Synthesis and Properties of Novel Platinum(IV) Complexes Involving Asymmetric Chiral Diamines as Carrier Ligands

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Novel platinum(IV) complexes with asymmetric chiral diamine ligands *cis,cis,trans*-$A_2PtCl_2(X)_2$ (X = OH, $OCOCH_3$, $OCOC_2H_5$, A_2 = $NH_2CH(CH_3)CH_2NH(c\text{-}C_6H_{11})$(apcha), $NH_2CH(CH_3)CH_2NH(c\text{-}C_5H_9)$(apcpa)) have been prepared. One of the platinum(IV) complexes, (apcpa)$PtCl_2(OCOC_2H_5)_2$(**6**), was subjected to X-ray crystallographic analysis. The crystal structure of (apcpa)$PtCl_2(OCOC_2H_5)_2$ (monoclinic, $P2_1$ (No. 4), a = 9.1391(1), b = 22.2517(1), c = 10.0687(1) Å, β = 109.105(1)°, V = 1934.80(3) Å^3, Z = 4, R_1 = 0.0532) exhibits that the platinum atom achieves a typical octahedral arrangement with two nitrogen atoms in *cis* positions and two carboxylato group in *trans* positions. The spectroscopic data disclose that these platinum(IV) complexes are stable and their molecular structures are retained in aqueous solution. The title complexes are highly cytotoxic *in vitro* but do not exhibit oral anticancer activity *in vivo*.

Introduction

The conventional structure-activity relationship has played a key role in attempts to optimize the structure of the cisplatin analogues. The relevant studies have led to some important guidelines[1-4] for the design of new complexes, and new strategies have recently been developed.[4-7]

A desirable alternative approach to reduce side effects and to enhance the quality of life in the treatment of cancer patient is to develop an orally active platinum antitumor agent. Platinum complexes suitable for oral adminstration should be neutral, liphophilic, water soluble and stable in gastric environment. In order to meet such criteria, platinum(IV) compounds are usually prepared by carboxylation of dihydroxoplatinum(IV) complexes which are attainable by oxidation of the platinum(II) species with hydrogen peroxide.

cis,trans,cis-$NH_3(c\text{-}C_6H_{11})Pt(OCOCH_3)_2Cl_2$ (JM216) is one of such platinum complexes currently in clinical trials.[8-13] However, the impediment to the development of this series of compounds and other platinum(IV) complexes with two different amines in *cis* positions has been the difficult access to the *cis*-$Pt(II)Cl_2AA'$ core, because of difficulty to prepare the $[Pt(II)Cl_3NH_3]^-$ anion.

In order to overcome such drawbacks of the conventional synthetic methods, we have recently reported[14] a facile synthetic method to prepare a series of chelating asymmetric diamineplatinum(II) complexes, which exhibited excellent antitumor activity against the leukemia L1210 cell line. Therefore in this study we have synthesized platinum(IV) complexes with chelating asymmetric diamine ligands by oxidation of these platinum(II) complexes to investigate their oral anticancer activity along with their physicochemical properties.

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Experimental Section

Materials and Instrumentation. Potassium tetrachloroplatinate(II) purchased from Kojima, and S-alanine(ala), (cbz)-glycine, cyclohexylamine(cha), cyclopenthylamine(cpa), benzylchloroformate (cbzCl), and N,N'-dicyclohexylcarbodiimide(DCC) from Aldrich were used as received. $NH_2CH(CH_3)CH_2NH(c\text{-}C_6H_{11})$(apcha), $NH_2CH(CH_3)CH_2NH(c\text{-}C_5H_9)$(apcpa) and their platinum(II) complexes, (apcha)$PtCl_2$ and (apcpa)$PtCl_2$ were prepared by our previous method.[14-16]

Elemental analyses were performed by the Advanced Analysis Center at KIST. ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker 250MH/52MM spectrometer relative to TMS as an external standard. The infrared spectra in the 4000-400 cm^{-1} region were measured as KBr pellets on a Nicolet Impact 400 FT-IR spectrophotometer. Melting points were observed with a Mettler FP 82 Hot Stage and a Mettler FP 90 Central Processor.

Synthesis of $A_2PtCl_2(OH)_2$ (A_2 = apcha, apcpa). To a suspension of A_2PtCl_2 (0.2 mmol) in water (20 mL) was added an aqueous solution of 30% of H_2O_2 (2.0 mL), and the solution was stirred for 2 h. The resulting pale yellow solution was concentrated to 5 mL in a rotavapor at 40 °C, to which acetone (100 mL) was added. The light yellow precipitate was filtered and washed with ethyl ether. The crude product was recrystallized from water to obtain the crystalline solid product.

(apcha)$PtCl_2(OH)_2 \cdot H_2O$ (**1**). Yield 40%; Found (Calc. for $C_9H_{22}N_2PtCl_2O_2 \cdot H_2O$): C, 22.4 (22.8); H, 4.9 (5.1); N, 5.7 (5.9). IR (KBr cm^{-1}): ν(Pt-O-H), 3450; ν(N-H), 3200, 3140; ν(C-H), 2932, 2857; ν(Pt-O), 556. ^{1}H NMR (D_2O, ppm): 3.1-3.2 (m, 1H), 2.90-2.95 (m, 3H), 2.31-2.35 (m, 1H), 1.3-1.8 (m, 8H), 1.41 (d, 3H, J = 5.6 Hz), 1.0-1.2 (m, 2H).

(apcpa)$PtCl_2(OH)_2$ (**2**). Yield 68%; Found (Calc. for $C_8H_{20}N_2PtCl_2O_2$): C, 21.9 (21.7); H, 4.5 (4.6); N, 6.1 (6.3). IR (KBr cm^{-1}): ν(Pt-O-H), 3430; ν(N-H), 3230, 3171; ν(C-H), 2959, 2870; ν(Pt-O), 544. ^{1}H NMR (D_2O, ppm): 3.7-3.8

(m, 1H), 3.4-3.5 (m, 1H), 2.8-3.0 (m, 2H), 1.9-2.2 (m, 2H), 1.4-1.7 (m, 6H), 1.41 (t, 3H, J = 7.0 Hz).

Synthesis of $A_2PtCl_2(OCOR)_2$ (A_2 = apcha, apcpa; R = CH_3,C_2H_5). To a suspension of $A_2PtCl_2(OH)_2$ (0.7 mmol) in CH_2Cl_2 (50 mL) was added acetic anhydride (5.0 mL) or propionic anhydride (5.0 mL), and the mixture was stirred until the solution became clear. The solvent was removed by evaporation under reduced pressure and the residue was recrystallized from methanol.

(apcha)$PtCl_2(OCOCH_3)_2 \cdot H_2O$ (**3**). Yield 40%; Found (Calc. for $C_{13}H_{26}N_2PtCl_2O_4 \cdot H_2O$): C, 28.2 (28.0); H, 4.9 (5.1); N, 5.0 (5.0). IR (KBr cm^{-1}): ν $(C=O)_{asym}$, 1623; ν $(C=O)_{sym}$, 1299. ^1H NMR (D_2O, ppm): 3.12-3.20 (m, 1H), 2.9-3.0 (m, 2H), 2.2-2.3 (m, 1H), 1.9-2.1 (m, 1H), 2.01 (s, 6H), 1.6-1.8 (m, 4H), 1.10-1.41 (m, 2H), 1.38 (t, 3H, J = 6.8 Hz).

(apcpa)$PtCl_2(OCOCH_3)_2 \cdot H_2O$ (**4**). Yield 48%; Found (Calc. for $C_{12}H_{24}N_2PtCl_2O_4 \cdot H_2O$): C, 26.2 (26.5); H, 4.7 (4.8); N, 5.4 (5.2). IR (KBr cm^{-1}): ν $(C=O)_{asym}$, 1623; ν $(C=O)_{sym}$, 1292. ^1H NMR (D_2O, ppm): 3.8-3.9 (m, 1H), 3.4-3.5 (m, 1H), 3.0-3.1 (m, 2H), 2.01-2.19 (m, 3H), 2.03 (s, 6H), 1.55-1.68 (m, 5H), 1.40 (t, 3H, J = 7.0 Hz).

(apcha)$PtCl_2(OCOC_2H_5)_2$ (**5**). Yield 40%; Found (Calc. for $C_{15}H_{30}N_2PtCl_2O_4$): C, 31.5 (31.7); H, 4.9 (5.3); N, 5.0 (4.9). IR (KBr cm^{-1}): ν $(C=O)_{asym}$, 1628; ν $(C=O)_{sym}$, 1333, 1233. ^1H NMR (D_2O+CD_3OD, ppm): 3.12-3.20 (m, 1H), 2.9-3.0 (m, 2H), 2.42 (qu., 4H, J = 6.8 Hz), 2.2-2.3 (m, 1H), 1.9-2.1 (m, 1H), 1.6-1.8 (m, 4H), 1.41 (t, 3H, J = 6.4 Hz), 1.1-1.4 (m, 2H), 1.04 (t, 6H, J = 6.7 Hz).

(apcpa)$PtCl_2(OCOC_2H_5)_2$ (**6**). Yield 68%; Found (Calc. for $C_{14}H_{28}N_2PtCl_2O_4$): C, 30.0 (30.3); H, 5.0 (5.1); N, 5.0 (5.1). IR (KBr cm^{-1}): ν $(C=O)_{asym}$, 1624; ν $(C=O)_{sym}$, 1329, 1233. ^1H NMR (D_2O+CD_3OD, ppm): 3.8-3.9 (m, 1H), 3.4-3.5 (m, 1H), 2.82-3.03 (m, 2H), 2.43 (qu., 4H, J = 6.7 Hz), 2.0-2.1 (m, 2H), 1.54-1.68 (m, 6H), 1.44 (t, 3H, J = 6.5 Hz), 1.03 (t, 6H, J = 6.5 Hz).

X-ray Crystallography. The crystallographic data were obtained on an Enraf-Nonius CAD4 automatic diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at ambient temperature. Unit cell parameters and orientation matrix for the crystal were obtained from a least squares procedure with setting angles of 25 reflections. Absorption correction were applied to the data. The structure was solved by a conventional heavy atom method, followed by successive full-matrix least-squares refinement and different Fourier synthesis. Hydrogen atoms were placed in calculated positions and refined isotropically. The C(7) and C(25) atoms are disordered and should have been expressed, respectively, as C(7a) and C(7b) and C(25a) and C(25b). These disordered atoms, however, have been refined isotropically and labeled as C(7a) and C(25a) in Figure and Table. The occupancy factor is (C(7a), C(7b) = 0.66, 0.34) and (C(25a), C(25b) = 0.62, 0.38). All calculations were performed using SDP running on VAX/VMS V5.3 and SHELXL-97 programs running on PC.[17] A listing of observed and calculated structural factor is available as supplementary material.

***In Vitro* and *in vivo* Assay.** Murine leukemia L1210 cells were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum (Gibco). Cell were adjusted to 1×10^6 cells/mL and distributed to 24 well tissue culture plates (0.5 mL/well). Test complexes were serially diluted and added to the wells (0.5 mL/well). Following 48 h incubation in 5% CO_2 atmosphere at 37 °C, cell counts were determined with a Coulter model ZM cell counter. Cell growth in the presence of test complexes was expressed as a percentage of growth in untreated control wells and the concentration of complexes producing 50% inhibition of cell growth was determined (ED_{50}). *In vivo assay* was carried out using the ascites cell of L1210 lymphoid leukemia, which was obtained from DBA/2 donor mice bearing 3-5 day tumor growth. L1210 leukemia cells (1×10^5) in acetic fluid were implanted i.p. in $BD2F_1$ mice (6-8 week old, 20-25 g; 8 mice per group), and the test compound was given orally at 1, 2, 3, 4 and 5 days after leukemia inoculation. Mice were observed daily and antitumor drug activity was determined based upon the T/C (%).

Results and Discussion

Synthesis and Properties. A new class of asymmetric diamineplatinum(II) compounds were reported in our previous work[14] and the A_2PtCl_2 (A_2 = apcha, apcpa) complexes were synthesized by the literature method.[14,15]

The oxidation of these platinum(II) complexes with hydrogen peroxide afforded smoothly the octahedral platinum(IV) complexes with two hydroxyl groups in axial positions. These complexes were further reacted with acetic or propionic anhydride in dichloromethane to generate the corresponding *trans*-(dicarboxylato)PtA_2Cl_2 complexes. The products were recrystallized by precipitation using a solvent pair of n-hexane or ethyl ether and methanol.

The (dicarboxylato)PtA_2Cl_2 complexes are all soluble in water and polar organic solvent such as alcohol and acetone but insoluble in diethylether and n-hexane. The acetylaion products of the platinum(IV) complexes could be readily identified by their characteristic Pt-O-H and Pt-O stretching frequencies at 3450 and 3430 cm^{-1}, and at 556 and 544 cm^{-1}, respectively, which disappeared after carboxylation. The IR spectra of the carboxylated platinum(II) complexes display typical patterns expected for coordination of the carboxylate ligands to the platinum atom in a unidentate fashion. The broad asymmetric and symmetric stretching absorptions of the carboxylate ligands were observed in the range of 1624-1628 cm^{-1} and 1233-1333 cm^{-1}, respectively, resulting in $\Delta\nu$ > 300 cm^{-1} for the *trans*-dicarboxylatoplatinum(IV) complexes.[22]

The ^1H NMR spectra of the *trans*-diacetatoplatinum(IV) complexes show that the methyl protons of the two axial acetato ligands resonate at 2.01 and 2.03 ppm as singlets due to their interactions with the asymmetric amine ligands. Thus the ^1H NMR spectral data of the octahedral platinum (IV) complexes are consistent with the structures in the solid state. For the *trans*-dipropionatoplatinum(IV) complexes the methylene and methyl protons of the two *trans*-propionate groups resonate at 2.42 and 2.43 ppm as quartets and at 1.04

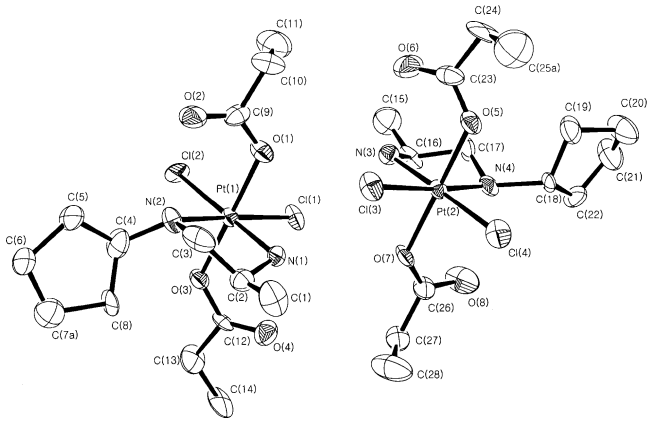

Figure 1. ORTEP drawing of (apcpa)$PtCl_2(OCOC_2H_5)_2$ along with the atomic labelling Scheme. The disordered C(7b) and C(25b) were omitted.

and 1.03 ppm as triplets, respectively. Such results suggest that the symmetrical coordination of both propionate groups to the platinum atom is retained in aqueous solution. Thus all spectral data of the (apcpa)$PtCl_2$ $(OCOC_2H_5)_2$ complex are consistent with the X-ray structure.

Crystal Structure of (apcpa)$PtCl_2(C_2H_5COO)_2$. For (apcpa)$PtCl_2(OCOC_2H_5)_2$ there are two independent molecules in the asymmetric region of the monoclinic unit cell and the features of the two molecules are within error of being identical. One of the molecules and its labelling scheme for (apcpa)$PtCl_2(OCOC_2H_5)_2$ is depicted in Figure 1. The local geometry around the platinum atom is an approximately octahedron: the distances of Pt(1)-N(1), Pt(1)-Cl(1) and Pt(1)-O(1) are 2.01(1), 2.317(5) and 2.035(12) Å, respectively, and the bond angles of N(1)-Pt(1)-N(2), N(1)-Pt(1)-O(1), N(1)-Pt(1)-Cl(1), and Cl(1)-Pt(1)-Cl(2) are 84.8(6)°, 88.0(6)°, 90.6(5)° and 91.97(19)°, respectively. The distortion appears to be caused by limitation of the bite angle of the chelating ligand. Two adjacent corners of the Pt(IV) plane are occupied by the nitrogen atoms of the apcpa ligand, and the remaining *cis* equatorial positions are used for two chloride ions. Two additional axial positions are occupied by propionato ligands. The average Pt-N bond length of 2.04 Å in within the normal range for other diamine platinum(IV)

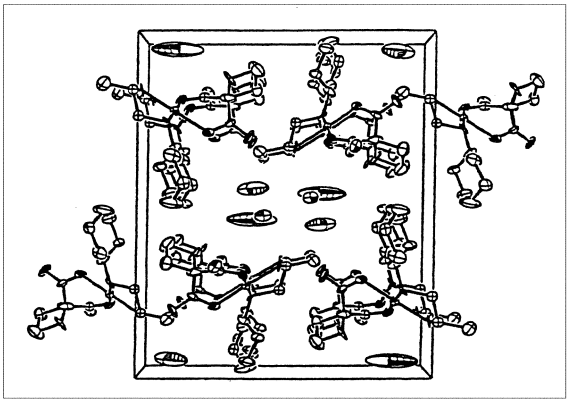

Figure 2. View showing the weak paring of (apcpa)$PtCl_2(OCOC_2H_5)_2$ molecules within the unit cell.

Table 1. Crystal parameters and experimental details for (apcpa)$PtCl_2(OCOC_2H_5)_2$

complex	(apcpa)$PtCl_2(OCOC_2H_5)_2$
formula	$C_{14}H_{28}Cl_2N_2O_4Pt$
fw	554.37
space group	$P2_1$ (No. 4)
a(Å)	9.1391(1)
b(Å)	22.2517(1)
c(Å)	10.0687(1)
β	109.105(1)
V(Å^3)	1934.80(3)
Z	4
$D_{cal.}$ g/cm^3	1.884
μ (abs. coeff), mm^{-1}	7.546
no. total observation	8877
no. unique data	4910
GOF on F^2	1.188
final R indicies	R_1 = 0.0532,
[I > 2sigma(I)]	wR_2 = 0.1251
R indices(all data)	R_1 = 0.0585
	wR_2 = 0.1269

Table 2. Selected bond lengths (Å) and angles [°] for (apcpa)$PtCl_2(OCOC_2H_5)_2$

Pt(1)-O(3)	2.00(1)	Pt(2)-O(5)	2.01(1)
Pt(1)-N(1)	2.01(1)	Pt(2)-O(7)	2.02(1)
Pt(1)-O(1)	2.04(1)	Pt(2)-N(3)	2.07(2)
Pt(1)-N(2)	2.06(2)	Pt(2)-N(4)	2.07(2)
Pt(1)-Cl(2)	2.305(4)	Pt(2)-Cl(4)	2.306(6)
Pt(1)-Cl(1)	2.317(5)	Pt(2)-Cl(3)	2.322(5)
N(1)-C(2)	1.54(2)	N(3)-C(16)	1.47(2)
N(2)-C(3)	1.44(3)	N(4)-C(17)	1.46(2)
N(2)-C(4)	1.51(3)	N(4)-C(18)	1.55(2)
O(1)-C(9)	1.27(2)	O(5)-C(23)	1.29(3)
O(2)-C(9)	1.21(2)	O(6)-C(23)	1.22(3)
O(3)-C(12)	1.31(2)	O(7)-C(26)	1.30(2)
O(4)-C(12)	1.21(2)	O(8)-C(26)	1.21(2)
O(3)-Pt(1)-N(1)	94.8(6)	O(5)-Pt(2)-O(7)	174.1(6)
O(3)-Pt(1)-O(1)	176.4(7)	O(5)-Pt(2)-N(3)	96.5(6)
N(1)-Pt(1)-O(1)	88.0(6)	O(7)-Pt(2)-N(3)	87.1(6)
O(3)-Pt(1)-N(2)	89.4(7)	O(5)-Pt(2)-N(4)	89.4(7)
N(1)-Pt(1)-N(2)	84.8(6)	O(7)-Pt(2)-N(4)	95.7(6)
O(1)-Pt(1)-N(2)	92.9(7)	N(3)-Pt(2)-N(4)	82.1(6)
O(3)-Pt(1)-Cl(2)	87.2(5)	O(5)-Pt(2)-Cl(4)	86.5(5)
N(1)-Pt(1)-Cl(2)	176.7(5)	O(7)-Pt(2)-Cl(4)	90.2(5)
O(1)-Pt(1)-Cl(2)	90.0(5)	N(3)-Pt(2)-Cl(4)	175.9(5)
N(2)-Pt(1)-Cl(2)	92.7(5)	N(4)-Pt(2)-Cl(4)	95.1(5)
O(3)-Pt(1)-Cl(1)	91.3(4)	O(5)-Pt(2)-Cl(3)	89.9(4)
N(1)-Pt(1)-Cl(1)	90.6(5)	O(7)-Pt(2)-Cl(3)	85.3(4)
O(1)-Pt(1)-Cl(1)	86.6(4)	N(3)-Pt(2)-Cl(3)	91.2(5)
N(2)-Pt(1)-Cl(1)	175.3(5)	N(4)-Pt(2)-Cl(3)	173.1(4)
Cl(2)-Pt(1)-Cl(1)	91.97(19)	Cl(4)-Pt(2)-Cl(3)	91.7(2)

Symmetry transformations used to generate equivalent atoms:

complexes.[18-21] The two axial Pt(IV)-O bond distances are not significantly different from each other. The averaged Pt-

Table 3. Antitumor activity of *cis*-$A_2PtCl_2X_2$ against leukemia L1210 cell line

complexes	A_2	X	*in vitro*	*in vivo* (oral)	
			ED_{50} (μg/mL)	Dose (mg/kg)	T/C[a] (%)
1	apcha	OH	3.6	150	107.6
2	apcpa	OH	3.1	150	101.2
3	apcha	$OCOCH_3$	1.7	150	101.2
4	apcpa	$OCOCH_3$	2.9	150	93.6
6	apcpa	$OCOC_2H_5$	1.6	150	100.0
JM216			0.9	150	160.0

[a] T/C (%) = T/C × 100; T = mean survival time of the drug treated mice; C = mean survival time of the control mice.

O bond length is 2.02 Å, which is comparable with those found in other Pt(IV) carboxylate complexes.[21] Comparison of the bond distances between the C=O double bonds and the C-O single bonds indicates no significant delocalization of the C=O bonds.[21] Figure 2 gives a view of the molecular packing in the unit cell. Hydrogen bonding between the neighboring molecules in a crystal is common.[18-21] The two independent (apcpa)$PtCl_2(OCOC_2H_5)_2$ molecules depicted in Figure 2 show a dimeric interaction through the intermolecular N-HO hydrogen bonding interactions (N···O distance 2.907 Å).

Antitumor Activity. The present Pt(IV) complexes were subjected to *in vitro* and *in vivo* assay against murine leukemia L1210 cell line and the results are listed in Table 3. It is surprising that all the title platinum(IV) complexes exhibit significantly high cytotoxicity comparable to that of their parent platinum(II) complexes. However, these platinum(IV) complexes do not show significant oral anticancer activity regardless of variation of their axial ligands. It is generally accepted that Pt(IV) complexes are inert in ligand substitution reactions and therefore, must be reduced to Pt(II) species before binding to DNA. If *in vivo* reduction rate to platinum(II) is the only important factor in the mechanism of action of the Pt(IV) compounds, the trans-dicarboxylate analogues should be more active than their *trans*-dihydroxoplatinum(IV) complexes, since the carboxylate complexes are known to have the greatest destabilization effect on Pt(IV).[20] However, as is seen in the table, there is no significant difference in the oral antitumor activity, and therefore, it is presumed that these platinum(IV) complexes are not efficiently absorbed in the gastrointestinal tract regardless of the structures of their axial ligands.

In conclusion, a series of the platinum(IV) complexes involving asymmetric diamine ligands were synthesized and characterized. The crystal structure of (apcpa)$PtCl_2(COOC_2H_5)_2$ exhibits that platinum atom achieves a typical octahedral arrangement with two nitrogen atoms in *cis* positions and two propionate groups in *trans* position. The spectroscopic data disclose that these platinum(IV) complexes are stable and their molecular structures are retained in aqueous solution. These platinum(IV) complexes are highly cytotoxic *in vitro* but do not show significant oral anticancer activity.

Supporting Information Available. Table for details of x-ray data collection parameters, atomic coordinates, anisotropic thermal parameters, bond length and angles, hydrogen atom parameters, and torsion angle for **6**. Ordering information is given upon your request to the correspondence author.

References

1. Bellon, S. F.; Coleman, J. H.; Lippard, S. J. *Biochemistry* **1991**, *30*, 8026.
2. Bitha, P.; Morton, G. O.; Dunne, T. S.; Deloss Santos, E. F.; Lin, Y.-i.; Boone, S. R.; Haltiwanger, R. C. C.; Pierpont, C. G. *Inorg. Chem.* **1990**, *29*, 645.
3. Clare, M. J.; Hoeschele, J. D. *Bioinorg. Chem.* **1973**, *2*, 187.
4. Afeharian, A.; Butour, J. L.; Castan, P.; Wimmer, S.; Lons, M. *Biol. Proc. Int. Symp.* 1990; p 514.
5. Urban, F.; John, D. R.; Reter, J. S. *Inorg. Chem.* **1993**, *32*, 1333.
6. Veer, J. L. v.d.; Peter, A. R.; Reedjik, J. *J. Inorg. Biochem.* **1986**, *26*, 137.
7. Elmroth, S. C.; Lippard, S. J. *Inorg. Chem.* **1995**, *34*, 5234.
8. Arpalahti, J.; Klika, K. D.; Sillanpaa, R.; Kivekas, R. *J. Chem. Soc., Dalton Trans.* **1998**, 1397.
9. Giandomenico, C. M.; Abrams, M. J.; Murrer, B. A.; Vollen, J. F.; Rheinheimer, M. I.; Wyer, S. B.; Bossard, G. E.; Higgins, J. D. *Inorg. Chem.* **1995**, *34*, 1015.
10. Khokear, A. R.; Deng, Y. J.; Kido, Y. C.; Siddik, Z. H. *J. Inorg. Biochem.* **1993**, *50*, 791.
11. Clare, M. J.; Hydes, P. C.; Hepburn, D. R.; Malerbi, B. W. In *Cisplartin: Current Status and New Developments*, Prrestako, A. W., Crooke, S. T., Carter, S. K. Eds.; Academic Press, Inc.: N.Y., 1980.
12. Mong, S.; Eubanks, C. H.; Prestakyo, A. W.; Crooke, S. T. *Cancer Res.* **1980**, *40*, 3318.
13. Blatter, E. E.; Vollano, F.; Krishnan, B. S.; Dabrowiak, J. C. *Biochemistry* **1984**, *23*, 4817.
14. (a) Lee, E. J.; Jun, M. J.; Sohn, Y. S. *Bull. Korean Chem. Soc.* **1999** submitted. (b) Bodanszky, M.; Bodanszky, A. In *Reactivity and Structure Concepts in Organic Chemistry 21: The Practice of Peptide Synthesis*; Springer-Verlag: Berlin, Heidelberg, New York, 1984; p 284.
15. Bradon, R. J.; Darbrowiak, J. C. *J. Med. Chem.* **1984**, *27*, 861.
16. Lee, S. S.; Jun, M. J.; Kim, K. M.; Jung, O. S.; Sohn, Y. S. *Polyhedron* **1994**, *13*, 1397.
17. Sheldrick, G. M. *SHELX-97: Program for Crystal Structure Determination*; University of Cambridge: Cambridge, U.K., 1997.
18. Jung, C. S.; Lee, S. S.; Jung, O. S.; Sohn, Y. S. *Polyhedron* **1996**, *15*, 1677.
19. Lee, E. J.; Jun, M. J.; Lee, S. S.; Sohn, Y. S. *Polyhedron* **1997**, *16*, 2421.
20. Talman, E. J.; Brunig, W.; Reedijk, J.; Spek, A. L.; Veldmen, N. *Inorg. Chem.* **1997**, *36*, 854.
21. Khokear, A. R.; Deng, Y. J. *J. Coord. Chem.* **1992**, *25*, 349.
22. Nakamoto, K. *Infrared and Raman Spectra of Inorganic and Coordination Compounds*, 5th ed.; Wiley Inter-Science: 1997; Part B, p 59.