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Reactions of *cis*-[$Pt(NH_3)_2Cl_2$] and *cis*-[Pt(en)Cl_2] with Nucleosides

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Platinum-nucleoside complexes with amine ligands have been prepared. The complexes are of the formula [$Pt(NH_3)_2L_2$]Cl_2, where L = guanosine, inosine, and xanthosine. Proton nmr spectra of the complexes have been observed and analyzed. Platinum-proton (H_8) spin coupling constants are 20-30 Hz and give good evidence of Pt-N_7 bonding in the complexes.

Recently the cis platinum complexes of amines and ethylenediamines were found to be very effective against several tumors.[1,2] It was suggested that platinum complexes attacked DNA (deoxyribonucleic acid)[1] and later shown that *cis*-[$Pt(NH_3)_2Cl_2$] formed interstrand cross-links in DNA extracted from HeLa cells.[3]

This work was motivated by the thought that information on the nature of interaction of platinum with DNA can be obtained by reactions of platinum-amine complexes with nucleosides which are the main components of DNA. Very recently the binding between platinum and nucleosides was studied with uv spectrophotometry.[4] The nmr technique was used to study nucleoside complexes of inorganic salts in DMSO (dimethyl sulfoxide) by several investigators.[5-7] Although the results obtained were the same, the conclusions were not completely in agreement as to whether the nucleosides acted as monodentate or polydentate ligands. Substitution reactions in aqueous solution of platinum complexes with a variety of nucleophilic reagents were extensively studied[8] and the final products from displacement of chlorides of $Pt(NH_3)_2Cl_2$ and Pt(en)Cl_2 by nitrogen ligands were well defined.[8a] Using the nmr technique on platinum complexes, not only the chemical shifts of protons but also the couplings of aromatic protons with ^{195}Pt ($I = 1/2$; 33.7% naturally abundant) can be used to probe the coordinating sites. Reasonable structures of platinum-nucleoside complexes could be deduced from the combination of nmr information and stereochemical properties of the platinum complexes.

Experimental Section

Microanalyses were performed by Chemalytics Inc., Tempe, Ariz. Nuclear magnetic resonance spectra were obtained in D_2O solutions (pD 5.0-5.5) on a Varian T60 spectrometer using DSS as internal reference. The concentration range of these solutions was 0.05-0.1 mol. Uv spectra were obtained as aqueous solutions (pH 5.80) on a Cary Model 14 spectrophotometer. Infrared spectra were obtained as Nujol mulls or KBr pellets on a Perkin-Elmer 621. Nucleosides were purchased from Raylo Chemical Limited.

cis-[Pt(en)Cl_2], *cis*-[$Pt(NH_3)_2Cl_2$], and both *cis*- and *trans*-[$Pt(py)_2Cl_2$] were prepared according to the published methods[9] (en = ethylenediamine, py = pyridine).

Preparation of Platinum Complexes with Guanosine and Xanthosine. A 1-mmol amount of platinum-amine complex was mixed with about 2.5 mmol of guanosine or xanthosine in 150 ml of water heated to 50-60° with agitation. The solution was, at first, yellow and became colorless after 3-5 hr. The solution was stirred overnight and then filtered. The filtrate was evaporated to half-volume at ~40° and then left in a refrigerator to precipitate out the excess ligand which was filtered off. The filtrate was again evaporated to half its volume and left in the refrigerator. This procedure was repeated a few times until the final volume of the filtrate was about 10 ml.

The 10-ml solution was evaporated at room temperature to 2-4 ml, then left in the refrigerator for 2 days, and filtered off. When acetone was added to the filtrate, a white precipitate was obtained which was washed with acetone and ether and then dried under vacuum (~5 mm) at 110°. Guanosine complexes were isolated with two molecules of water, while xanthosine complexes had one molecule of acetone which could be taken off by dissolving the complexes in water and evaporating the water to dryness. The acetone can be seen in nmr spectra. The conductivities of [$Pt(NH_3)_2G_2$]Cl_2 and [Pt(en)G_2]Cl_2 in water are 180 and 210 ohm^{-1}, respectively. The conductivity data were taken in the concentration range $(0.5-1) \times 10^{-3}$ mol.

The uv spectrum of the complex [$Pt(NH_3)_2G_2$]Cl_2 (4.06×10^{-5} *M*, pH 5.70) showed an absorption at 2560 Å (ϵ 2370), whereas the free ligand, guanosine (4.52×10^{-5} *M*, pH 5.90) absorbs at 2500 Å (ϵ 1410).

The ir spectrum of the complex [$Pt(NH_3)_2G_2$]$Cl_2 \cdot 2H_2O$ shows important bands at 3300 (br, vs) (H_2O), 1690 (vs), 1630 (vs), 1580 (vs), 1530 (m), 1490 (m), 1415 (m), 1340 (s), 1170 (ms), 1080 (s), 1045 (s), 770 (m), and 620 (m) cm^{-1} and guanosine bands at 3310 (s), 3220 (s), 1730 (s), 1690 (m), 1635 (s), 1610 (sh), 1570 (m), 1540 (m), 1485 (m), 1381 (m), 1180 (m), 1080 (s), 1040 (m), 780 (s), and 685 (m) cm^{-1}.

Preparation of Platinum Complexes with Inosine. The method is the same for guanosine except that the amount of inosine is exactly 2 mmol, and the solution is evaporated to 10 ml only. The inosine complexes had one molecule of acetone which was still in the complexes at 80° under 5 mm. The nmr peak corresponding to the acetone molecule is shown at 136 Hz ($\tau(CH_3)$ 7.74) which is the ordinary position for the methyl signal.

Results and Discussion

The complexes were prepared by the reaction

$$cis\text{-}[Pt(en)Cl_2] \xrightarrow[50-60°,\ H_2O]{Nucl} [Pt(en)(Nucl)_2]Cl_2$$

where en = $NH_2CH_2CH_2NH_2$ and Nucl = nucleoside.

The analytical data are listed in Table I. The complexes had no definite melting points; they started to change their color at about 180° and decomposed. The conductivities (see Experimental Section) showed that the complexes were 2:1 electrolytes[10] in water and had no change on aging. The complexes are very soluble in cold water and these useful properties permitted us to isolate them pure. In their uv spectra, the strong bands of the nucleosides shifted only

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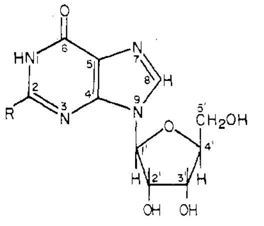
Table I. Analytical Data of Platinum-Nucleoside Complexes

Compd	% C		% H		% N		% Cl		% Pt	
	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
cis-$[Pt(NH_3)_2G_2]Cl_2 \cdot 2H_2O$	26.6	27.0	3.99	3.77	18.6	18.7				
cis-$[Pt(en)G_2]Cl_2 \cdot 2H_2O$	28.6	28.1	3.78	3.90	18.2	18.2	7.70	7.72	21.1	22.0
cis-$[Pt(NH_3)_2X_2]Cl_2$	26.7	26.8	3.33	3.41	15.6	15.8				
cis-$[Pt(NH_3)_2X_2]Cl_2 \cdot CH_3COCH_3$	28.8	28.1	3.76	3.71	14.6	14.9				
cis-$[Pt(en)X_2]Cl_2$	28.5	28.9	3.46	3.42	15.1	14.8				
cis-$[Pt(NH_3)_2In_2]Cl_2 \cdot CH_3COCH_3$	30.8	30.6	4.21	3.99	15.6	16.0				
cis-$[Pt(en)In_2]Cl_2 \cdot CH_3COCH_3$	32.6	32.1	4.13	3.97	16.4	15.2				
cis-$[Pt(py)_2G_2]Cl_2$	36.4	36.0	3.64	3.69	17.0	16.3				
trans-$[Pt(py)_2G_2]Cl_2 \cdot 2H_2O$	35.2	35.0	3.52	3.59	16.4	16.4	6.96	6.63	19.1	18.9



Nucl

guanosine (G), R = NH_2
inosine (In), R = H
xanthosine (X), R = OH

Table II. Nmr Spectra of Platinum-Nucleoside Complexes (Hz)

Compd	H_2	H_8	J_{Pt-H_8}
cis-$[Pt(NH_3)_2G_2]Cl_2$		524	26
cis-$[Pt(en)G_2]Cl_2$		516	26
Guanosine[a]		471	
cis-$[Pt(NH_3)_2X_2]Cl_2$		534	26
cis-$[Pt(en)X_2]Cl_2$		525	26
Xanthosine[a]		468	
cis-$[Pt(NH_3)_2In_2]Cl_2$	507	539	26
cis-$[Pt(en)In_2]Cl_2$	490	520	26
Inosine	484	490	

[a] Due to limited solubility in D_2O the spectra were taken in DMSO.

slightly on complexation. The infrared bands in the region of 1650-1750 cm^{-1} shifted to lower frequency by about 30 cm^{-1} in the complexes. Since ethylenediamine is a strong chelating ligand, the cis configuration of the complexes should be retained.

In Figure 1 are the nmr spectra of inosine and its complexes in D_2O. Inosine is quite soluble in water and has less stacking effects[11] and we can make a comparison for free and complexed inosine. All the bands of hydroxyl groups, amino groups, and protons on N_1 are removed by D_2O. There is no real difference in the region of 200-400 Hz in Figure 1(a)-(c); the bands in this region are from sugar groups of nucleosides and H_2O or HDO. The sugar groups do not participate in bonding. On the right side of Figure 1(a) at 174 Hz a triplet with a spin coupling constant J_{Pt-H} = 44 Hz is from methylene groups of ethylenediamine and it is worth noting that J_{Pt-H} of $[Pt(en)_2]Cl_2$ in D_2O is 41 Hz, found by Appleton and Hall.[12] On the left side of Figure 1(a), the two signals of protons (H_2, H_8) on the aromatic rings of inosine are close together (8 Hz or 0.13 ppm), while in Figure 1(b) and (c) they are separated by about 30 Hz (0.50 ppm) on complexation. The downfield peak is a triplet and the upfield a singlet. One signal was observed for guanosine or xanthosine, because there is only one aromatic proton (H_8). In Figure 2 are the spectra of $[Pt(en)G_2]Cl_2$ and $[Pt(en)X_2]Cl_2$ and protons H_8 show triplets due to spin coupling with ^{195}Pt. Charge densities are generally affected more at the atom which is closest to the binding site and protons attached to it shift more downfield.[13] Additional evidence may be found in platinum complexes, where this proton can be also coupled with ^{195}Pt. For example, the couplings of pyridine complexes are J_{Pt-H_o} = 33 Hz and J_{Pt-H_m} = 10 Hz for ortho protons (H_o) and meta protons (H_m), respectively.[14] The magnitude of the coupling constant decreases with increasing number of bonds between platinum and the proton if no conformational behavior is involved.[15] Since protons H_8 of both guanosine and xanthosine couple with ^{195}Pt, the indication is that N_7 is the binding site. If the binding site is one of the other nitrogen atoms, it would be too far to observe a coupling between H_8 and ^{195}Pt, because there is only one peak with coupling in the inosine complex (see Figure 1(b)). By comparing the basicity of N_7 of inosine to that of guanosine and of xanthosine[16] and the magnitudes of coupling constants of all the complexes (see Table II), we assign N_7 as the binding site for inosine. Berger and Eichhorn[17] found that N_7 of poly(I) was the only binding site with Cu(II) while O_6 of IMP in addition to N_7 are possibly involved in chelation in D_2O. Li, *et al.*,[6] assigned guanosine as a chelating ligand involving N_7 and O_6 with Zn(II) in DMSO. Coordination complexes of platinum(II) are normally four-coordinate if the ligands in the complexes are not rigid tripods or have a high trans effect.[8,18] In these nucleoside complexes, platinum is already fully coordinated (two nitrogen atoms from amines and two from nucleosides) and it is unlikely that O_6 is involved in bonding. Infrared spectra of the solid complexes showed $\nu_{C=O}$ of the carbonyl group shifted to a lower region. This shift may be due to hydrogen bonding or to electron shifting from the aromatic ring to the metal atom through the binding site N_7 or to intermolecular crystal contacts of O_6 with the metal atom.

Attempts to isolate $[Pt(en)G]Cl_2$ were unsuccessful. Guanosine is expected to be a bidentate ligand in this mononucleoside complex. The analytical data of carbon were higher than the theoretical values. $[Pt(en)Cl_2]$ crystallized out when its aqueous solution was left in a refrigerator. The reaction may be

$$2[Pt(en)G]Cl_2 \rightarrow [Pt(en)G_2]Cl_2 + [Pt(en)Cl_2]\downarrow$$

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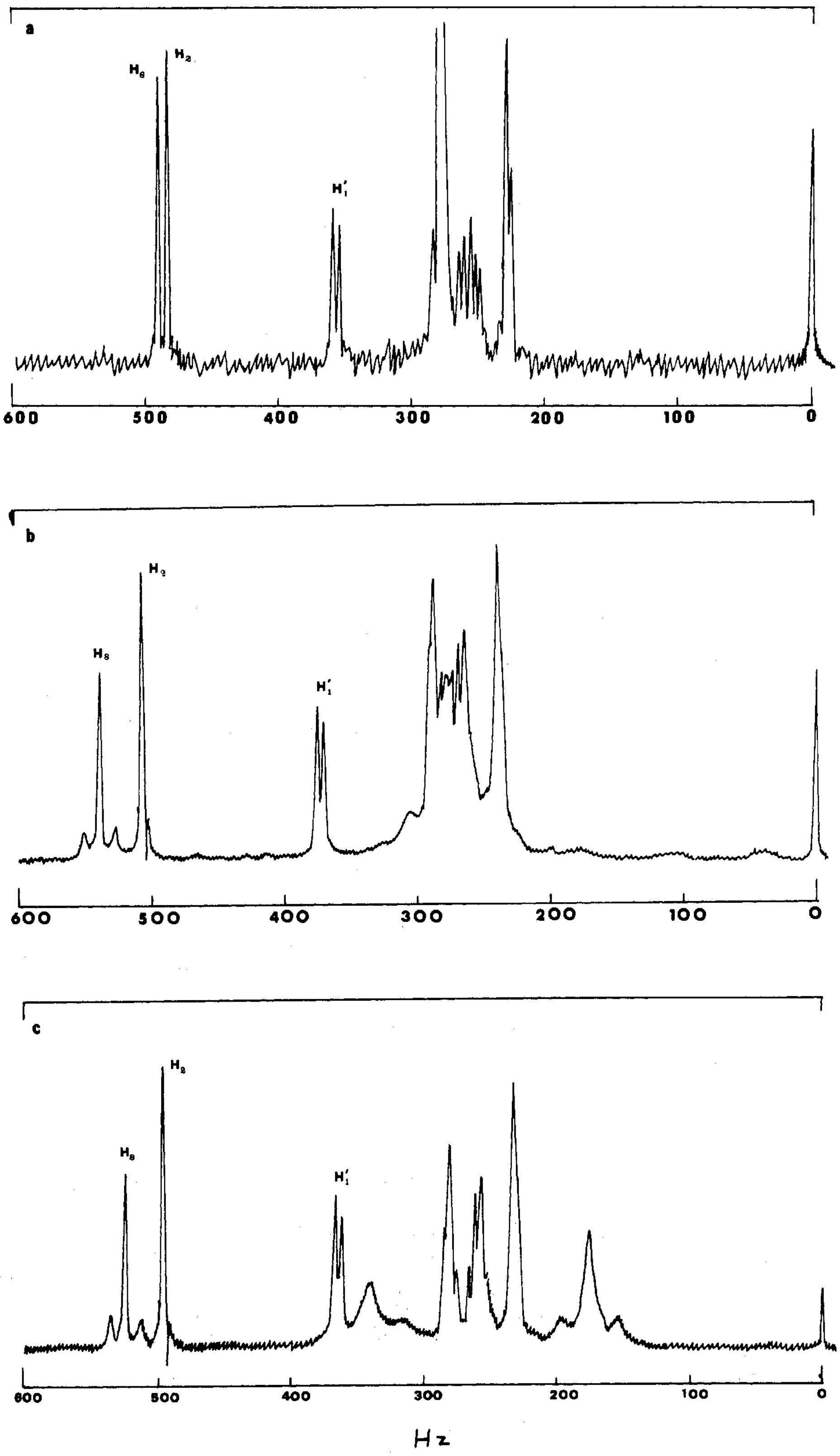

Figure 1. Nmr spectra of inosine and its complexes in D_2O using DSS as standard: (a) free inosine, (b) *cis*-$[Pt(NH_3)_2In_2]Cl_2$, and (c) $[Pt(en)In_2]Cl_2$. These complexes were prepared by evaporating the aqueous solutions to dryness instead of precipitating with acetone and therefore do not have acetone.

This may indicate that guanosine is a poor bidentate ligand for platinum. In Table II the frequencies in hertz of the amine complexes are higher than those of the corresponding ethylenediamine complexes. This is expected, ethylenediamine chelate being a stronger base than amine. The platinum atom in $[Pt(en)_2G_2]Cl_2$ accepts less electronic charge from the nucleoside than in $[Pt(NH_3)_2G_2]Cl_2$. As a result the aromatic protons in the ethylenediamine complex shift to lower frequencies (downfield) than in the amino complex. In addition, if two water molecules were loosely coordinated

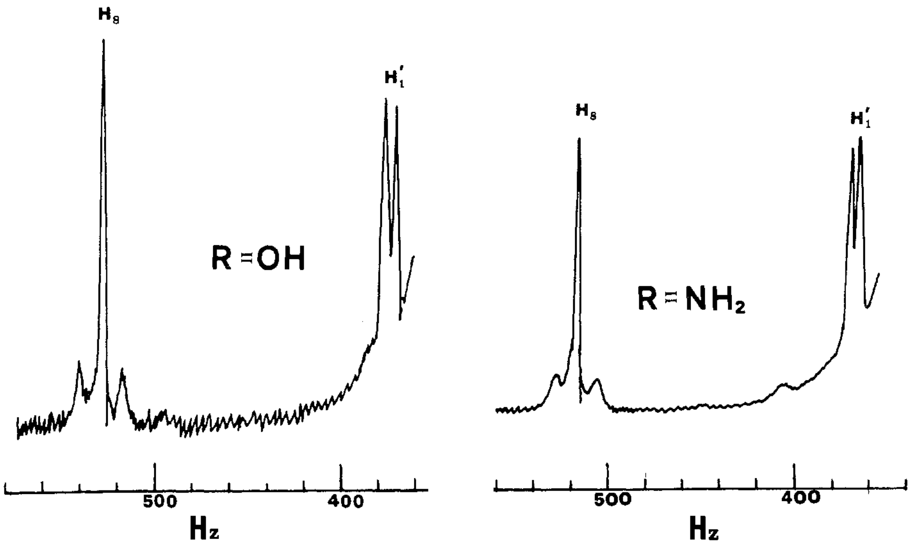

Figure 2. Nmr spectra of $[Pt(en)G_2]Cl_2$ (left) and $[Pt(en)X_2]Cl_2$ (right).

to the platinum atom along the *z* axis, this would also favor higher frequencies for the amine complexes.

Pyridine complexes (see bottom of Table I) are not very stable in the solid state at room temperature and were not studied further. Adenosine complexes were also studied and nmr spectra showed several species due to different binding sites (N_1 and N_7). We shall report the details of these reactions elsewhere.

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Registry No. *cis*-$[Pt(NH_3)_2G_2]Cl_2$, 50790-41-5; *cis*-$[Pt(en)G_2]Cl_2$, 40790-42-6; *cis*-$[Pt(NH_3)_2X_2]Cl_2$, 50790-42-6; *cis*-$[Pt(en)X_2]Cl_2$, 50790-44-8; *cis*-$[Pt(NH_3)_2In_2]Cl_2$, 50883-28-8; *cis*-$[Pt(en)In_2]Cl_2$, 50790-45-9; *cis*-$[Pt(py)_2G_2]Cl_2$, 50790-46-0; *trans*-$[Pt(py)_2G_2]Cl_2$, 50883-29-9; guanosine, 118-00-3; xanthosine, 550-26-5; inosine, 58-63-9.

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Entering Group, Leaving Group, and Cis Effects of Alicyclic Primary Amines in Substitution Reactions of Platinum(II) Complexes Containing Sulfur-Bonded Dimethyl Sulfoxide[1]

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Series of complexes of the types *cis*-$[Pt(am)_2(DMSO)Cl]Cl$, *cis*-$[PtCl_2(am)(DMSO)]$, and $[Pt((am')(DMSO))((am)Cl)]Cl$, where am is an alicyclic primary amine, $C_nH_{2n-1}NH_2$ (n = 3-8), am' is cyclopropylamine, and DMSO is dimethyl sulfoxide bonded through the sulfur, have been prepared and characterized. The kinetics of the forward and reverse steps of the process, *cis*-$[PtCl_2(DMSO)(am)]$ + am $\rightleftarrows$ *cis*-$[Pt(am)_2(DMSO)Cl]^+ + Cl^-$ (and also the analogous reaction with cyclopropylamine as entering group), have been studied in methanol at 30.0° at constant ionic strength and the equilibrium constants have been determined. The normal two-term rate law is observed but the first-order (nucleophile-independent) path is of little importance. In addition to the expected dependence of rate on the basicity of the leaving group, a very strong cis effect is observed where the least basic amine produces the most reactive substrate. This cis effect is as dependent on basicity as the leaving group effect. It is concluded that the very strong trans effect of S-bonded dimethyl sulfoxide is due to transition-state stabilization that results from the π-acceptor properties of the sulfur in this ligand.

Introduction

Although a number of studies have been made of the way in which the nature of the leaving group affects the reactivity of four-coordinate, planar d^8 metal ion complexes,[3] little attention has been paid to a systematic study of the relationship between the basicity and the lability of coordinated amines. Some studies have been made with Au(III) substrates[4-6] and a small amount is known about Pd(II) com-

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[1] Presented, in part, with Dr. A. R. Khokhar, at the Second International Symposium on Platinum Coordination Complexes in Cancer Chemotherapy, Oxford, England, April 16-18, 1973.

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[3] See, for example, L. Cattalini, *MTP (Med. Tech. Publ. Co.) Int. Rev. Sci.*: *Inorg. Chem., Ser. One*, 9, 278 (1972).

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