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Studies on Metal Complexes of Isocytosine Derivatives: The Molecular Structures of Platinum(II) and Platinum(IV) Complexes of 2-Hydrazino-4-hydroxy-6-methylpyrimidine[1)]

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The Pt(II) and Pt(IV) complexes of 2-hydrazino-4-hydroxy-6-methylpyrimidine (LH) were synthesized and their structures investigated. We found that Pt(II) and Pt(IV) ions form novel 1 : 1 and 1 : 2 complexes with LH, respectively. The Pt(II) complex of LH, $[Pt^{II}Cl_2(LH)]$, is a square planar complex with a Pt(II) coordination number of four. On the other hand, in the $[Pt^{IV}Cl_6](LHH)_2$ complex, one $[Pt^{IV}Cl_6]^{2-}$ group forms a double salt with two LHH^+ molecules which are connected to each other by hydrogen bonds as shown by X-ray structure determination. Crystals of $[Pt^{IV}Cl_6](LHH)_2$, $C_{10}H_{18}Cl_6N_8O_2Pt$, belong to the space group $P\bar{1}$ with the unit cell dimensions, $a=6.825(2)$, $b=11.496(4)$, $c=6.775(2)$ Å, $\alpha=101.17(3)°$, $\beta=90.01(3)°$, $\gamma=85.69(3)°$, $V=506.(3)$ Å^3, and $Z=1$. The atomic parameters were refined to a final R value of 0.050 for 4441 reflections. The Pt(IV) ion is situated at the crystallographic center of symmetry. Six ligated Cl^- ions and two protonated LHH^+ are arranged symmetrically around the Pt(IV) ion, and the $[Pt^{IV}Cl_6]^{2-}$ complex ion takes an octahedral coordination geometry.

Keywords X-ray; crystal structure determination; double salt complex; 2-hydrazino-4-hydroxy-6-methylpyrimidine; pyrimidine; Pt(II); Pt(IV); platinum complex; IR spectrum; isocytosine derivative

Introduction

Currently, *cis*-platinum complex is being widely used in clinical cancer therapy as an antitumor agent. We showed[2)] that treatment with *cis*-platinum (*cis*-$[PtCl_2(NH_3)_2]$), vinblastin, and bleomycin resulted in a noticeable improvement of therapeutic effect against advanced nonseminomatous tumors of the testis. When strong diuretic agents (patients passed over 3 l of urine) were administered together with *cis*-platinum complex, no renal or otic damage was found in any of 6 cases.[2)] Many antitumor platinum complexes containing various amines have been synthesized and tested in various tumor systems.[3—5)] It is now recognized that the antitumor activity of *cis*-platinum complex involves interstrand cross linking by *cis*-platinum complex between guanine and cytosine bases and also guanine and guanine bases, resulting in an inhibition of deoxyribonucleic acid (DNA) synthesis.[6—10)] The *trans*-platinum complex, on the other hand, does not exhibit antitumor activity.

Shiho and Takabayashi observed that 2-hydrazino-4-hydroxy-6-methylpyrimidine (LH) acts as a color reagent for metal cations but the structures of the color reaction products have not yet been fully investigated.[11)] We have been doing structural studies of LH (isocytosine derivative) complexes with various metal ions (zinc(II), copper(II), iron(II), nickel(II), and cobalt(II)).[12)] X-Ray crystallographic studies on the metal(II) complexes using crystals of $[Cu(LH)_2(H_2O)]Cl_2 \cdot 2H_2O$, $[Zn(LH)_2(H_2O)_2]Cl_2 \cdot 2H_2O$, $[Ni(LH)_2(H_2O)_2]Cl_2 \cdot 2H_2O$, and $[Co(LH)_2(H_2O)_2]Cl_2 \cdot 2H_2O$ showed that the coordination sites of LH to metal ion were the N(3) and hydrazino N_{amino} atoms.[13—15)]

As a part of our continuing research on metal complexes with nucleotide bases, we found that platinum(II) and platinum(IV) ions form novel 1 : 1 and 1 : 2 complexes with LH, respectively. The results are presented in this paper.

Experimental

Preparation of $[Pt^{II}Cl_2(LH)]$ [I] In an ice bath, a one molar aqueous solution of 2-hydrazino-4-hydroxy-6-methylpyrimidine monohydrochloride (LH·HCl) was added to an aqueous solution containing 1 mol of K_2PtCl_4 under nitrogen bubbling. The mixed solution was concentrated under a reduced pressure at room temperature, the first precipitate being removed by filtration. When the filtrate was allowed to stand for a half hour under nitrogen gas in an ice bath, dark brown crystalline I precipitated out. *Anal.* Calcd for $C_5H_8Cl_2N_4OPt$: C, 14.79; H, 1.99; N, 13.80, Found: C, 14.86; H, 1.98; N, 13.44.

Preparation of $[Pt^{IV}Cl_6](LHH)_2$ [II] In an ice bath, 2 mol of 2-hydrazino-4-hydroxy-6-methylpyrimidine (LH) in 1 N HCl was added to a one molar aqueous solution of H_2PtCl_6. The dark yellow mixed solution was quickly concentrated under a reduced pressure at room temperature. Yellow prismatic crystals of II, obtained in refrigerator after several hours, were washed with a small amount of ice-cold water and dried with ether. *Anal.* Calcd for $C_{10}H_{18}Cl_6N_8O_2Pt$: C, 17.40; H, 2.62; N, 16.23, Found: C, 17.47; H, 2.64; N, 16.24.

Infrared (IR) Spectra of LH–Metal Complexes IR spectral data of LH–metal complexes are listed in Table I. IR spectra were taken with KBr pellets of each sample on a Hitachi EPI-G3 or 260-30 infrared spectrometer.

Crystal Data of II The crystal used for the data collection (0.1 × 0.1 × 0.2 mm), was coated with vaseline and mounted on the top of a fine glass rod. The crystal data are given in Table II. The intensities were

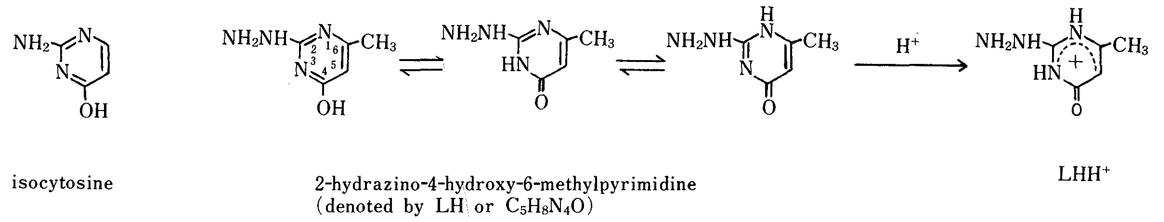

Chart 1

Table I. IR Data for LH, LH·HCl, and Its Metal Complexes (cm^{-1})

Tentative assignment	LH	LH·HCl	$[Pt^{II}Cl_2(LH)]$ [I]	$[Pt^{IV}Cl_6](LHH)_2$ [II]	$[Cu(LH)_2(H_2O)]Cl_2 \cdot 2H_2O$	$[Zn(LH)_2(H_2O)_2]Cl_2 \cdot 2H_2O$
OH str.						3450s
NH, NH_2 str.	3330m	3290m	3260m	3290m	3270 s	3325s
		3130s	3100s	3145m	3150w	
	3050w	3045m		3050w	3060m	
CH str.	2925s	2975w				
		2885w		2870w	2850m	2830s
CO, CC str.,	1658s	1696s	1665s	1710s	1682s	1660s
HNC, HCO, NH_2 def.		1654w	1630s	1654w	1631s	
CN, CC str.	1570s	1588m		1600m	1596s	1570s
		1560m	1560m	1555m	1550s	
CO str.,	1535s		1535m			1535s
NCO, CCO def.	1486w	1465m	1475w	1465w	1475m	1480w
CH_3 def.		1425m	1435w	1425m	1436w	
	1408m		1382w		1405m	1405m
	1378m	1382m	1360w	1320w	1371m	1375m
CO str.,	1205w				1210m	1200w
HNC, NH_2 def.	1190s	1140m	1197s	1145w	1179s	1185s
NH_2 torsional	1090s	1056m	1120w	1065w	1100w	1081s
Pyrimidine ring	978w	972m		980w	976w	972w
vib.	915m	935w		940w		

s, strong; m, medium; w, weak.

Table II. Crystal Data for $[Pt^{IV}Cl_6](LHH)_2$ [II]

$C_{10}H_{18}Cl_6N_8O_2Pt$	FW = 690.10	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Cell constants	$a = 6.825$ (2) Å	$\alpha = 101.17$ (3)°
	$b = 11.496$ (4) Å	$\beta = 90.01$ (3)°
	$c = 6.775$ (2) Å	$\gamma = 85.69$ (3)°
	$V = 506.3$ (3) Å^3	
Z	1	
Density (obsd)	2.225 $g \cdot cm^{-3}$	
(calcd)	2.263 $g \cdot cm^{-3}$	

$(C_5H_9N_4O)^+ = (LHH)^+$. FW: formula weight.

measured on a Rigaku four-circle automatic diffractometer with monochromated MoK_α radiation using a graphite crystal. The intensities of reflections with 2θ values up to 70° were collected by the θ–2θ scan method with a 2θ scan rate of 2° min^{-1}. The background was measured at each end of the scan range for 10 s. The intensities were collected for Lorentz and polarization factors but not for absorption factors. The total number of independent observed reflections above the $3\sigma(F)$ level was 4441 out of 4486 theoretically possible reflections.

Determination and Refinement of the Structure [II] The crystal structure was solved by the heavy-atom method. Since the space group is $P\bar{1}$ and $Z = 1$, the platinum(IV) ion was located at (0, 0, 0). The resulting Fourier map revealed all the atoms with exception of hydrogen atoms.

Refinement of the structure was carried out by using the full-matrix least-squares method.[16] A refinement with three cycles of isotropic least-squares calculations for one platinum(IV), three chlorine, one oxygen, four nitrogen, and five carbon atoms gave $R = 0.089$. A further three cycles of anisotropic least-squares refinement for all 14 non-hydrogen atoms gave the R index of 0.050. In this calculation, anisotropic thermal motions were assumed for all 14 atoms and the following weighting scheme was applied: $\sqrt{w} = 30/F_0$, when $F_0 \geqq 30$ and $\sqrt{w} = 1$ otherwise. The atomic scattering factors used in the calculations were taken from International Tables for X-Ray Crystallography[17] and from Cromer and Mann's paper.[18] The final atomic coordinates are listed in Table III.[19] No further refinement including hydrogen atoms was attempted, since platinum(IV) is a very heavy atom and the hydrogen atoms were not clearly seen on the difference electron-density map.

Calculations The calculations for X-ray structure determinations of the platinum(IV) complex II were carried out on HITAC 8800/8700 and HITAC M-200H computers at the University of Tokyo Computer Center using the X-Ray System.[16]

Results and Discussion

Molecular Structure of $[Pt^{II}Cl_2(LH)]$ [I]

The crystal

Table III. Atomic Parameters of $[Pt^{IV}Cl_6](LHH)_2$ [II]

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Pt	0	0	0	15 (0.1)	16 (0.1)	21 (0.1)	1 (0.1)	1 (0.1)	5 (0.1)
Cl(1)	2044 (3)	−1795 (2)	−898 (3)	30 (1)	23 (1)	38 (1)	10 (1)	5 (1)	7 (1)
Cl(2)	−1961 (3)	−766 (2)	−2805 (3)	30 (1)	36 (1)	33 (1)	1 (1)	−9 (1)	2 (1)
Cl(3)	−1963 (3)	767 (2)	2038 (3)	30 (1)	37 (1)	44 (1)	1 (1)	12 (1)	22 (1)
N(1)	−2950 (8)	4053 (5)	7018 (10)	16 (2)	21 (2)	37 (3)	0 (2)	1 (2)	6 (2)
C(2)	−1660 (9)	3065 (6)	6529 (11)	18 (2)	22 (3)	29 (3)	0 (2)	1 (2)	6 (2)
N(3)	288 (8)	3231 (6)	6613 (12)	15 (2)	26 (3)	54 (4)	3 (2)	2 (2)	7 (2)
C(4)	1051 (10)	4368 (7)	7183 (14)	16 (3)	33 (3)	51 (5)	−2 (2)	−1 (3)	10 (3)
C(5)	−388 (10)	5400 (7)	7700 (14)	18 (3)	26 (3)	50 (4)	−1 (2)	1 (3)	7 (3)
C(6)	−2336 (10)	5225 (6)	7610 (12)	19 (3)	24 (3)	40 (4)	1 (2)	2 (2)	7 (3)
N(7)	−2226 (9)	1957 (5)	5975 (11)	23 (2)	22 (2)	39 (3)	−1 (2)	2 (2)	6 (2)
N(8)	−4250 (10)	1802 (7)	5886 (15)	20 (3)	33 (3)	73 (6)	−5 (2)	−1 (3)	9 (3)
O(9)	2836 (8)	4429 (7)	7219 (15)	14 (2)	50 (4)	99 (6)	−2 (2)	0 (3)	17 (4)
C(9)	−3903 (12)	6259 (7)	8127 (18)	23 (3)	25 (3)	79 (7)	8 (3)	4 (4)	9 (4)

Non-hydrogen atoms. Values are × 10^4. Anisotropic temperature factors are of the form: $T = \exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$.

structure of the complex I was not determined by X-ray diffraction because only very small crystals were obtainable.

The platinum(II) ion forms a square planar complex with the four coordination number of four, taking the electronic configurations of the *dsp*^{2} hybrid orbitals as low spin type. Furthermore, the LH ligand has shown to have two coordination sites in the metal(II) complexes studied so far by X-ray analysis, such as $[Zn(LH)_2(H_2O)_2]Cl_2 \cdot 2H_2O$, $[Co(LH)_2(H_2O)_2]Cl_2 \cdot 2H_2O$, $[Cu(LH)_2(H_2O)]Cl_2 \cdot 2H_2O$, $[Ni(LH)_2(H_2O)_2]Cl_2 \cdot 2H_2O$, and $[Fe(LH)_2(H_2O)_2]Cl_2 \cdot 2H_2O$.[13-15] In all these metal(II) complexes, the coordination sites of LH to metal(II) ion are the N(3) atom of the pyrimidine ring and the N_{amino} atom of the hydrazino group in the *cis* position.

Therefore, the molecular structure of I having four planar coordination sites around the platinum(II) ion could be presumed to be as shown in Fig. 1 from a consideration of previous X-ray crystallographic results on the above metal(II)–LH complexes,[13-15] IR spectra of LH metal complexes (see Table I), and elementary analysis of I. In the IR spectrum of complex I, the absorption of C=O stretching vibration appeared at 1665 cm^{-1}, in the same range (1660—1682 cm^{-1}) as those of $[Zn(LH)_2(H_2O)_2]Cl_2 \cdot 2H_2O$, $[Co(LH)_2(H_2O)_2]Cl_2 \cdot 2H_2O$, $[Cu(LH)_2(H_2O)]Cl_2 \cdot 2H_2O$, *etc.*[12] involving metal(II)–LH coordination. On the other hand, the absorptions of the C=O band for protonated LHH$^+$ of $[Pt^{IV}Cl_6](LHH)_2$ [II] without metal(II)–LH coordination and LH·HCl appeared at higher wavelengths of 1710 and 1696 cm^{-1}, respectively. Therefore, it was assumed that the platinum(II) ion was coordinated to the N_{amino} nitrogen N(8) atom of the hydrazino group and the N(3) atom of the pyrimidine ring in LH base, and two Cl atoms in the *cis* position only.

Molecular and Crystal Structure of $[Pt^{IV}Cl_6](LHH)_2$ [II] The complex II has no LH–metal coordinations, which were present in the zinc(II) and copper(II) complexes of LH.[13,14] In the complex II, one $[Pt^{IV}Cl_6]^{2-}$ group and two LHH$^+$ molecules constitute a double salt complex, with hydrogen bonding. There is one complex molecule in the unit cell. The platinum(IV) ion is situated at the crystallographic center of symmetry and the $[Pt^{IV}Cl_6]^{2-}$ ion takes an octahedral coordination geometry (Fig. 2).

The bond lengths (Å) and angles (°) of II are listed in

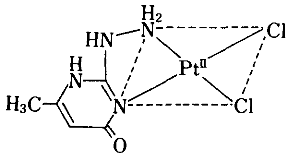

Fig. 1. Presumptive Structure of $[Pt^{II}Cl_2(LH)]$ [I]

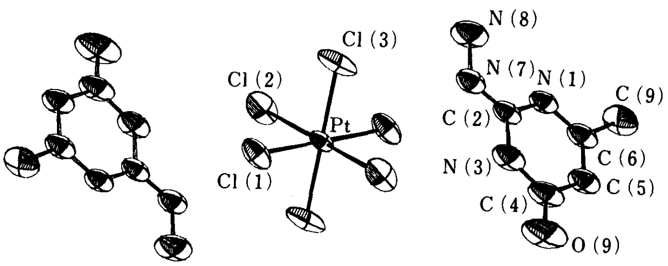

Fig. 2. Nomenclature and Perspective View of $[Pt^{IV}Cl_6](LHH)_2$ [II]
The Pt(IV) ion is on the crystallographic center of symmetry.

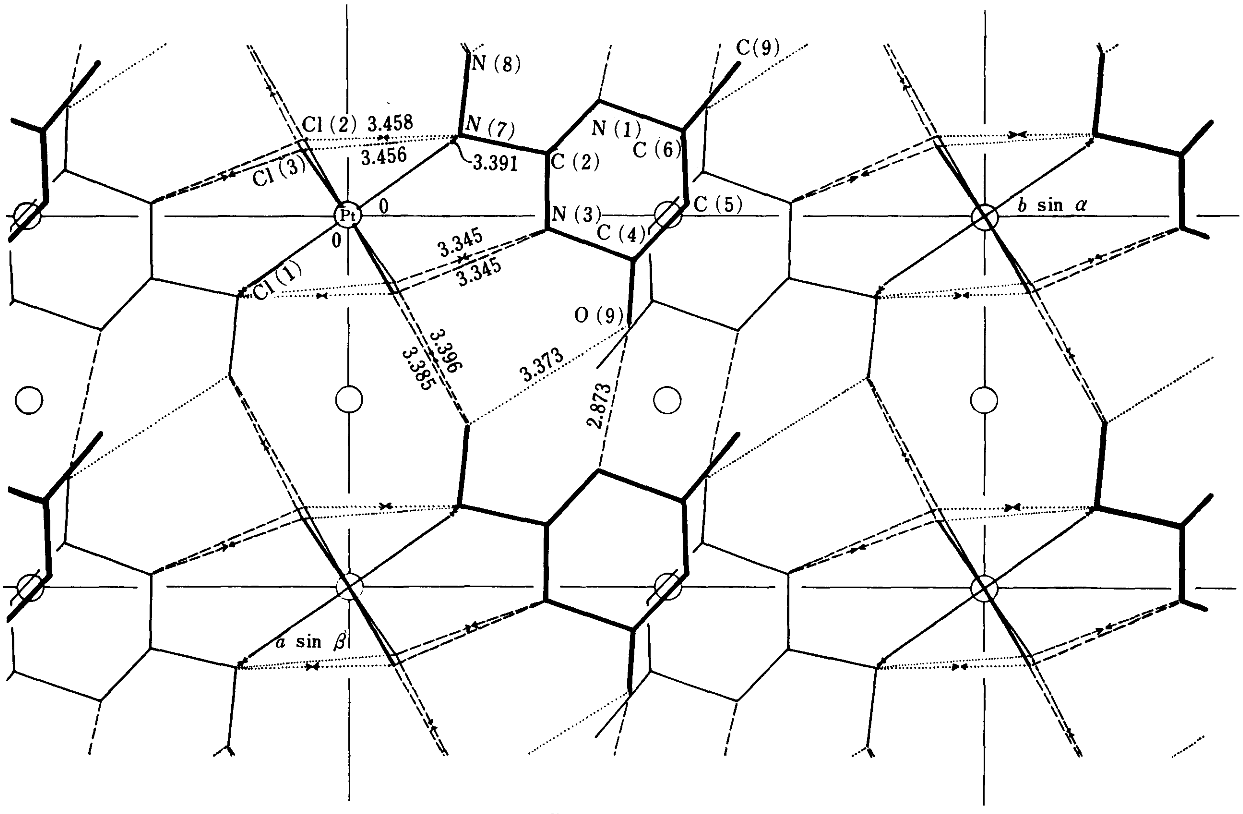

Fig. 3. Projection of the Crystal Structure along the *c* Axis in $[Pt^{IV}Cl_6](LHH)_2$ [II]
Centers of symmetry are denoted by ○. Hydrogen bonds are shown by broken lines, other intermolecular interactions less than 3.5 Å are shown by dotted lines.

TABLE IV. Bond Lengths (Å) and Angles (°) in $[\mathrm{Pt^{IV}Cl_6}](\mathrm{LHH})_2$ [II] with Their Estimated Standard Deviations in Parentheses

Bond lengths		Bond angles			
Pt–Cl(1)	2.324 (2)	Cl(1)–Pt–Cl(2)	91.0 (1)	C(2)–N(1)–C(6)	121.6 (6)
Pt–Cl(2)	2.317 (2)	Cl(1)–Pt–Cl(2)$^{a)}$	89.0 (1)	N(1)–C(2)–N(3)	118.6 (6)
Pt–Cl(3)	2.318 (2)	Cl(1)–Pt–Cl(3)	91.0 (1)	N(1)–C(2)–N(7)	122.0 (6)
N(1)–C(2)	1.343 (8)	Cl(1)–Pt–Cl(3)$^{a)}$	89.0 (1)	N(3)–C(2)–N(7)	119.4 (6)
N(1)–C(6)	1.385 (9)	Cl(2)–Pt–Cl(3)	90.1 (1)	C(2)–N(3)–C(4)	124.1 (6)
C(2)–N(3)	1.356 (9)	Cl(2)–Pt–Cl(3)$^{a)}$	89.9 (1)	N(3)–C(4)–C(5)	115.2 (6)
C(2)–N(7)	1.305 (9)			N(3)–C(4)–O(9)	119.5 (7)
N(3)–C(4)	1.390 (10)			C(5)–C(4)–O(9)	125.2 (8)
C(4)–C(5)	1.441 (10)			C(4)–C(5)–C(6)	120.2 (7)
C(4)–O(9)	1.225 (9)			N(1)–C(6)–C(5)	120.2 (6)
C(5)–C(6)	1.358 (10)			N(1)–C(6)–C(9)	117.0 (6)
C(6)–C(9)	1.497 (10)			C(5)–C(6)–C(9)	122.8 (7)
N(7)–N(8)	1.405 (9)			C(2)–N(7)–N(8)	118.6 (6)

a) Inverted by a center of symmetry at (0, 0, 0).

TABLE V. Deviations (Å) of Atoms from the Least-Squares Plane of the Pyrimidine Ring

N(1)	−0.002	C(4)	−0.001	N(7)$^{a)}$	0.002
C(2)	0.001	C(5)	0.000	N(8)$^{a)}$	−0.004
N(3)	0.000	C(6)	0.001	O(9)$^{a)}$	0.002
				C(9)$^{a)}$	0.002

a) These atoms are not included in the least-squares calculation.

TABLE VI. Important Intermolecular Distances (Å) of Less than 3.5 Å in $[\mathrm{Pt^{IV}Cl_6}](\mathrm{LHH})_2$ [II]

No.	From$^{a)}$	To	Distance
1	O(9)	N(1)$^{b)}$	2.873 (8)$^{h)}$
2	O(9)	N(8)$^{b)}$	3.373 (10)
3	N(3)	Cl(3)$^{d)}$	3.345 (7)$^{i)}$
4	N(3)	Cl(2)$^{e)}$	3.345 (6)$^{i)}$
5	N(7)	Cl(3)$^{a)}$	3.456 (6)
6	N(7)	Cl(2)$^{c)}$	3.458 (7)
7	N(7)	Cl(1)$^{e)}$	3.391 (8)$^{h)}$
8	N(8)	Cl(3)$^{f)}$	3.396 (9)$^{h)}$
9	N(8)	Cl(2)$^{g)}$	3.385 (8)$^{h)}$

Key to the symmetry operations: *a*) x, y, z; *b*) $1+x, y, z$; *c*) $x, y, 1+z$; *d*) $-x, -y, 1-z$; *e*) $-x, -y, -z$; *f*) $-1-x, -y, 1-z$; *g*) $-1-x, -y, -z$. *h*) Hydrogen bond suggested. *i*) These hydrogen bonds are bifurcated.

Table IV. The coordination distances of Pt–Cl(1), Pt–Cl(2), and Pt–Cl(3) are 2.324, 2.317, and 2.318 Å, respectively. On the other hand, the length of C(4)–O(9), 1.225 Å, in $\mathrm{LHH^+}$ suggests the keto form ($>\mathrm{C=O}$ double bond). Therefore, oxo-amino type LH in the complex II is presented as the cation ($\mathrm{LHH^+}$) with addition of a proton, and forms hydrogen bonds involving both N(1) and N(3) (see Fig. 3). The $\mathrm{LHH^+}$ cations and metal–Cl complex anions are connected by the hydrogen bonds. Thus, the platinum(IV) complex II is presented as $[\mathrm{Pt^{IV}Cl_6}]^{2-}(\mathrm{LHH^+})_2$.

The pyrimidine ring is planar (Table V) with very small deviations of atoms from the least-squares plane.

The *c* axis projection of the crystal structure is shown in Fig. 3. The $[\mathrm{Pt^{IV}Cl_6}]^{2-}$ anions are situated at the corners of the unit cell, and are connected with the $\mathrm{LHH^+}$ cations by hydrogen bonds and other intermolecular interactions (Table VI). The pyrimidine rings are arranged parallel to each other across the center of symmetry at (0, 1/2, 0) and (0, 1/2, 1/2), and are stacked along the *c* axis (see Fig. 3). These rings are separated with perpendicular distances of 3.388 and 3.381 Å, respectively.

As described before, in the $[\mathrm{Zn(LH)_2(H_2O)_2}]\mathrm{Cl_2 \cdot 2H_2O}$[13] and $[\mathrm{Cu(LH)_2(H_2O)}]\mathrm{Cl_2 \cdot 2H_2O}$[14] complexes which were obtained by adding hydrochloric acid (pH = 1) in excess, directed coordinations between metal and LH are found but metal–Cl coordination is not present. Thus the tendency of coordination of LH base to metal ions ($\mathrm{Zn^{II}}$ and $\mathrm{Cu^{II}}$) may be greater than that of Cl atom to the metal ions. On the other hand, in $[\mathrm{Pt^{IV}Cl_6}](\mathrm{LHH})_2$ [II] which formed a double salt complex (in pH = 1) by the same preparation method, the platinum(IV) ion is coordinated to Cl atoms and there is no direct Pt(IV)–LH coordination. From the present study, the tendency of coordination of LH base to platinum(IV) is just the reverse, and the Pt(IV)–Cl coordination is stronger than the Pt(IV)–LH coordination in the crystal. The Pt–LH coordination is seen in $[\mathrm{Pt^{II}Cl_2(LH)}]$ [I], involving LH–Pt–Cl mixed ligands, which was obtained without addition of hydrochloric acid to the reaction mixture. Therefore, in the LH metal complexes, the coordination type of ligands varies with changes of pH and kinds of metal ions. Different metal ion species seen to exhibit different coordination selectivity for coexisting ligands such as the LH base, Cl ion, and H_2O.

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