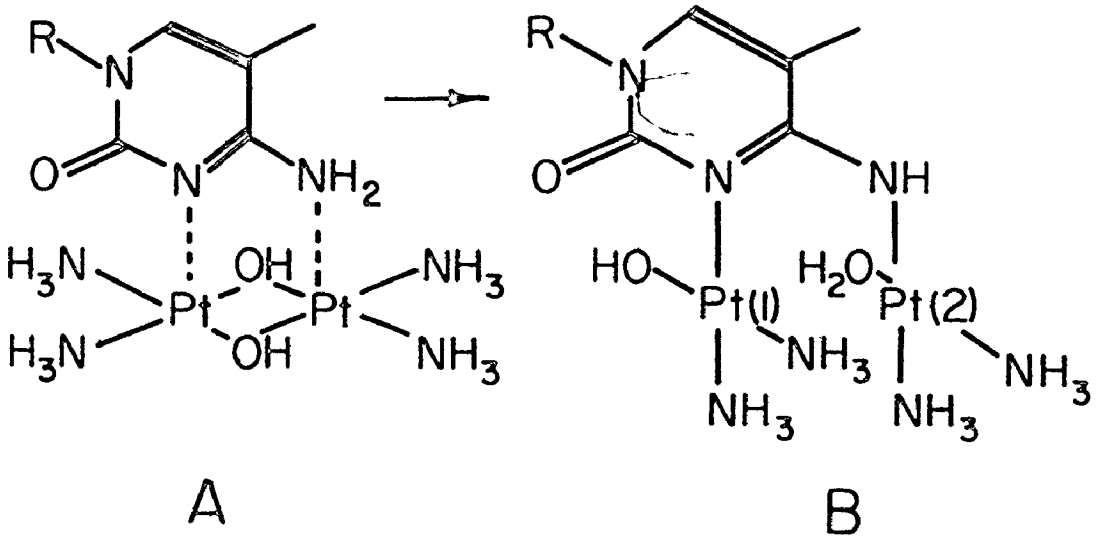


Figure 30

Possible initiating step in ligand bridged dimer formation. Dimers A and B have a charge of +2.

hydroxyl group of Pt(1) is followed by a nucleophilic substitution of H_2O at Pt(1) by N(4).

An alternate mechanism could also be described. Hoffman and Taube[165] have studied the acid cleavage of hydroxo bridged complexes of Co^{3+} and have proposed the mechanism in Figure 31 where A and B are intermediates. Since the reactions of Pt dimers with bases are carried out under slightly acidic conditions, pH ≈ 6.5, it is conceivable that acid cleavage could be the initiating step for ligand bridge formation as illustrated in Figure 32. Cytosine could bind nucleophilically at Pt(2) to produce intermediate B (which is the same as B in Figure 30). The deprotonation induced at N(4) and subsequent transfer of a proton to the second bridging hydroxyl group could be followed by rearrangement and nucleophilic substitution by deprotonated N(4) at Pt(1) to produce intermediate C. The binding of the second cytosine would occur as described above. Intermediate B (Figure 32) could also be degraded further by acid cleavage to monomeric platinum-cytosine compounds, D and E, in a competing reaction to ligand bridged formations.

Unfortunately, evidence cannot be presented to verify <u>either</u> of these mechanisms.

Figure 31

Mechanism for acid cleavage of hydroxo bridged complexes (of Co^{3+}).

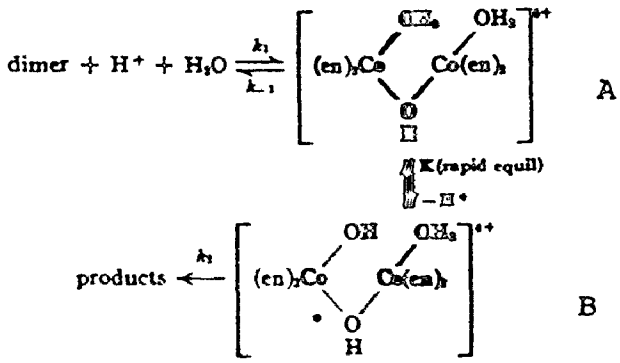


Figure 31 was reproduced from ref. 166; originally published by A.B. Hoffman and H. Taube, Inorg. Chem., 7, 903 (1968), ref. 165.

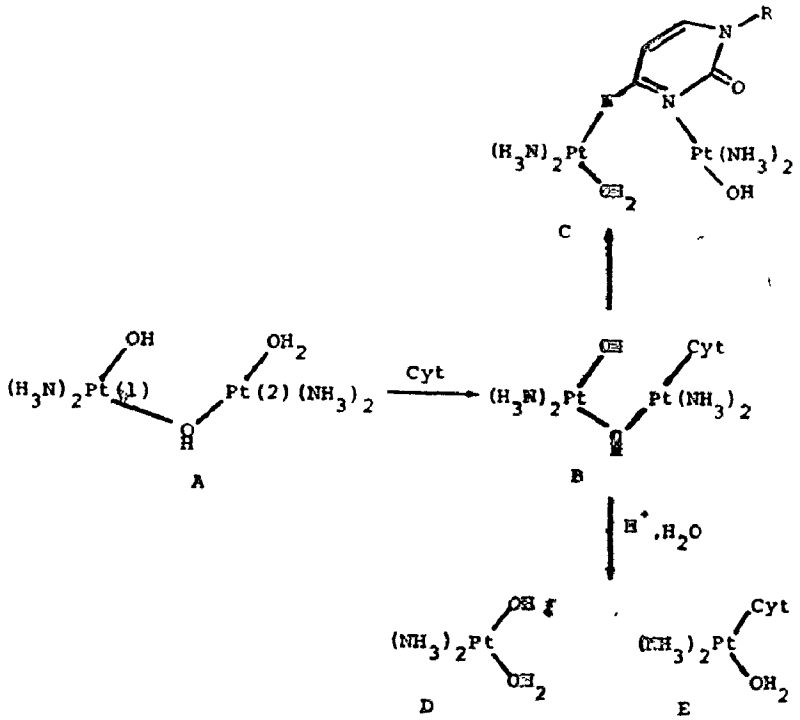


Figure 32

Possible mechanism for formation of ligand bridged dimers. Dimers A, B, C and E each have a charge of +2. D has a charge of +1.

CHAPTER 4

EXTENSION

CHAPTER 4

EXTENSION

4.1 THE LINK BETWEEN BASE BRIDGED PLATINUM COMPOUNDS AND ANTICANCER ACTIVITY

Irrespective of the mechanisms of their formation, the ligand bridged compounds of cis-$Pt(NH_3)_2Cl_2$ are stable and well characterized. The bridging mode of binding, although unexpected for compounds of cis-$Pt(NH_3)_2Cl_2$ with cytosine, uracil and thymine, is reasonable.

If cis-$Pt(NH_3)_2Cl_2$ binding in this manner to any of the DNA bases were to cause the lethal lesion in cancer cells, one could explain the differing specificity of cis and trans on the basis of the differing stereochemical requirements of the isomers. It is conceivable, although not probable, that trans-$Pt(NH_3)_2Cl_2$ could form ligand bridged compounds.

An alternate explanation of the differing specificity of cis and trans-$Pt(NH_3)_2Cl_2$ exists. If the link between concentration of hydroxo bridged dimers in solution and the

formation of cis ligand bridged dimers is real, the differing specificity of cis and trans-$Pt(NH_3)_2Cl_2$ could be explained on the basis of the differing chemistry of the isomers. The ability of cis-$Pt(NH_3)_2Cl_2$ to bind in this manner could be based on its' ability to form hydroxo bridged dimers (where trans cannot).

Support for the postulate that the anticancer activity of cis compounds is somehow related to the bridging mode of binding is afforded by consideration of the platinum pyrimidine "blues" which are active antitumor agents.[168] Lippert has very recently synthesized and crystallographically characterized a ligand bridged compound (made by reacting $[(H_3N)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ with 1-methyluracil). In the compound, two cis-$Pt(NH_3)_2$ moieties are N(3)-O(4) bridged by two uracilato ligands arranged head-to-head. When these ligand bridged species were dissolved in water, a blue pyrimidine compound resulted. This mechanism for formation of the "blues" has been suggested by Lippert et al.[102] The blue compound formed is undoubtedly analogous to "Lippard's blue", the α-pyridone oligomer which was crystallographically characterized[160] (see Figure 34). Although it is very difficult to assess how important these oligomers are in describing the primary lesion in DNA, the recurring hint of a link between ligand bridged dimer formation and anticancer activity cannot be dismissed casually.

The logic of the following discussion has been

Figure 34

The molecule $[(NH_3)_2Pt(C_5H_4ON)_2Pt(NH_3)_2]_2(NO_3)_5$

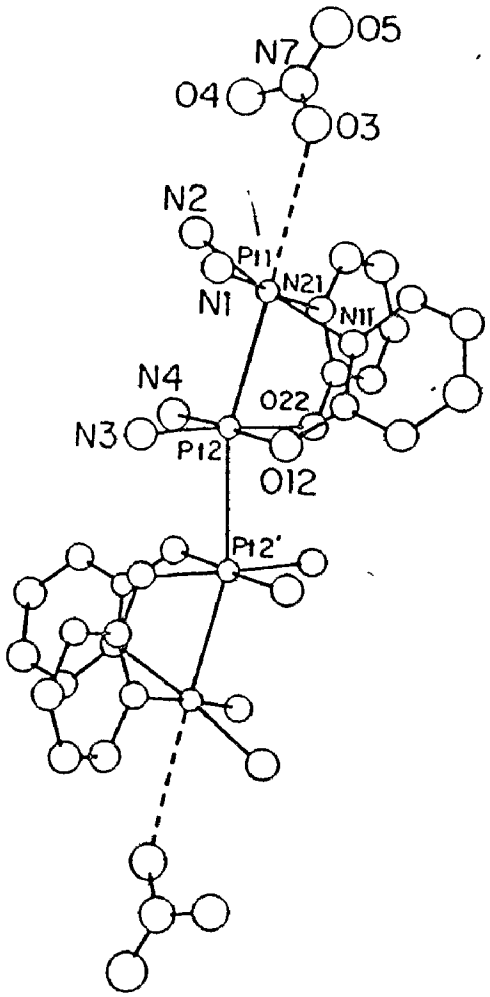


Figure 34 was reproduced from ref. 160, J.K. Barton, H.N. Rabinowitz, D.J. Szalda, and S.J. Lippard, J. Amer. Chem. Soc., 99, 2827 (1977).

outlined previously by van den Berg[169] et al. and expanded upon by B. Rosenberg.[15] The discussion that follows is slightly modified and expanded in light of the proposed link between the ligand bridged binding mode and anticancer activity.

In general, DNA can repair itself by either an excision repair mechanism where DNA template damage is recognized and removed, or by a post replication repair mechanism where repair is effected on the new strand after the damaged (unexcised) strand replicates. Both mechanisms are used by cells to repair damaged DNA and aid the recovery of cells. There are two types of excision repair mechanisms. The first repairs damage such as that caused by uv-irradiation photodimerization of thymine.[170] An endonuclease recognizes the photodimer (causing the lesion) and inserts a nick in the DNA adjacent to the dimer. The dimer is subsequently removed (by an exonuclease) and the damaged section of DNA is resynthesized (by DNA-polymerase). The newly synthesized strand is then reattached to the original strand by a DNA ligase.[170,175] Drobnik et al.[176] and Beck and Brubaker,[119] in studies with E. coli, have shown that genes which code for enzymes which excise photodimers of thymine also code for removal of lesions induced by platinum compounds.

The results of sedimentation studies[169] (time dependent) of cells in culture treated with platinum compounds can be interpreted as being caused by initial formation of

lesions that were subsequently removed during several hours of excision repair. Munchausen[174] showed, however, that the excision repair mechanism contributes little to the recovery of biological activity of platinum-treated bacteria. She did this by treating hosts of different excision repair capacity with cis-$Pt(NH_3)_2Cl_2$. Even though bacteria can excise platinum-induced lesions, this excision does not prevent cell kill. This is consistent with other studies showing that interstrand crosslinks are not thought to cause cell kills.[35,36] Van den Berg et al.[169] deduced from this that the lesions excised were interstrand crosslinks. They suggested that the primary cell killing lesions result from Pt(II) complexes binding to only one strand of the double helix. These apparently are chemically stable and refractory to excision removal. (This persistence is consistent with the platinum complexes intrastrand binding to two adjacent DNA bases as in ligand bridged compounds.)

It is possible that bases on one strand monofunctionally bound to platinum complexes could be excised according to the second type of excision repair mechanism which operates in bacterial and mammalian cells. This excision mechanism repairs DNA damage caused by methylating agents and other groups which bind to primary hydrogen bonding sites (as Pt compounds have been postulated to do). The mechanism is very similar to that described above, except nicking of the DNA near the lesion and removal of the damaged DNA base are effected

by two separate enzymes working cooperatively (N-glycosidase and an apyrimidinic acid endonuclease). It is postulated here, that trans compounds, as well as mono aquated cis compounds, $(NH_3)_2Pt(OH_2)Cl^+$ or $(NH_3)_2Pt(OH)(OH_2)^+$, which have high equilibrium fractions, and which can only bind monofunctionally, are removed by excision repair mechanisms.

The post replication repair mechanism acts after replication to repair the gaps in newly synthesized DNA that result from replication using a damaged template strand.[177] Van den Berg et al.[169] have shown that Chinese hamster cells can efficiently bypass the Pt lesions by a post replication repair process, while HeLa cells cannot (they are more sensitive to the toxic effects of cis-$Pt(NH_3)_2Cl_2$). They have deduced from this that differences in the response of various human tumors to platinum compounds could be accounted for by similar differences in effectiveness of the post replication pathway. It might be that healthy cells can effectively bypass the lesions caused by cis-$Pt(NH_3)_2Cl_2$ according to the post replication repair mechanism whereas the cancer cells cannot. The buildup of unrepairable pieces of DNA in cancer cells could increase the antigenicity of these cells and result in cell death (e.g., DNA repair becomes impossible if two lesions occur near one another on opposite strands). This mechanism explains the specificity of platinum drugs for cancer cells as opposed to healthy cells where platinum compounds can be concentrated by as much as a factor of 4.

An important point in this discussion is that certain lesions are persistent and refractory to excision repair. It is proposed here that these persistent lesions are the ligand bridged dimers. Even if equilibrium concentrations of $(NH_3)_2Pt(OH_2)_2^{++}$, $(NH_3)_2Pt(OH_2)Cl^+$, or $(NH_3)_2Pt(OH)(OH_2)^+$ are high, their mode of binding to DNA bases does not result in lesions which are refractory to excision repair. It is important to note that in this postulated mechanism, no attempt is made to imply that aquo complexes of the type $(NH_3)_2PtCl(OH_2)^+$ and $(NH_3)_2Pt(OH)(OH_2)$ do not bind to DNA bases in vivo. This position would be untenable in view of the wealth of equilibrium, kinetic and structural studies done in vitro. The point is to describe a mode of binding that causes a persistent lesion and which has a reasonable chance of being refractory to both excision and post replication repair.

One might criticize that in this postulate platinum complexes are suggested to bind at primary hydrogen bonding sites, i.e., sites which are already bound. DNA is, however, not inactive and is constantly unwinding and rewinding locally. During this "breathing", binding sites become exposed to attack by platinum complexes.[37b,171] Hence, strand separation is not necessary for cis-$Pt(NH_3)_2Cl_2$ binding.

Also, since N(7) of guanine is an unprotected site in the DNA spiral[40,54] and is not involved in base pairing, it is quite likely that initial binding occurs here, perhaps preferentially. Monofunctional attack at N(7) by any of the hydrolysis species of platinum could occur.

Since the DNA bases are extremely delocalized, measureable inductive effects can be detected at sites remote from the binding site (see Section 2.7). Subtle changes may be effected in the hydrogen bonding of the bases in DNA by a platinum complex binding at the remote N(7) site of guanine. The platinum complex would inductively weaken the N(1)-H bond resulting in increased acidity. This would alter the hydrogen bonding[54,171] to cytosine and could cause partial denaturation. A second platinum complex could then bind to guanine or cytosine in the postulated way.

In this mechanism describing cell kill, inhibition of DNA was not invoked. Initial studies were undertaken with the erroneous assumption of a causal relationship between DNA replication inhibition and cytotoxic action of cis-$Pt(NH_3)_2Cl_2$, i.e., that DNA replication inhibition results in cell death. Rosenberg has suggested otherwise,[172] perhaps on the basis of his early results where cell replication was inhibited but not cell growth. Cell death did not occur.

To explain DNA replication inhibition, a template inactivation mechanism can be invoked. Harder and Smith[173] have studied the ability of cis-$Pt(NH_3)_2Cl_2$ to inactivate reactions of copolymeric nucleotides with DNA polymerase α + β obtained from cultured human cells. Their results suggested that reactions of cis-$Pt(NH_3)_2Cl_2$ with A-T sequences in DNA inactivated template replication by a factor of 6-20 times those of cis-$Pt(NH_3)_2Cl_2$ and G-C

sequences. This is clearly consistent with Rosenberg's premise that those DNA strands rich in G-C pairs be allowed to replicate and in the process of replication, induce mutations, while those strands rich in A-T were inactivated and led to DNA replication inhibition. Support for this premise that template inactivation is not related to anticancer action is provided by Munchausen,[174] who showed that *trans* compounds also inactivated transforming DNA, although *cis* compounds were more efficient.

4.2 CONCLUSION

Rosenberg has postulated that platinum complexes chelating to guanine molecules cause mispairings in DNA strands which increases the antigenicity of tumor cells. Unfortunately, chelating by a platinum complex across N(7)-O(6) of guanine is improbable and experimental evidence quoted as supporting this postulate is tenuous and contradictory.

Very recently, a mispairing of the type proposed by Rosenberg has been characterized in our laboratory.[107,163] This mispairing was induced in pairs of guanine molecules not by cis-$Pt(NH_3)_2Cl_2$ chelating at N(7)-O(6), but simply by Pt binding monofunctionally at N(7). As noted previously, a platinum complex binding at N(7) of guanine induces a pK_a shift in the N(1) proton. In this case, Pt causes deprotonation to occur at N(1) of one guanine out of each pair. (Note that the pH of the solution of reagents was held constant near 7.) This deprotonated N(1) site is then H bonded to N(1) of the second guanine. As well, each O(6) atom of guanine is strongly H bonded to the exocyclic nitrogen atom N(2) of the second guanine in a similar way to that hydrogen bonding occurring in the normal Crick Watson G-C pair (where O(6) hydrogen bonds to N(4) of cytosine) (see Figure 5, p. 30). Although this evidence is encouraging in that it supports

Rosenberg's postulate, it must be remembered that platinum moieties monofunctionally bound to DNA can be easily excised.

Criticisms can be directed at the postulate that ligand bridged compounds of cis-$Pt(NH_3)_2Cl_2$ with the DNA bases result in the primary lesion which induces increased antigenicity and subsequent cell kill. It is admitted that the link between the binding mode and anticancer activity is speculative. It is stressed, however, that the actual mode of binding to DNA bases that is described is the only mode of all postulated which meets both criteria. It explains the differing specificity of cis + trans-$Pt(NH_3)_2Cl_2$ and it has been well characterized.

4.3 SUGGESTIONS FOR FURTHER WORK

(1) Inherent in the premise that $[(H_3N)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ is the reactive antitumor agent which causes the primary lesion, is that these species exist in significant concentrations in the body. As was suggested earlier, $Pt(NH_3)_2Cl_2$ remains chlorinated until it is inside the cells, at which point it hydrolyzes and reacts with DNA. Both Harder and Rosenberg, and Howle and Gale, in their initial studies[7,8] noted that the response of DNA synthesis to the platinum compounds was delayed (by as much as 6 h). Since $Pt(NH_3)_2Cl_2$ is unreactive and hydrolysis occurs relatively slowly (see p. 8), equilibrium concentrations of reactive platinum species occur in cells in about 3 h.[16,28] It can be legitimately argued that aquo species (and even some, ~ 10%, of $Pt(NH_3)_2Cl_2$) will react quickly with nucleophiles in the cells. However, both Howle and Gale[120] and Harder and Rosenberg[121] have postulated alternate mechanisms which Cleare has described as invalid from a chemical viewpoint. Howle and Gale[120] suggested:

$$\underline{cis}\text{-}Pt(NH_3)_2Cl_2 \rightarrow \underline{cis}\text{-}Pt(NH_3)_2Cl^+ \rightarrow A$$

where $\underline{cis}\text{-}Pt(NH_3)_2Cl^+$ is unselective against DNA, RNA and protein synthesis. A is slowly formed and is selective against DNA synthesis. Harder and Rosenberg[121] suggested:

$$\underline{cis}\text{-}Pt(NH_3)_2Cl_2 + B \rightleftarrows C$$

where B is slowly increasing and is selective against DNA synthesis. C is not selective. These suggestions, although apparently unreasonable, are consistent with the following mechanism:

$$2Pt(NH_3)_2(OH_2)^{2+} \rightarrow 2Pt(NH_3)_2(OH_2)(OH)^{+} + 2H^{+}$$

$$k_2 \;\; ++ \;\; k_{-2}$$

$$[(H_3N)_2Pt(OH)_2Pt(NH_3)_2]^{2+} + 2H_2O$$

where $k_2 = 6.1 \times 10^{-3}\ M^{-1}\ sec^{-1}$

$k_{-2} = 1.3 \times 10^{-7}\ sec^{-1}$

Clearly, the hydroxo bridged species is similar to A and B as described above, and is postulated to selectively react with DNA.

It is very important to perform <u>in vivo</u> tests on the distributions of platinum species in cells to verify these suggestions. The equilibrium could be aided, perhaps, by membrane transport effects (since hydrolysis starts after $Pt(NH_3)_2Cl_2$ enters the cytoplasm and yet reactions with DNA do not occur until hydrolysis products enter the nucleus).

(2) $Pt(NH_3)_2Cl_2$ is administered in single doses of approximately 8 mg/kg of body weight.[2] It is important to consider what implications the small doses have for possible reactions. The 8 mg/kg dose results in initial concentrations of 2.6×10^{-5} M in the body. Since 85%

is excreted within hours, the active dose is probably 4×10^{-6} M. Although dimerization occurs less slowly at low total [Pt(II)], this effect will be offset by the increased temperatures in the body (37°C). Lim and Martin[28] estimated the equilibrium constant for dimer formation to be 10^6 M^{-1} and calculated that at pH 6.7 and for total [Pt(II)] = 2×10^{-6} M, the dimer and mononuclear hydroxo complex would be present in equal concentrations. Verification of this is essential.

(3) $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ has been postulated to react with N(1)-O(6) of guanine to cause a primary lesion. This complex must be crystallographically characterized to prove its existence.

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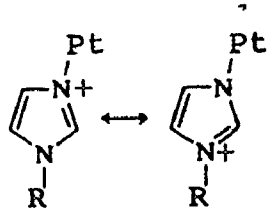
APPENDICES

APPENDIX 1

(a) The amount of platinum (enriched in ^{195m}Pt) excreted was measured at regular intervals.[17] The half-time for excretion of trans-$Pt(NH_3)_2Cl_2$ was ~ 20 h for tumored and untumored mice, while for cis-$Pt(NH_3)_2Cl_2$ the half-time varied from ~ 15 h to ~ 1.6 h for tumored and untumored mice, respectively. Hence, initial concentrations in the blood were higher for the trans isomers. After 5 days, the amounts of platinum compounds retained were approximately equal (trans still higher), and no selective uptake of the platinum compounds into tumor tissues could be detected.

(b) Theophanides has studied reactions of $Pt(en)Cl_2$ and [Pt(dien)Cl]Cl with nucleosides (50-60°C, 3-5 h, no pH control).[48,53] He has used nmr data to verify his postulate that platinum atom binding sites can be correlated with basicity. Platinum complexes do bind at N(3) of cytidine (tertiary amine site) and no binding occurs with uridine (N(3) is a secondary amine). Similarly, for guanosine binding occurs at the more basic N(7) imidazole site in preference to the N(1) secondary amine site. The correlation between binding site and basicity can probably not be extended beyond this. In fact, in guanosine, although N(3) is a basic tertiary amine site, platinum atoms do not bind here. Similarly in adenosine, platinum atoms bind preferentially at N(7) (imidazole) instead of at the more basic N(1) and N(3) sites (although some binding does occur at N(1)). The stability of the imidazole bound moieties is probably related to the ability of the moiety to delocalize charge effectively according to:



(c) Rosenberg and Toth-Allen[65] studied the distribution and retention of cis-$Pt(NH_3)_2Cl_2$ in the major organs of Swiss white mice (with and without Sarcoma 180 tumors). A neutron activation technique was used to analyze for platinum[122] (γ counting for ^{199}Au) in sacrificed animals. They found that there was no selective uptake of cis-$Pt(NH_3)_2Cl_2$ in the tumor tissue. (Hoeschele has recently found that there is preferential, although not exclusive, uptake in tumor tissue.[178]) For a therapeutic does of 8 mg/kg of cis-$Pt(NH_3)_2Cl_2$, tissue samples contained about 1 to 5 micrograms of platinum complex, per gram of tissue just after injection. In spite of the higher concentrations (4-5x) of platinum complex found in the filtering and excretory organs (liver and kidney), only the tumor cells disappeared. No toxic effects were detectible in the healthy tissues. Even after six days, 15% of the original injected drug is detectible.

APPENDIX 2

1-Methyl-cytosine bond distances (Å)
Rings bound to Pt(II) on position N(3)

Name/Bond	N(1)-C(2)	C(2)-N(3)	N(3)-C(4)	C(4)-C(5)	C(5)-C(6)	C(6)-N(1)	C(2)-O(2)	C(4)-N(4)	N(1)-C(1)	N(3)-Pt	Average of σ for all length
trans-$PtCl_2$((i-Pr)$_2$SO)($C_5H_7N_3O$)	1.372	1.387	1 330	1.415	1.359	1.353	1.231	1.334	1.471	2.058	0 017
cis-[$Pt(NH_3)_2(C_5H_7N_3O)(C_7H_9N_5O)$][$ClO_4$]$_2$[a,c]	1.386	1.373	1.369	1.422	1.358	1.330	1 214	1.298	1.511	2.031	0.030
cis-[$Pt(NH_3)_2(C_5H_7N_3O)(C_7H_9N_5O)$][$ClO_4$]$_2$[a,c]	1.395	1.370	1.352	1.400	1.312	1 376	1.221	1.310	1.479	2.039	0.031
cis-[$PtCl(NH_3)_2(C_5H_7N_3O)$]Cl; $P2_1/c$	1.374	1.366	1.352	1.414	1.351	1.366	1.244	1.326	1.456	2.026	0 011
cis-[$PtCl(NH_3)_2(C_5H_7N_3O)$]Cl; C2/c	1.380	1.367	1.335	1.426	1.352	1.358	1 212	1.323	1.477	2.056	0.018
trans-$PtCl_2(NH_3)(C_5H_7N_3O)\cdot\frac{1}{2}H_2O$	1.343	1.380	1.377	1.408	1.318	1.393	1.216	1.318	1.453	2.031	0 018
trans-[$Pt(NH_3)_2(C_5H_7N_3O)_2$](NO_3)$_2$	1.388	1.418	1.338	1.399	1.408	1.365	1.206	1.365	1.476	2.023	0 012
[$(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2$]($NO_3$)$_2\cdot 2H_2O$[b,c]	1.339	1.337	1.378	1.453	1.291	1.395	1.320	1.313	1.497	2 039	0 046
[$(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2$]($NO_3$)$_2$ $2H_2O$[b,c]	1.356	1.348	1.352	1.442	1 419	1.361	1.247	1.232	1.457	2.057	0.042
Average	1.371	1.384	1.346	1.412	1.359	1.367	1.222	1.333	1.467	2.039	
σ	0.012	0.021	0.019	0.010	0.032	0.015	0.015	0.019	0.011	0.017	

[a] Not included in the average or σ due to large uncertainties in the bond lengths and angles.

[b] Not included in the average or σ due to lack of similarity with other molecules.

[c] One of two independent cytosine molecular units within the cell.

σ (esd or rms) the standard deviation from the average, was calculated in the usual manner $\sigma^2 = \sum_{i=1}^{n} (x_i - x_{av})^2 / (n-1)$.

APPENDIX 3

1-Methyl-cytosine bond angles (°)
Rings bound to Pt(II) on position N(3)

Name/Angle	6-1-2	1-2-3	2-3-4	3-4-5	4-5-6	5-6-1	1-2-O(2)	3-2-O(2)	3-4-N(4)	5-4-N(4)	2-1-C(1)	6-1-C(1)	2-3-Pt	4-3-Pt	Average of for all ang
cis-$PtCl_2(1\text{-}Pr)_2SO)(C_5H_7N_3O)$	120.92	118.83	119.52	121.95	117.20	121.50	120 39	120.76	118 12	119 93	118 73	120 31	115 25	125 14	0.96
$[Pt(NH_3)_2(C_5H_7N_3O)(C_7H_5N_5O)](ClO_4)_2$ [a,c]	122.49	117.19	121.44	119 36	118 00	121 43	120.24	122.16	118 73	121 91	118.22	119 17	114 38	123 49	2 00
$[Pt(NH_3)_2(C_5H_7N_3O)(C_7H_9N_5O)](ClO_4)_2$ [a,c]	120.69	117.04	121.18	120.56	118 85	121.47	118.89	124.03	117 92	121 52	116.29	123.06	114 66	124 04	2 02
$[PtCl(NH_3)_2(C_5H_7N_3O)]Cl$; $P2_1/c$	120.31	119 10	121.01	119.91	118.24	121.34	120.09	120 79	119 08	120 94	118.98	120 71	118 78	120.20	0 74
$[PtCl(NH_3)_2(C_5H_7N_3O)]Cl$; $C2/c$	122.31	116.52	123.07	119.51	117.98	120.61	120.49	122.99	120.97	119 51	117.26	120.40	118 11	118.69	1 19
cis-$PtCl_2(NH_3)(C_5H_7N_3O)\cdot\frac{1}{2}H_2O$	120 72	118.72	120 25	119.98	118.07	122.01	120.39	120.89	118 30	121 63	119.88	119 39	117.59	122 13	1 17
$Pt(NH_3)_2(C_5H_7N_3O)_2](NO_3)_2$	123 30	116.40	120.60	122.98	117.04	119.55	121.32	122 28	117.83	119.18	116.95	119.69	115 37	123.93	0.80
$Pt(C_5H_6N_3O)_2Pt(NH_3)_2](NO_3)_2\cdot 2H_2O$ [b,c]	118.44	123.20	117.75	116.75	121.45	118.84	116.90	118.99	123.68	119 56	119.39	121.97	121.65	119 64	3 12
$Pt(C_5H_6N_3O)_2Pt(NH_3)_2](NO_3)_2\cdot 2H_2O$ [b,c]	122 02	120.56	121.31	118.52	118.91	117.58	117.26	121.67	122.92	118 37	122.50	115.25	115.87	122 58	2 82
	121 5	117 9	120.9	120.9	117.7	121.0	120.5	121.5	118.9	120.2	118.4	120.1	117.0	122 0	
	±1.2	1,3	1.3	1.5	0.5	0.9	0.5	1.0	1.3	1 0	1.2	0.5	1 6	2 6	

APPENDIX 4

Comparison of average 1-Methyl-cytosine bond distances (Å)

1. Rings bound to Pt(II) on position N(3)[b]

x:	N(1)-C(2)	C(2)-N(3)	N(3)-C(4)	C(4)-C(5)	C(5)-C(6)	C(6)-N(1)	C(2)-O(2)	C(4)-N(4)	N(1)-C(1)
Average x_1	1.371	1.384	1.346	1.412	1.358	1.367	1.222	1.333	1.467
σ_1	0.017	0.021	0.019	0.010	0.032	0.015	0.015	0.019	0.011

2. Neutral Molecules[a]

Average x_2	1.392	1.358	1.339	1.433	1.357	1.360	1.237	1.324	1.468
σ_2	0.015	0.013	0.007	0.015	0.026	0.008	0.024	0.020	0.028

3. Rings Protonated on position N(3)[a]

Average x_3	1.395	1.392	1.344	1.411	1.358	1.355	1.204	1.319	1.480
σ_3	0.008	0.015	0.008	0.012	0.010	0.008	0.004	0.006	0.007

[a] Numbers obtained from Appendix I, p. 248, D. Voet and A. Rich, ref. 105.

[b] Numbers extracted from APPENDIX 2.

APPENDIX 5

Comparison of average 1-Methyl-cytosine bond angles (°)

x:	6-1-2	1-2-3	2-3-4	3-4-5	4-5-6	5-6-1	1-2-O(2)	3-2-O(2)	3-4-N(4)	5-4-N(4)	2-1-C(1)	6-1-C(1)
1. Rings bound to Pt(II) on position N(3)[b]												
Average x_1	121.5	117.9	120.9	120.9	117.7	121.0	120.5	121.5	118.9	120.2	118.4	120.1
σ_1	1.2	1.3	1.3	1.5	0.5	0.9	0.5	1.0	1.3	1.0	1.2	0.5
2. Neutral Molecules[a]												
Average x_2	121.2	118.6	120.5	121.5	117.0	121.2	118.9	122.5	118.3	120.1	118.2	121.5
σ_2	1.2	1.3	1.3	1.7	2.0	0.8	1.2	0.8	1.6	0.8	1.4	0.4
3. Rings Protonated on position N(3)[a]												
Average x_3	122.1	113.7	125.3	118.4	117.8	123.1	124.2	122.0	120.2	121.3	117.6	120.0
σ_3	0.2	0.4	1.1	0.1	0.8	0.6	0.4	0.1	0.5	0.6	0.8	0.6

[a] Numbers obtained from Appendix II, p. 254, D. Voet and A. Rich, ref. 105.

[b] Numbers extracted from APPENDIX 3.