Notes

Structure of *cis*-3-Aminohexahydroazepine(1,1-cyclobutanedicaboxylato)platinum(II)

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The antitumor platinum (II) complexes are generally represented by the general formula PtL_2X_2, where L_2 is a bidentate or two monodentate amine ligands, and X_2 is a bidentate or two monodentate anionic groups. *cis*-Diamminedichloroplatinum(II) (cisplatin) of these complexes has been clinically used as an effective antineoplastic agent for malignant tumors such as testicular, ovarian, and bladder cancers[1-5]. However, its usefulness is limited due to its severe toxicities and development of resistance in tumor cells[6-10]. Accordingly, a great number of analogues have been synthesized and screened for more effective anticancer agents with less nephrotoxicity[11-15]. The title complex, in particular, was patented as a low toxic antitumor agent a few years ago[16]. Thus, in order to explore the characteristic properties of the complex, this paper reports the X-ray crystal structure of the platinum complex along with physicochemical properties.

Chemical analysis was carried out by the Advanced Analysis Center at KIST. The IR spectrum in the 4000-400 cm^{-1} region was measured on KBr pellet with an Analect fx 6160 FT-IR spectrometer. ^1H- and ^{13}C-NMR spectra were recorded on a Varian Gemini-300 NMR spectrometer relative to external Me_4Si. The electrolytic conductivity was determined by using a YSI Model 32 conductance meter.

The title complex was prepared according to literature method[16]. Recrystallization of the white solid from water gave colorless crystals suitable for X-ray crystallography. IR (KBr, cm^{-1}): ν $(COO)_{as}$, 1653, 1628; ν $(COO)_s$, 1352, ^{13}C-NMR (δ, ppm; H_2O): 181.9, 57.6, 57.0, 56.1, 52.7, 32.8, 31.6, 30.4, 26.6, 21.7, 15.3.

All the crystallographic data were obtained on an Enraf-Nonius CAD 4 automatic diffractometer with graphite-monochromated molybdenum radiation ($\lambda(K_{\alpha 1})=0.70930$ Å, $\lambda(K_{\alpha 2})=0.71359$ Å) at ambient temperature of 23± 2℃. Preliminary diffractometric investigation indicated orthorhombic system. Accurate cell dimensions were obtained from the setting angles of 25 well-centered reflections by using a least-square procedure. During the data collection, three standard reflections monitored after every 1 hour did not reveal any systematic variation in intensity. Space group of the crystal was determined uniquely from the systematic absences. The structure was solved by a conventional heavy atom method, followed by successive difference Fourier synthesis. The non-hydrogen atoms were refined anisotropically by using SHELX-76[17]. Hydrogen atoms were placed in calculated positions and refined only for the isotropic thermal factors. Crystal parameters and procedural information corresponding to data collection and structure refinement are given in Table 1.

Table 1. Crystal data, Data Collection, and Refinement of the Structure for *cis*-3-Aminohexahydroazepine(1,1-cyclobutanedicarboxylato)platinum(II)

formula	$PtN_2O_4C_{12}H_{20}$
formula weight	451.40
space group	$P2_12_12_1$
a, Å	9.664(2)
b, Å	10.323(2)
c, Å	13.174(3)
V, Å^3	1314.2(5)
Z	4
d_{calcd}, g cm^{-3}	2.281
crystal size, mm	0.23×0.32×0.36
F(000)	863.82
μ, cm^{-1}	102.65
scan method	$\omega/2\theta$
2θ range(°)	3-50
collected octants	h, k, l
no. total observations	1368
no. unique data>3σ(I)	1272
no. parameters refined	175
abs. corr. factor range	0.6929-0.9995
gof	0.9408
$R=\Sigma\|F_o-F_c\|/\Sigma\|F_o\|$	0.038
$Rw=\Sigma\|F_o-F_c\|w^{1/2}/\Sigma\|F_o\|W^{1/2}$	0.042
Max. peak in final difference Fourier map (e/Å^3)	1.10

$w=1.00/(\sigma/2(F)+0.003437F^*F)$

Crystal Structure. The molecular structure and labeling scheme are shown in Figure 1, and the final values of the refined positional parameters are presented in Table 2. Bond distances and bond angles are listed in Table 3. The complex is a discrete molecule with no close intermolecular contacts. The local geometry around the Pt atom is a slightly distorted square planar. The amine ligand is bonded to the platinum in a bidentate which is essentially *cis* position to provide a suitable bite angle. The small bite angle (N(2)-Pt-N(1), 85.1(5)°) of 3-aminohexahydroazepine is in part responsible for the slight distortion from the square planar. The oxygen and nitrogen atoms are splayed out to give O(1)-Pt-N(2) (92.7(14)°) and O(2)-Pt-N(1) (92.3(5)°) angles with the concomitant closing of the bite angle of the bidentate amine ligand. The bond lengths between platinum and donating atoms are Pt-N(1) (1.998(13) Å), Pt-N(2) (2.018(12) Å), Pt-O(1) (2.020(10) Å), and Pt-O(2) (2.039(9) Å). The overall

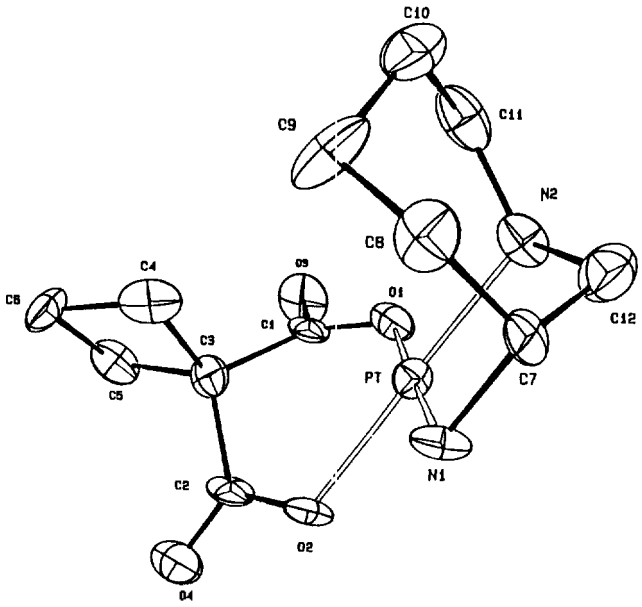

Figure 1. ORTEP drawing and labeling scheme of *cis*-3-aminohexahydroazepine(1,1-cyclobutanedicarboxylato)platinum(II).

Table 2. Positional Parameters for *cis*-3-Aminohexahydroazepine (1,1-cyclobutanedicarboxylato)platinum(II)

Atom	X/A	Y/B	Z/C
Pt	0.4604(0)	0.4431(0)	0.1882(0)
N(1)	0.3031(13)	0.3175(11)	0.1935(11)
N(2)	0.3219(11)	0.5729(12)	0.2411(10)
O(1)	0.6140(10)	0.5756(9)	0.1838(8)
O(2)	0.5936(11)	0.3055(9)	0.1356(8)
O(3)	0.7947(13)	0.6582(11)	0.1096(9)
O(4)	0.7710(13)	0.2583(11)	0.0407(8)
C(1)	0.7024(15)	0.5753(13)	0.1138(10)
C(2)	0.6884(13)	0.3379(13)	0.0706(11)
C(3)	0.6866(15)	0.4736(13)	0.0276(10)
C(4)	0.5614(13)	0.4972(14)	−0.0433(12)
C(5)	0.7800(15)	0.4968(16)	−0.0631(12)
C(6)	0.6529(19)	0.4921(16)	−0.1334(11)
C(7)	0.1679(14)	0.3862(17)	0.2206(10)
C(8)	0.0879(16)	0.4182(15)	0.1249(11)
C(9)	0.1566(20)	0.5123(19)	0.0557(12)
C(10)	0.1565(20)	0.6476(19)	0.1004(13)
C(11)	0.2831(16)	0.6749(15)	0.1680(12)
C(12)	0.2022(18)	0.4947(18)	0.2858(12)

environment of the platinum atom is similar to that of cis (diammine)(1,1-cyclobutanedicarboxylato)platinum(II)[18]. Another interesting feature of the structure is the bonding mode of the carboxylate ligand. The bond lengths of C(1)-O(3) (1.237(18) Å) and C(2)-O(4) (1.211(17) Å) are shorter than those of C(1)-O(1) (1.257(17) Å) and C(2)-O(2) (1.298(17) Å), indicating that the carboxylate ligands are simple monodentate. Finally, the molecule consists of four rings which are 4-membered (C(3), C(4), C(6), and C(5)), 5-membered(Pt, N (1), C(7), C(12), and N(2)), 6-membered (Pt, O(1), C(1), C(3),

Table 3. Bond Distances and Angles for *cis*-3-Aminohexahydrozaepine(1,1-cyclobutanedicarboxylato)platinum(II)

Pt-O(1)	2.020(10)	Pt-O(2)	2.039(9)
Pt-N(1)	1.998(13)	Pt-N(2)	2.018(12)
C(7)-N(1)	1.528(17)	C(11)-N(2)	1.476(21)
C(12)-N(2)	1.529(19)	C(2)-O(2)	1.298(17)
O(1)-C(1)	1.257(17)	O(3)-C(1)	1.237(18)
C(3)-C(1)	1.554(18)	O(4)-C(2)	1.211(17)
C(3)-C(2)	1.512(19)	C(4)-C(3)	1.548(18)
C(5)-C(3)	1.517(19)	C(6)-C(4)	1.481(21)
C(6)-C(5)	1.539(21)	C(8)-C(7)	1.515(19)
C(12)-C(7)	1.450(25)	C(9)-C(8)	1.488(21)
C(10)-C(9)	1.515(28)	C(11)-C(10)	1.540(23)
O(2)-Pt-O(1)	89.9(4)	O(1)-Pt-N(2)	92.7(4)
O(2)-Pt-N(1)	92.3(5)	O(1)-Pt-N(1)	177.8(4)
O(2)-Pt-N(2)	177.4(5)	N(2)-Pt-N(1)	85.1(5)
C(7)-N(1)-Pt	110.9(9)	C(11)-N(2)-Pt	114.7(10)
C(12)-N(2)-Pt	106.5(9)	C(1)-O(1)-Pt	121.3(9)
C(2)-O(2)-Pt	119.4(8)	C(12)-N(2)-C(11)	115.9(11)
C(3)-C(1)-O(1)	118.0(12)	O(3)-C(1)-O(1)	121.4(12)
O(4)-C(2)-O(2)	120.3(13)	C(3)-C(1)-O(3)	120.4(13)
C(3)-C(2)-O(4)	121.0(14)	C(3)-C(2)-O(2)	118.5(11)
C(4)-C(3)-C(1)	114.3(12)	C(2)-C(3)-C(1)	110.6(11)
C(5)-C(3)-C(1)	114.2(11)	C(4)-C(3)-C(2)	112.4(10)
C(5)-C(3)-C(4)	88.0(10)	C(5)-C(3)-C(2)	115.8(12)
C(6)-C(5)-C(3)	89.7(11)	C(6)-C(4)-C(3)	90.7(11)
C(8)-C(7)-N(1)	110.1(11)	C(5)-C(6)-C(4)	89.6(10)
C(12)-C(7)-C(8)	116.2(15)	C(12)-C(7)-N(1)	107.5(13)
C(11)-C(10)-C(9)	113.2(14)	C(9)-C(8)-C(7)	115.1(13)
C(7)-C(12)-N(2)	110.6(13)	C(10)-C(9)-C(8)	111.3(16)
C(10)-C(11)-N(2)	116.7(13)		

C(2), and O(2), and 7-membered(N(2), C(11), C(10), C(9), C (8), C(7), and C(12)). Each ring is essentially puckered to accommodate favorable stable conformation.

Spectroscopic and Physical Properties. The IR spectrum of the title complex is not simple, as expected, owing to its crowded anionic leaving group and amine carrier ligand. However, the difference ($\Delta\nu$) between the asymmetric and the symmetric carbonyl stretching frequencies gives an information about the bonding fashion of carboxylate ligand[19]. The $\Delta\nu$ values>200 cm^{-1} (301 cm^{-1} and 276 cm^{-1} for the present complex) indicate that the two carboxylates of the anionic ligand act as monodentate. The complexity of ^{1}H-NMR in the proton region of aliphatic hydrocarbon do not give any conclusive information for the structure of the present complex. Instead, ^{13}C-NMR can be used as a good tool for the bonding mode of carboxylate in solution[20]. Appearance of a single carboxylate ^{13}C-resonance at 181.9 ppm in water solution supports that the bonding mode of the carboxylates is remained even in solution without dissociation of the carboxylates ligand. Conductivity measurements (Figure 2) in aqueous solution indicate that the title complex is essentially nonelectrolyte in water solution at least for 1 day. Conductivity was measured also in dimethylsulfoxide solution since DMSO itself is a more favorable ligand for Pt(II) system than water. The conductances in DMSO are almost constant

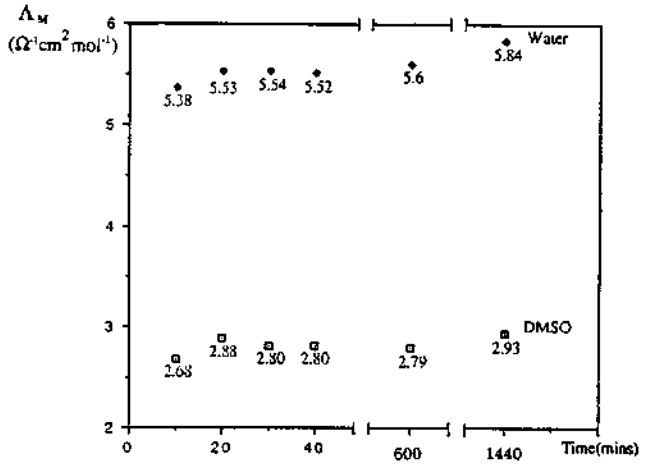

Figure 2. Molar conductance in water(◆) and dimethylsulfoxide (□) of *cis*-3-aminohexahydroazepine(1,1-cyclobutanedicarboxylato) platinum(II) at room temperature.

irrespective of time indicating the covalent nature of Pt-O bonds and the absence of separated ionic species even in DMSO solution in contrast to *cis*-$Cl_2(NH_3)_2Pt$[21]. In conclusion, the spectroscopic data together with conductance measurement are consistent with the stable molecular structure in the solid state for the title complex.

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Use of Lanthanide Metal Ions in Chiral Ligand Exchange Chromatography

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Chiral ligand exchange chromatography has been extensively used for resolving racemic α-amino acids without derivatization.[1] Transition metal ion complexes of optically pure α-amino acids have been usually applied as chiral mobile phase additives[2] or chiral stationary phases[3] after binding to solid column support such as silica gel or polymer in chiral ligand exchange chromatography. The most frequently used transition metal ion in chiral ligand exchange chromatography is Cu^{2+}. Other transition metal ions such as Zn^{2+}, Co^{2+}, Ni^{2+}, Cd^{2+} and Hg^{2+} have also been rarely adopted in chiral ligand exchange chromatography.[1] However, lanthanide metal ions have not been selected previously in chiral ligand exchange chromatography.[4] In our recent study,[5] we demonstrated that lanthanide metal ions form 1 : 1 complex with optically active L-proline. It was reported, in that study, that the heterocyclic nitrogen atom and the carboxylate of L-proline are involved in the chelate formation and the thermodynamic constants for the complexation of L-proline with lanthanide metal ions are similar to those with Cu^{2+} and Zn^{2+}. Based on these results, the possibility of the use of lanthanide metal ions in chiral ligand exchange chromatography was proposed in that paper.[5] To elucidate the proposal, we report the examples for the use of lanthanide metal ions in chiral ligand exchange chromatography.

Recently, we showed that a dynamic chiral stationary phase containing Cu^{2+} complex with (1S, 2R)-N,N-carboxymethyldodecylnorephedrine monosodium salt 1 tentatively