Synthesis, Structure, and Antitumor Activity of Novel Platinum(II) Complexes Involving Asymmetric Chiral Diamines as Carrier Ligands

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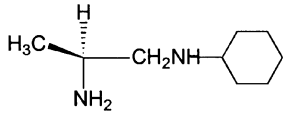
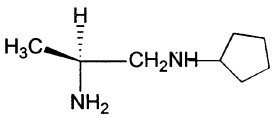
New platinum(II) complexes with asymmetrically substituted chiral diamine ligands A_2PtX_2, (A_2 = $NH_2CH(CH_3)CH_2NH(c\text{-}C_5H_9)$ (apcpa), $NH_2CH(CH_3)CH_2NH(c\text{-}C_6H_{11})$ (apcha); X_2 = 2Cl, isopropylidenmalonate (IPM), 1,1'-cyclobutandicarboxylate (CBDCA)) have been synthesized and characterized by means of elemental analyses, infrared and NMR spectroscopies, and X-ray crystallography. The crystal structures of (S-apcha)Pt[CBDCA] · $3H_2O$ (orthorhombic, $P2_12_12$(No. 18), a = 6.926(3), b = 15.243(3), c = 19.319(4) Å, V = 2039.5(10) Å^3, Z = 4, R = 0.072) and (S-apcha)Pt[IPM] · $2.5H_2O$ (monoclinic, $P2/c$(No. 13), a = 9.882(1), b = 18.502(1), c = 22.056(1) Å, V = 4032.8(5) Å^3, Z = 8, R=0.093) exhibit that the platinum atoms achieve a typical square planar arrangement with two nitrogen atoms in *cis* position and with the chiral center retained. The spectroscopic data disclose that these platinum complexes are stable and their molecular structures are retained in aqueous solution. Among these platinum complexes, the asymmetric diamine-Pt(II) complexes with chloride leaving group exhibit high *in vivo* activity comparable to cisplatin against leukemia L1210 cell line.

Introduction

According to the conventional structure-activity relationships, for the platinum anticancer drugs[1-7] the carrier amine ligand is known to play an important role not only in the determination of antitumor activity but also in overcoming the cross-resistance of the platinum complexes. Recently, the platinum complexes involving two different amines in *cis*-positions were reported, and the results of their bioassay indicate that these new drugs are more active against some tumors but less toxic than the parent cisplatin. For example, *cis,trans,cis*-ammine(cyclohexylamine)dichlorodiacetatoplatinum(IV) (JM216) is one of such platinum complexes, which is in clinical trials.[8-10] However, to our knowledge, no platinum complexes with asymmetric chelating diamines have been reported. Therefore, we have prepared several platinum(II) complexes with asymmetric chelating diamine involving a chiral center synthesized by a peptide bond formation of alanine isomers, and examined the effects of chelation and chirality of the amine ligands on the antitumor activity.



(S)-apcha



(S)-apcpa

Here we report synthesis and characterization of a series of new platinum(II) complexes with asymmetric chiral diamines along with antitumor activity.

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Experimental Section

Materials and Instrumentation. Potassium tetrachloroplatinate(II) from Kojima, and S-, R- and R,S-alanine (ala), cyclohexylamine (cha), cyclopenthylamine (cpa), benzylchloroformate (cbzCl), N,N'-di-cyclohexylcarbodiimide (DCC), diethylisopropylidenemalonate (IPM) and 1,1'-cyclobutandicarboxylic acid (CBDCA) from Aldrich were used as received. Diethylisopropylidenemalonate (IPM) and 1,1'-cyclobutandicarboxylic acid (CBDCA) were converted to barium salt by the literature method.[11,12] *cis*-Diaminediiodoplatinum(II) was prepared also by the known method.[11,12]

Elemental analyses were performed by the Korea Basic Science Institute Seoul Branch. ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker 250MHz/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 Amine Ligands.

N-(3R)- and N-((3S)-aminopropyl)cyclopentylamine (R- and S-apcpa): N-cbz-(S)-alanine and N-cbz-(S)-ala-cpa-amide were prepared by a modification of the method described by Bodanszky *et al.*[13] N-cbz-(S)-alanine (6.7 g, 30 mmol), cyclo- pentylamine (2.6 g, 30 mmol) and N,N'-dicyclohexylcarbodiimide (6.2 g, 30 mmol) were mixed in purified methylene chloride (20 mL) and the reaction mixture was stirred for 5 h at room temperature. Hydrogenolysis of the cbz group was followed in methanol solution.

After (S)-ala-cpa-amide (3.1 g, 20 mmol) was reduced by $LiAlH_4$ in sodium-dried THF (30 mL), the crude product was distilled at reduced pressure to give a colorless oily product (S-apcpa). Yield 60%. IR ($CHCl_3$, cm^{-1}): ν, 3290, 3078, 2954, 2868, 1645, 1570, 1451, 1368, 1112, 880, 832.

^{1}H NMR ($CDCl_3$, ppm): 0.99 (d, 3H, J = 6.3 Hz), 1.0-1.3 (m, 5H), 1.4-1.9 (m, 5H), 2.2-2.3 (m, 1H), 2.51 (d-d, 1H, J_1 = 11.5 Hz, J_2 = 4.3 Hz), 2.8-3.1 (m, 1H); ^{13}C NMR ($CDCl_3$, ppm): 60, 57, 47, 34, 33, 24, 23, 22. R-apcpa was prepared using the same procedure used for S-apcpa. Yield 50%. The NMR and IR spectra of this compound were identical to those of S-apcpa.

N-(3R,S)- and N-((3S)-aminopropyl)cyclohexylamine (R,S- and S-apcha): R,S- and S-apcha were prepared by the same procedure used for the apcpa ligands using N-cbz-(R,S)-alanine (6.7 g, 30 mmol) and N-cbz-(S)-alanine[13] (6.7 g, 30 mmol), respectively.

S-apcha. Yield 65%. IR (KBr, cm^{-1}): ν, 3281, 3081, 2928, 2854, 1648, 1570, 1451, 1370, 1116, 893. ^{1}H NMR ($CDCl_3$, ppm): 1.03 (d, 3H, J = 6.3 Hz), 0.96-1.23 (m, 5H), 1.41-1.70 (m, 5H), 1.81-1.86 (br. d, 2H), 2.30-2.37 (m, 2H), 2.63 (d-d, 1H, J_1 = 11.6 Hz, J = 4.2 Hz), 2.88-2.90 (m, 1H); ^{13}C NMR ($CDCl_3$, ppm): 57, 55 47, 34, 33, 26, 25, 22. R,S-apcha. Yield 55%. The NMR and IR spectra of R,S-apcha were identical to those of the S-apcha ligand.

Synthesis of A_2PtCl_2 (A_2 = R- and S-apcpa, R,S- and S-apcha). To a suspension of *cis*-A_2PtI_2 (3.0 mmol) in water (50 mL) was added silver nitrate (0.97 g, 5.7 mmol) in water (50 mL), and the reaction mixture was stirred for 6 h. After silver iodide formed was filtered off, the filtrate was condensed to 10 mL and potassium chloride (2.2 g, 30 mmol) in water (10 mL) was dropped into the condensed filtrate, which gave rise to precipitation of the dichloride compound. The product was filtered, washed with ethanol and diethyl ether, and then dried *in vacuo* at room temperature.

(R-apcpa)PtCl$_2$ (1): Yield 48%. Found (Calc. for $C_8H_{18}N_2PtCl_2$): C, 23.3 (23.5); H, 4.0 (4.4); N, 6.7 (6.9). IR (KBr, cm^{-1}): ν (N-H), 3230, 3190, 3110; ν (C-H), 2962, 2865.

(S-apcpa)PtCl$_2$ (2): Yield 48%. Found (Calc. for $C_8H_{18}N_2PtCl_2$): C, 23.6 (23.5); H, 4.2 (4.4); N, 7.0 (6.9). IR (KBr, cm^{-1}): ν (N-H), 3230, 3171, 3124; ν (C-H), 2942, 2855.

(R,S-apcha)PtCl$_2$ (3): Yield 50% Found (Calc. for $C_9H_{20}N_2PtCl_2$): C, 25.3 (25.6); H, 4.7 (4.8); N, 6.9 (6.6). IR (KBr, cm^{-1}): ν (N-H), 3234, 3170, 3133; ν (C-H), 2930, 2857.

(S-apcha)PtCl$_2$ (4): Yield 58%. Found (Calc. for $C_9H_{20}N_2PtCl_2$): C, 25.5 (25.6); H, 4.5 (4.8); N, 6.7 (6.6). IR (KBr, cm^{-1}): ν (N-H), 3234, 3171, 3137; ν (C-H), 2933, 2857.

Synthesis of $A_2Pt[CBDCA]$ (A_2 = S-apcpa, S-apcha). To a suspension of *cis*-A_2PtI_2 (3.0 mmol) in water (50 mL) was added silver sulfate (0.87 g, 2.8 mmol) in water (100 mL), and the reaction mixture was stirred for 6 h. After the silver iodide formed was filtered off, an equimolar solution of Ba[CBDCA] (0.78 g, 2.8 mmol) in water (50 mL) was dropped into the filtrate, and the reaction mixture was stirred further for 3 h. After barium sulfate was filtered off, the filtrate was condensed to 5 mL, to which excess acetone was added to precipitate the solid product. The resultant crude product was recrystallized from water to obtain crystals suitable for X-ray crystallography.

(S-apcpa)Pt[CBDCA] · H$_2$O (5): Yield 80%. Found (Calc. for $C_{14}H_{24}N_2O_4Pt \cdot H_2O$): C, 33.5 (33.8); H, 5.2 (5.3); N, 5.3 (5.6). IR (KBr cm^{-1}): ν (N-H), 3230, 3091; ν (C-H), 2928, 2855; ν_a (C=O), 1642; ν_s (C=O), 1354. ^{1}H NMR (D_2O, ppm): 1.0-1.1 (b, 1H), 1.25 (t, 3H, J = 7.8 Hz), 1.21-1.40 (m, 2H), 1.45-1.56 (m, 3H), 1.71-1.79 (m, 4H), 2.32-2.45 (m, 2H), 2.44-2.49 (br, d, 1H), 2.72-2.89 (m, 5H); ^{13}C NMR (D_2O, ppm): 178, 60, 57, 47, 34, 33, 24, 23, 22.

(S-apcha)Pt[CBDCA] · 3H$_2$O (6): Yield 75%. Found (Calc. for $C_{15}H_{26}N_2O_4Pt \cdot 3H_2O$) C, 32.6 (32.9); H, 5.9 (5.9); N, 5.3 (5.1). IR (KBr, cm^{-1}): ν (N-H), 3230, 3126; ν (C-H), 2932, 2850 ν_a (C=O), 1649; ν_s (C=O), 1356. ^{1}H NMR (D_2O, ppm): 1.02-1.24 (m, 1H), 1.30 (t, 3H, J = 7.6 Hz), 1.30-1.42 (m, 2H), 1.46-1.59 (m, 4H), 1.72-1.84 (m, 5H), 2.24-2.37 (m, 2H), 2.47-2.51 (d-d, 1H), 2.74-2.87 (m, 6H); ^{13}C NMR (D_2O, ppm): 178, 57, 55, 47, 34, 33, 26, 25, 22.

Synthesis of $A_2Pt[IPM]$ (A_2 = S-apcpa, S-apcha). *cis*-A_2PtI_2 (3.0 mmol) was treated with Ba[IPM] · 2H$_2$O (0.88 g, 2.8 mmol) in the same procedure as for **5**. The crude products were recrystallized from water to obtain crystals suitable for X-ray crystallography.

(S-apcpa)Pt[IPM] · H$_2$O (7): Yield 78%. Found (Calc. for $C_{14}H_{24}N_2O_4Pt \cdot H_2O$): C, 33.8 (34.0); H, 5.7 (5.3); N, 5.6 (5.6). IR (KBr, cm^{-1}): ν (N-H), 3230, 3171; ν (C-H), 2942, 2855; ν_a (C=O), 1640; ν_s (C=O), 1344. ^{1}H NMR (D_2O, ppm): 1.23 (t, 3H, J = 6.8 Hz), 1.4-1.7 (m, 6H), 1.88 (d, 6H, J = 5.8 Hz), 1.8-1.9 (m, 2H) 2.3-2.6 (m, 2H), 2.7-2.8 (m, 1H), 2.9-3.08 (b, 1H); ^{13}C NMR (D_2O, ppm): 174, 123, 60, 57, 47, 33, 24, 23, 22.

(S-apcha)Pt[IPM] · 2.5H$_2$O (8): Yield 68%. Found (Calc. for $C_{15}H_{26}N_2O_4Pt \cdot 2.5H_2O$): C, 33.1 (33.5); H, 5.6 (5.8); N, 5.3 (5.2). IR (KBr cm^{-1}): ν (N-H), 3246, 3108; ν (C-H), 2935, 2858 ν_a (C=O), 1652; ν_s (C=O), 1365. ^{1}H NMR (D_2O, ppm): 1.02-1.16 (m, 1H), 1.22 (t, 3H, J = 7.8 Hz), 1.21-1.24 (m, 2H), 1.45-1.56 (m, 4H), 1.87 (s, 6H), 1.8-1.9 (m, 3H), 2.29-2.45 (m, 2H), 2.49-2.59 (m, 1H), 2.89 (m, 1H); ^{13}C NMR (D_2O ppm): 174, 125, 57, 55, 47, 34, 33, 26, 25, 22.

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. All calculations were performed using SDP running on VAX/VMS V5.3 and SHELXL-97 programs running on PC.[14] 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

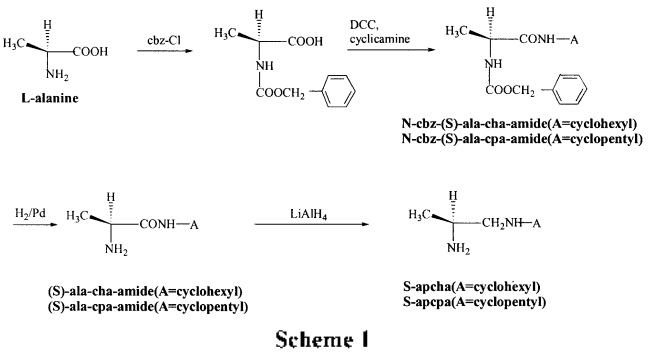
1×10^6 cells/mL and distributed to 24 well tissue culture plates (0.5 mL/well). Test complexes were serially diluted and added to the wells (0.5 mL/well). Following 48 h incubation in 5% CO_2 atmosphere at 37 °C, cell counts were determined with a Coulter model ZM cell counter. Cell growth in the presence 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 (10^6) were inoculated i.p. in BDF mice(6-8 week old, 20-25 g; 8 mice per group), and 24 h later the complexes were administered i.p. on days 1, 5, 9. Mortality was recorded and the mean survival time was calculated for each group.

Results and Discussion

Synthesis and Properties. Asymmetric diamine ligands with a chiral center were prepared by using alanine and cyclic amines. The synthetic route to the apcha and apcpa ligands are shown in Scheme 1. (Cbz)-alanine and (3S)-(cbz)-ala-cyclohexyl- and (3S)-(cbz)-ala-cyclopentyl- amides were prepared by modification of the method described by Bodanszky *et al.*,[15] and finally hydrogenolysis of the cbz group and reduction of the amide group were performed to obtain the apcha and apcpa ligands. These ligands were characterized by IR and NMR spectroscopic methods. The resonances of the methyl and CH protons of apcha appear at 1.03 ppm and 2.34 ppm as a doublet (J = 6.3 Hz) and a multiplet, respectively, which are shifted up-field relative to N-cbz-(L)-alanine (CH_3 1.40 ppm; CH 4.32 ppm). In addition, a new resonance of the CH_2 protons in the S-apcha ligand appears at 2.63 ppm as a doublet of doublet (J_1 = 11.6 Hz, J_2 = 4.2 Hz), and the carbonyl ^{13}C resonance disappears in the ^{13}C NMR spectrum, which is also seen in its IR spectrum.

For S-apcpa, the resonances of the methyl and CH protons appear at 0.99 ppm and 2.26 ppm as a doublet (3H, J = 6.3 Hz) and a multiplet (1H), respectively, which are shifted up-field relative to L-alanine (CH$_3$, 1.49 ppm, d, J = 6.3 Hz; CH 3.79 ppm, m). A new resonance of the CH_2 protons in the S-apcha ligand appears at 2.51 ppm as a doublet of doublet (J_1 = 11.5 Hz, J_2 = 4.3 Hz).

The isomeric R,S-apcha and R-apcpa ligands were prepared by the same procedure from (D)-alanine and (D,L)-alanine. The IR and NMR spectra of these ligands are identical to those of their S-forms.



Scheme 1

The Pt(II) complexes were synthesized via the $[PtI_4]^{2-}$ intermediate by the literature method.[10-12] A_2PtCl_2 could be routinely obtained as a precipitate simply by mixing the aqueous solutions of KCl and water soluble diamineplatinum(II) nitrate resultant from the reaction of the corresponding A_2PtI_2 with silver nitrate. These dichloroplatinum(II) complexes may be prepared by direct reaction of K_2PtCl_4 and diamine ligands in aqueous solution, but both purity and yield of the product were lower. The yellow precipitates were recrystallized from DMF to obtain pure solids (> 40% yield). For the preparation of platinum(II) complexes with CBDCA and IPM anionic leaving groups, barium salts of CBDCA and IPM ligands were reacted with diamine platinum(II) sulfate, resulting in precipitation of barium sulfate. All the platinum(II) complexes of dicarboxylate anionic ligands were obtained as fairly stable yellow or pale yellow solid products and could be recrystallized using a solvent pair of water and acetone.

All these platinum complexes were characterized by chemical analyses and spectroscopic data along with X-ray crystal structures for two representative complexes. All the complexes are fairly air-stable up to 165-180 °C. The complexes are moderately soluble in water and fairly stable in water and methanol. All the present dicarboxylate complexes show that their $\Delta\nu$ values are larger than 200 cm^{-1} suggesting that both carboxylate groups of the IPM and CBDCA ligands act as monodentate ligands.[19-21]

For the IPM complex, the resonance of the methyl protons

Table 1. Crystal data and structure refinement for complexes **6** and **8**

Complex	6	8
Formula	$C_{15}H_{26}N_2O_4Pt \cdot 3H_2O$	$C_{15}H_{29}N_2O_4Pt \cdot 2.5H_2O$
fw	547.51	493.46
Crystal system	orthorhombic	monoclinic
space group	$P2_12_12$ (No. 18)	P2/c(No. 13)
a(Å)	6.926(3)	9.882(1)
b(Å)	15.243(3)	18.502(1)
c(Å)	19.319(4)	22.056(1)
V(Å^3)	2039.5(10)	4032.8(5)
Z	4	8
d_{cal}(g/cm^3)	1.703	1.731
F(000)	982	2016
Crystal size(mm)	$0.12 \times 0.15 \times 0.3$	$0.12 \times 0.15 \times 0.3$
Scan method	$\omega/2\theta$	$\omega/2\theta$
2θ range	1.70-24.99 deg.	2.06-24.97 deg.
Data collected	h, k, l	$h, k, \pm l$
No. total observation	1588	7262
No. unique data > 2σ(I)	1588	6824
No. parameters refined	226	424
R	0.072	0.093
wR	0.073	0.118
GOF on F^2	1.119	1.108

of the IPM ligand appears at 1.87 ppm as a singlet in D_2O, which is shifted down field by 0.11 ppm from that of Ba(IPM) (1.76 ppm), and for the CBDCA complex such reasonance is also shifted downfield by 0.5 ppm to 2.75 ppm. Such results indicate that both carboxylate groups are symmetrically coordinated to the platinum atom in aqueous solution. The ^{13}C NMR spectra show the ^{13}C resonance of the carboxylate groups at 174 and 178 ppm for the IPM and CBDCA complexes, respectively, which also indicates that both carboxylates of the anionic ligands are symmetrically coordinated to the platinum atom. Therefore, the molecular structure of the Pt(II) complexes seems to be retained in aqueous solution at room temperature.

Crystal Structures of 6 and 8. The ORTEP drawing and labelling scheme for **6** are shown in Figure 1, and selected bond distances and bond angles are listed in Table 2. The complex is a discrete molecule with no close intermolecular contacts. The local geometry around the platinum atom is slightly distorted square plane: the distances of Pt-N(1) and Pt-O(1) are 2.00(2) and 2.04(2) Å, respectively,

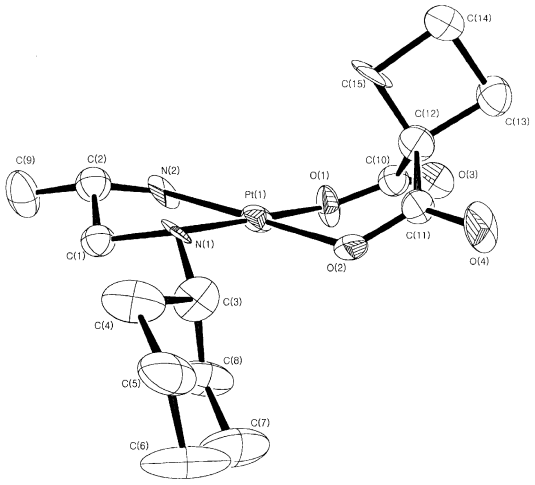


Figure 1. ORTEP drawing of (S-apcha)Pt(CBDCA) · $3H_2O$ along with the atomic labelling scheme. Hydrogen atoms and solvated molecules were omitted for clarity.

Table 2. Selected bond lengths (Å) and angles [°] for **6**

	$C_{15}H_{26}N_2O_4Pt3H_2O$ (**6**)		
Pt(1)-N(1)	2.00(2)	O(3)-C(10)	1.21(3)
Pt(1)-N(2)	2.02(3)	O(4)-C(11)	1.25(4)
Pt(1)-O(1)	2.04(2)	N(1)-C(3)	1.48(4)
Pt(1)-O(2)	2.03(2)	N(1)-C(1)	1.49(3)
O(1)-C(10)	1.24(3)	N(2)-C(2)	1.44(4)
O(2)-C(11)	1.30(3)	C(3)-C(8)	1.48(5)
		C(3)-C(4)	1.50(4)
N(1)-Pt(1)-N(2)	83.5(11)	O(3)-C(10)-O(1)	122(3)
N(1)-Pt(1)-O(1)	179.2(8)	O(1)-C(10)-C(12)	118(2)
N(2)-Pt(1)-O(1)	95.7(10)	O(2)-C(11)-C(12)	120(3)
N(1)-Pt(1)-O(2)	92.9(9)	C(11)-C(12)-C(10)	110(3)
N(2)-Pt(1)-O(2)	176.4(11)	N(2)-C(2)-C(9)	113(3)
O(1)-Pt(1)-O(2)	87.9(8)	N(1)-C(3)-C(4)	113(3)

and the bond angles of N(1)-Pt-N(2), N(2)-Pt-O(1), N(1)-Pt-O(2), and O(2)-Pt-O(1) are 83.5(11)°, 95.7(10)°, 92.9(9)° and 87.9(8)°, respectively, which are consistent with those of the similar Pt(II) complexes.[15-17] The amine ligand is bonded to the platinum atom in a bidentate fashion resulting in chelation to provide a suitable bite angle. The angles of N(2)-Pt-O(1) [95.7(10)°] and N(1)-Pt-O(2) [92.9 (9)°] are splayed out with the concomitant closing of the bite angle of the bidentate amine ligand. The bite angle of N(1)-Pt-N(2) [83.5(11)°] is in partially responsible for the slight distortion form square plane. The NH_2 moiety of the amine has an equatorial orientation toward the ring and the chirality of the amine ligand is retained. The C(3)-N(1) distance [1.48(4) Å] of cyclohexylamine group in the present complex is nearly in accord with the value of 1.470(18) Å in JM216.[18] The CBDCA ligand chelates to the platinum atom via two carboxylate oxygen atoms whose bite angle is 87.9(8)°. The ring conformation of the CBDCA ligand adopts a boat form. This study further confirms the earlier suggestion[19] that the malonate ligand prefers to adopt the boat conformation rather than any other conformational varieties. The dihedral angle between the O(1)-Pt-O(2) plane and the plane of O(1), O(2), C(1), and C(2) is 33.62, which is similar to those of other platinum(II) analogues.[15-17]

The ORTEP drawing of **8** in depicted along with its atomic numbering scheme in Figure 2, and the selected bond distances and angles are listed in Table 3. The local geometry around the platinum atom also approximates to a square plane with each nitrogen atom in *cis* positions and the cyclic amine rings disordered. The bonding mode of the carboxylate groups is similar to that in **6**.

For (apcha)Pt(IPM), there are two independent molecules in the asymmetric unit and the features of the two molecules are within error of being identical. Even though the IPM ligand is an α,β-unsaturated carboxylic acid, the bending prevents delocalization of its π electrons. As a proof of localization, the bond length of the double bond C(12)-C(13) (1.32(2) Å) is not significantly different from the corresponding bonding length (1.34 Å) of the normal ethylene group. Furthermore, the mean bond length (1.48 Å) of

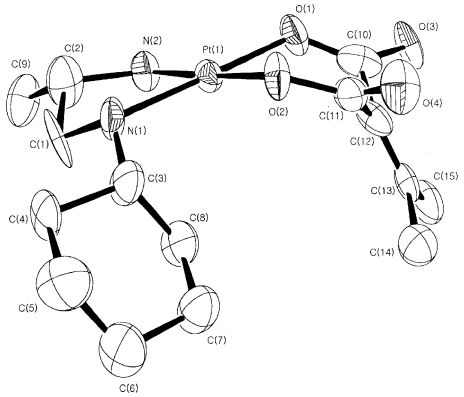


Figure 2. ORTEP drawing of (S-apcha)Pt(IPM) · $2.5H_2O$ along with the atomic labelling scheme. Hydrogen atoms were omitted for clarity.

Table 3. Selected bond lengths (Å) and angles (°) for **8**

	$C_{15}H_{26}N_2O_4Pt \cdot 2.5H_2O$ (**8**)		
Pt(1)-O(1)	2.000(11)	O(3)-C(10)	1.27(2)
Pt(1)-N(2)	2.023(13)	O(4)-C(11)	1.25(2)
Pt(1)-O(2)	2.040(11)	C(10)-C(12)	1.48(3)
Pt(1)-N(1)	2.035(15)	C(12)-C(13)	1.32(2)
O(1)-C(10)	1.28(2)	C(12)-C(11)	1.47(2)
O(2)-C(11)	1.287(19)	C(13)-C(14)	1.50(3)
		C(13)-C(15)	1.54(2)
O(2)-Pt(1)-N(2)	91.7(9)	N(2)-C(2)-C(1)	117(3)
O(2)-Pt(1)-O(1)	89.1(8)	N(1)-C(1)-C(2)	117(4)
N(2)-Pt(1)-O(1)	177.8(9)	C(10)-O(1)-Pt(1)	119.3(12)
O(2)-Pt(1)-N(1)	174.7(9)	C(11)-O(2)-Pt(1)	118.7(11)
N(2)-Pt(1)-N(1)	84.2(9)	C(3)-N(1)-C(1)	114.0(16)
O(1)-Pt(1)-N(1)	94.9(7)	C(3)-N(1)-Pt(1)	114.3(10)
O(3)-C(10)-O(1)	119(3)	C(1)-N(1)-Pt(1)	108.3(11)
O(1)-C(10)-C(12)	119(3)	C(2)-N(2)-Pt(1)	107.4(10)
C(10)-C(12)-C(11)	112(3)	C(1)-C(2)-N(2)	109.7(15)
		C(8)-C(3)-C(4)	113.3(17)

C(12)-C(11) and C(12)-C(10) approaches that of a typical single bond. The two independent (apcha)Pt[IPM] molecules depicted in Figure 3 show a weak dimeric interaction through the intermolecular hydrogen bonding (NO distance 2.84-2.91 Å). Even though the R values are a little high, the structures of the **6** and **8** seem to be reasonable since the results of elemental analysis and spectroscopic data are consistent with their structures.

Antitumor Activity. The present Pt(II) complexes were subjected to *in vitro* and *in vivo* assay against the murine leukemia L1210 cell line and the results are listed in Table 4. Among the compounds the asymmetric diamine-Pt(II) complexes with chloride leaving group exhibit high *in vivo* activity comparable to cisplatin, but the IPM and CBDCA complexes do not show significant activity. Thus it can be seen from the table that the antitumor activity of the present platinum(II) complexes largely depends on the type of the leaving group rather than the structures of the amine ligand, although no clear structure-activity relationship can be established. It is not easy to explain why the present Pt(II) complexes with asymmetric chiral diamine ligands show remarkable differences in *in vivo* activity depending on their leaving groups, because cisplatin and carboplatin with the same carrier ligand, (NH_3) in *cis* positions show the similar *in vivo* activity at optimal doses, even though their leaving groups are different. The results of this study seem to imply that the pharmacokinetic behavior depending on the leaving group may be more important for the *in vivo* activity than the structural factor of the carrier amine ligand for certain complexes.

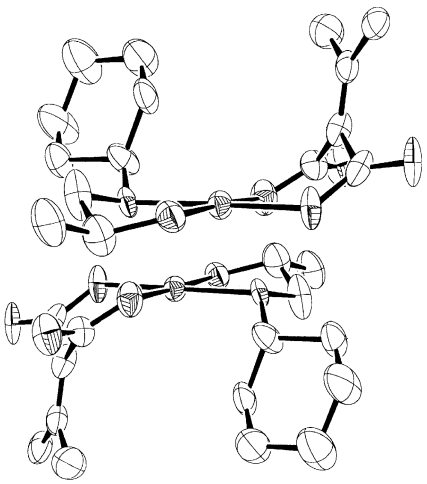


Figure 3. View showing the weak paring of (S-apcha)Pt(IPM) · $2.5H_2O$ molecules within the unit cell. Hydrogen atoms were omitted for clarity.

Table 4. Antitumor activity of *cis*-A_2PtX_2 against the leukemia L 1210 cell line

compexes	A_2	X_2	*in vitro* ED_{50} (μg/mL)	*in vivo* Dose (mg/kg)	*in vivo* T/C[a] (%)
1	R-apcpa	Cl_2	2.0	15	186.5
2	S-apcpa	Cl_2	1.7	15	159.7
3	R,S-apcha	Cl_2	25.9	30	179.0
4	S-apcha	Cl_2	13.0	40	146.3
5	S-apcpa	CBDCA	10.1	80	108.3
6	S-apcha	CBDCA	23.3	80	100.0
7	S-apcpa	IPM	18.5	80	127.9
8	S-apcha	IPM	34.3	80	100.0
Cisplatin	$2NH_3$	Cl_2	0.3	4	164
Carboplatin	$2NH_3$	CBDCA	3.8	40	168

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

In conclusion, a series of asymmetric diamine ligands with a chiral center were synthesized from alanine isomer and successfully chelated to platinum(II). The crystal structures of (S-apcha)Pt[CBDCA] · $3H_2O$ and (S-apcha)Pt[IPM] · $2.5H_2O$ exhibit that each platinum atom achieves a typical square planar arrangement with two nitrogen atoms in *cis* positions, and with the chiral center retained. The spectroscopic data disclose that these platinum complexes are stable and their molecular structures are retained in aqueous solution. Among these platinum complexes, the asymmetric diamine-Pt(II) complexes with chloride leaving group exhibit high *in vivo* anticancer activity against leukemia L1210 cell line whereas the complexes with IPM or CBDCA as a leaving group show no activity.

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Supporting Information Available. Table giving details of X-ray data collection parameters, atomic coordinates, anisotropic thermal parameters, bond length and angles, hydrogen atom parameters, and least-square planes for **6** and **8**. Ordering information is given upon your request to the correspondence author.

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