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Coordination and Protonation Sites of Metal Complexes Containing Adenine. Studies by Infrared Spectra

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The synthesis of complexes of platinum and palladium with adenine is reported. The composition of these polycrystalline complexes was a 1:1 ratio of the ligand to the metal. The coordination sites of these compounds were investigated by means of infrared (IR) spectroscopic analysis. The mixed ligand complex, $Cu(adeH_2)(oxa)Cl \cdot 3/2H_2O$ has been prepared. The complex was characterized by elementary and IR spectroscopic analyses. In case of $Cu(adeH_2)(oxa)Cl \cdot 3/2H_2O$, it was assumed that the nitrogen atom N9 of adenine coordinated to Cu^{2+} and that the N1 and N7 were protonated. From IR spectra of the complexes of platinum and palladium with adenine, it was supposed that N1 and N7 were the coordination sites.

Keywords——metal complexes of adenine; platinum, palladium, and copper complexes; IR spectra; metal complexes of biological importance; adenine; a compornent of nucleic acids; mixed ligand complex; oxalic acid; spectroscopic analyses

The biological importance of purine bases, constituents of the nucleic acids, is well known. Platinum and palladium are found to form very stable complexes with nitrogen bases. Since the discovery by Rosenberg and his collaborators of the anti-tumor activity of the certain platinum compounds[2] there has been a great interest in the structure and coordination site of the platinum complexes with purine bases. A large number of the platinum complexes have been prepared and tested for their ability to cause regression of tumor cells. Their activities depend on the chemical structures of the complexes. Recently Leh and Wolf have reported the assignments of their biological and toxicological effects.[3]

Several publications have appeared in recent years discussing the coordination site between purine derivatives and bivalent platinum ions.[4–7] The infrared (IR) spectra of $X(adeH)Cl_2$ where $X=Pt^{2+}$ and Pd^{2+} are discussed in order to investigate the coordination site in this paper.

We have reported the IR and electron paramagnetic reasonance (EPR) spectra of the mixed ligand complex containing adenine, Cu^{2+}, and 1,10-phenanthlorine.[8]

We report here the synthesis of $Cu(adeH_2)(oxa)Cl \cdot 3/2H_2O$,[9] and suggest its coordination and protonation sites.

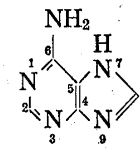

Fig. 1. Structure of Adenine (Denoted by adeH)

Results and Discussion

IR Spectra

IR Spectrum of $Cu(adeH_2)(oxa)Cl \cdot 3/2H_2O$

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[9] Adenine cation, adenine, and adenine anion are denoted by $adeH_2$, adeH, and ade, respectively.

The infrared spectra of adenine and its metal complexes have been reported.[10,11] Recently the mixed ligand complex containing adenine, $\mathrm{Cu^{2+}}$, and 1,10-phenanthlorine has been reported and its IR spectrum has been discussed in the 4000—400 $\mathrm{cm^{-1}}$ region.[8]

In the IR spectrum of the mixed ligand complex, $\mathrm{Cu(adeH_2)(oxa)Cl\cdot 3/2H_2O}$, the band at 3400 $\mathrm{cm^{-1}}$ was assigned to OH stretching. The absorption at 3180 $\mathrm{cm^{-1}}$ was assigned to $\mathrm{NH_2}$ stretching.[8,10,11] In $\mathrm{Cu(adeH_2)(oxa)Cl\cdot 3/2H_2O}$ the band at 2700 $\mathrm{cm^{-1}}$ due to N9–H of adenine disappeared.[11,12] The band at 2500 $\mathrm{cm^{-1}}$ was attributed to the presence of weak $\mathrm{NH^+ \ldots Cl^-}$ intermolecular hydrogen bonds of a ring protonated nitrogen atom and a chlorine atom.[13] No bands were observed in the region 2900—2500 $\mathrm{cm^{-1}}$ assignable to N9–H of adenine ligand.[11,12] The disappearence of the absorption due to N9–H suggested that $\mathrm{Cu^{2+}}$ bound to N9 in a similar way to the result reported by Tomita, *et al.*[14]

As shown in Fig. 2, the band assigned to $\mathrm{NH_2}$ bending shifted to higher wave numbers and appeared at 1726 $\mathrm{cm^{-1}}$ on the complex formation. The $\mathrm{NH_2}$ deformation vibration of adenine hydrochloride, the structure of which was determined by X-ray crystallography, was observed at 1712 $\mathrm{cm^{-1}}$,[11] and the extra proton was found to be located on the N1 atom. From the shift of the $\mathrm{NH_2}$ deformation vibration it is assumed that the complex contains an $\mathrm{NH_2}$ group affected by the addition of a neighbouring positive charge and that there is a proton on the N1 atom of adenine ligand.

The band at 1665 $\mathrm{cm^{-1}}$ was assigned to O–C–O asymmetric stretching according to Melnik, *et al.*[15] The absorption at 1620 $\mathrm{cm^{-1}}$ was assigned to O–C–O asymmetric stretching, probably conjugated to C=C and C=N stretching. This band shifted to 1580 $\mathrm{cm^{-1}}$ by complexation.

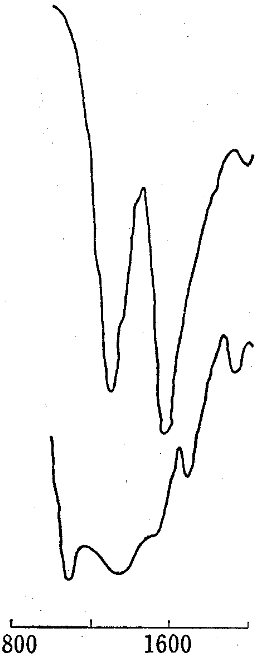

Fig. 2. IR Spectra of Adenine (upper) and $\mathrm{Cu(adeH_2)(oxa)Cl\cdot 3/2H_2O}$ (doen)

The band at 1280 $\mathrm{cm^{-1}}$ can be assigned to $\mathrm{NH_2}$ deformation, O–C–O symmetrical stretching and O–C–O deformation.[16] A new band appeared at 982 $\mathrm{cm^{-1}}$, which was assigned to NH vibration and several bands at 850—875 $\mathrm{cm^{-1}}$ due to adenine disappeared by complexation. The band at 840 $\mathrm{cm^{-1}}$ was attributed to NH out-plane deformation and probably also Cu–O–Cu asymmetric stretching.[16]

The aromatic carbon-aliphatic nitrogen stretching frequency is shifted to higher frequency and appeared at 1324 $\mathrm{cm^{-1}}$ by complex formation. This shift may be expected, as the lone pair of electrons on the amino groups would not be engaged in bonding.[17] Therefore, it is assumed that $\mathrm{Cu^{2+}}$ does not bind to $\mathrm{NH_2}$ group of adenine ligand in this compound. The band at 488 $\mathrm{cm^{-1}}$ can be assigned by O–Cu stretching, deformation and Cu–N stretching.[15,16]

Consequently, it is likely that the nitrogen atom N9 of adenine coordinates to $\mathrm{Cu^{2+}}$ and that the N1 and N7 are protonated.

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IR Spectra of Adenine-Pt^{2+} and Adenine-Pd^{2+} Complexes

IR data of polymeric $Me(adeH)Cl_2$ where $Me=Pt^{2+}$ and Pd^{2+} have not yet been reported. This is the first report that discuss the coordination site from IR spectroscopic analysis.

Hadjiliadis and Theophanides[7] prepared $Pt(9\text{-methyladenine})Cl_3$ from the solution of 3N HCl at room temperature and polymeric $Pt(9\text{-methyladenine})Cl_2$ using molar ratio of base: metal (2:1) in 0.1 N HCl. In the present study, a yellow complex was obtained by using molar proportions of base to metal (1:1) and heating the solution in 0.1 N HCl.

The bands in the 3500—3000 cm^{-1} were too broad to be assigned exactly. The band at 2360 cm^{-1} was assigned to NH stretching of adenine in both complexes.[10,11]

Table I. IR Data of Adenine and $Cu(adeH_2)(oxa)Cl\cdot 3/2H_2O$

Tentative assignment	Adenine	$Cu(adeH_2)(oxa)Cl\cdot 3/2H_2O$
OH str.		3400 s
NH_2 str.	3235 s	3180 s
	3055 s	
NH str.	2700 s	
$NH^+\cdots Cl^-$		2500sh
NH_2 bending	1680m	1726 s
O–C–O asym. str.		1665b, s
O–C–O asym. str. +C=C, C=N		1620sh
C=C, C=N	1610 s	1580m
Purine ring vib.	1510w	1520m
		1486w
Ring vib.	1458w	1435 s
	1426m	1405m
	1375m	
Ring. vib. +O–C–O sym. str.		1365w
NH ring vib.	1342m	1342m
C–NH_2 str.	1318m	1324w
NH_2 wagging def. +O–C–O sym. str. +O–C–O def.		1280m
NH_2 wagging and twisting def.	1260m	1220m
	1160w	
	1132m	1110 s
NH	1028m	1038m
		982w
NH_2 out-plane def.	945m	
	918m	922w
NH_2 out-plane def.	875w	
	850w	
NH out-plane def. +Cu–O–Cu asym. str.		840b, s
C–H out-plane def.	801m	792 s
NH_2 rocking def.	728m	730m
		695w
Ring and CN str.	644w	
	625w	616w
C=C, C=N +Cu–N str.	546m	570w
		540m
O–Cu str. +def. +Cu–N str.		488w

In adenine-Pt complex, the broad band extends to 2750 cm^{-1} which is consistent with a weaker intermolecular hydrogen bonding $NH^+ \ldots Cl^-$. The absorption assigned to NH_2 bending did not appear in the region 1700 cm^{-1}, so it was assumed that N1 of adenine was not protonated, and this band shifted to lower frequency. The aromatic carbon-aliphatic nitrogen stretching frequency shifted to a higher frequency as in the case of $Cu(adeH_2)(oxa)Cl \cdot 3/2H_2O$ and appeared at 1320 cm^{-1} suggesting that the amino group was not bound to the metals. Polymeric bridging structures, where Pt^{2+} and Pd^{2+} are coordinated through N1 and N7 of the adenine ligand, may be possible in these compounds.[7]

From the data of IR spectra the coordination sites is not assumed exactly but it is at least suggested that the metals do not bind to N9 and that N1 is not protonated. Therefore, it is likely that N1 and N7 are the coordination sites.

TABLE II. IR Data of Adenine-Pt and Adenine-Pd Complexes

Tentative assignment	Adenine-Pt complex	Adenine-Pd complex
NH_2 str.	Unassigned for broadening	
$NH^+ \cdots Cl^-$	2750sh	
NH str.	2360 w	2360 w
NH_2 bending + C=C, C=N	1655 s	1660 s
Ring vib.	1460 m	1470 m
	1420 m	1420 m
NH ring + C–NH_2 str.	1350 w	1350b, w
	1320 w	1320 w
NH_2 wagging and twisting	1216 m	1216 w
CH out-plane def.	782 w	782 m
	750 w	750 m
NH_2 rocking	720 w	722 w
Ring and CN str.	640 w	

Experimental

Apparatus——IR spectra were taken as KBr pellets on a Hitachi Infrared spectrometer, Model G3.

Reagents——Adenine was purchased from Tokyo Kasei Co. and other reagents were obtained from Wako Pure Chemical Industries, Tokyo. They were of reagent grade and were used without further purification.

Preparation——$Cu(adeH_2)(oxa)Cl \cdot 3/2H_2O$: One millimole of each reactant was used. Oxalic acid was dissolved in 10 ml of water and the pH adjusted to 5.8 with NaOH. Adenine and $Cu(ClO_4)_2 \cdot 6H_2O$ were dissolved in 10 ml of 0.1 N NaOH with stirring. In this solution the oxalic solution was added with stirring and the pH adjusted to 3.4 with 1 N HCl. A precipitate formed. The mixture was stirred for about an hour and filtered. The complex was washed three or four times with water and once with acetone. In this way the compound was obtained. *Anal.* Calcd. for $C_7H_9ClCuN_5O_7$: C, 23.89; H, 2.39; N, 19.65. Found: C, 23.99; H, 2.60; N, 20.00.

$[Pt(C_5H_5N_5)Cl_2]HCl \cdot 1/2H_2O$: To the solution of 0.1 N HCl 0.325 g of adenine and 1 g of K_2PtCl_4 were added. The solution was heated and immediately a yellow precipitate formed and was dried under a reduced pressure. *Anal.* Calcd. for $C_5H_7Cl_3O_{1/2}Pt$: C, 13.44; H, 1.58; N, 15.68. Found: C, 13.35; H, 1.52; N, 15.57.

$[Pd(C_5H_5N_5)Cl_2]HCl \cdot H_2O$: To the solution of 0.1 N HCl 0.354 g of $PdCl_2$ and 0.270 g of adenine were dissolved and immediately an orange precipitate formed and dried under a reduced pressure. *Anal.* Calcd. for $C_5H_8Cl_3N_5OPd$: C, 16.36; H, 2.20; N, 19.10. Found: C, 16.14; H, 1.84; N, 19.08.

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