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Synthesis, structure, and properties of isopropylidenemalonatoplatinum(IV) complexes

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Abstract—Diamineplatinum(II) complexes of the isopropylidenemalonate(ipm) ligand $A_2Pt(OOC)_2C{=}C(CH_3)_2$ (A = NH_3 or NH_2CH_3) have been prepared and oxidized by an aqueous solution of H_2O_2 to obtain dihydroxoplatinum(IV) complexes, *cis,cis,trans*-$A_2Pt((OOC)_2C{=}C(CH_3)_2)(OH)_2$. Subsequent reaction of these dihydroxoplatinum(IV) complexes with carboxylic anhydrides in CH_2Cl_2 leads to the dicarboxylatoplatinum(IV) complexes, *cis,cis,trans*-$A_2Pt((OOC)_2C{=}C(CH_3)_2)(OCOR)_2$ (R = CH_3, CF_3, C_2H_5 and *n*-C_3H_7). One of the platinum(II) complexes $(NH_3)_2Pt(OOC)_2C{=}C(CH_3)_2$ (**1**) and its corresponding diacetatoplatinum(IV) complex, *cis,cis,trans*-$(NH_3)_2Pt((OOC)_2C{=}C(CH_3)_2)(OCOCH_3)_2$ (**5**), have been characterized by X-ray crystallograpic analysis. The average Pt—N and Pt—O bond lengths of the complex **5** are similar to those of complex **1**. In the complex **5**, however, the boat conformation of the chelated dicarboxylate ring is less bent than that of complex **1**. When an aqueous solution of the title Pt^{IV} complexes was exposed to 1 equiv. of ascorbic acid in pH 7 buffer solution at room temperature, all the Pt^{IV} complexes were reduced to the corresponding Pt^{II} complexes with variable rates. We have examined the disappearance of the Pt^{IV} complexes, in aqueous HCl solution at 37°C. At 0.01 N HCl concentration, neligible decomposition occurs over a 72 h period. © 1997 Elsevier Science Ltd

Keywords: platinum(IV) complex; isopropyliden malonato ligand.

cis-Diamminedichloroplatinum(II) (cisplatin) is the first metal complex in clinical use as a chemotherapeutic agent. Although the "cisplatin" is effective against testicular, ovarian, bladder and other cancers [1–5], it exhibits severe side effects such as nephrotoxicity and ototoxicity. [6–7]. Therefore, a great deal of efforts have been made to find a third-generation platinum antitumor agent with high activity, low toxicity and lack of cross-resistance, since carboplatin was approved for clinical use in 1989. Recently, developments of orally active antitumor platinum complexes are underway to afford advantages to enhance quality of life and to reduce cost in the treatment of cancer patients.

Platinum complexes suitable for oral administration should be lipophilic to pentrate through the gut cell membrane, stable in the gastrointestinal tract and reducible to Pt^{II} complexes *in vivo*. In order to meet such criteria, platinum(IV) compounds have been synthesized by carboxylation of hydroxide platinum(IV) complexes which were prepared by oxidation of the Pt^{II} species with hydrogen peroxide. One of them, *cis,cis,trans*-$Pt(NH_3)(C_6H_{11}NH_2)Cl_2(OCOCH_3)_2$ (JM-216) is currently in clinical trials [7–9].

We report here the synthesis of a series of new platinum(IV) compound, *cis,cis,trans*-$A_2Pt((OOC)_2C{=}C(CH_3)_2)(OOCR)_2$, *via* the oxidation and carboxylation of the corresponding platinum(II) complexes, $A_2Pt(OOC)_2C{=}C(CH_3)_2$, along with their chemical properties depending on the variable axial ligands.

EXPERIMENTAL

Instrumentation and materials

Elemental analyses were performed by the Korea Basic Science Institute Seoul Branch. ^1H and ^{13}C

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NMR spectra were recorded on a Bruker 250MH/52MM spectrometer relative to TMS as an external standard. The IR 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.

Potassium tetrachloroplatinate(II) was purchased from Kojima. Methylamine (ma), acetic anhydride, trifluoroacetic anhydride, propionic anhydride, butyric anhydride and diethyl isopropylidenemalonate were obtained from Aldrich and used without further purification. Diethyl isopropylidenemalonate was converted to barium salt by the literature method [10–11]. *cis*-Diaminediiodoplatinum(II) was prepared also by the known method [12–13].

Synthesis of $A_2Pt(OOC)_2C{=}C(CH_3)_2$ (A = NH_3, ma)

To a suspension of *cis*-A_2PtI_2 (3.0 mmol) in water (50 cm^3) was added silver sulfate (3.0 mmol) in water (100 cm^3). The reaction mixture was stirred for 6 h and the silver iodide formed was filtered off. An equimolar solution of barium isopropylidenemalonate [Ba(ipm)] dihydrate in water (50 cm^3) was dropped into the filtrate and the reaction mixture was then stirred for 3 h. After barium sulfate was filtered off, the filtrate was concentrated to 5 cm^3, to which excess acetone was added to precipitate a solid product. The crude product was recrystallized from water to obtain crystals suitable for X-ray crystallography.

$(NH_3)_2Pt(ipm)$ (**1**). Yield 81%; m.p. 165°C (dec.). Found (Calc. for $C_6H_{12}N_2O_4Pt$): C, 19.2 (19.4); H, 3.2 (3.3); N, 7.3 (7.6)%. IR (KBr cm^{-1}): ν $(C{=}O)_{asym}$, 1624; ν $(C{=}O)_{sym}$, 1372. ^1H NMR (D_2O, ppm): 1.83 (s, 6H).

$(ma)_2Pt(ipm)$ (**2**). Yield 79%; m.p. 175°C (dec.). Found (Calc. for $C_8H_{16}N_2O_4Pt$): C, 24.2 (24.1); H, 3.7 (4.0); N, 6.7 (7.0). IR (KBr cm^{-1}): ν $(C{=}O)_{asym}$, 1624; ν $(C{=}O)_{sym}$, 1372. ^1H NMR (D_2O, ppm): 1.85 (s, 6H), 2.23 (s, 6H, $^3J_{Pt-H}$, 40.7).

Synthesis of $A_2Pt((OOC)_2C{=}C(CH_3)_2)(OH)_2$ (A = NH_3, ma)

To a suspension of $A_2Pt(OOC)_2C{=}C(CH_3)_2$ (2.0 mmol) in water (20 cm^3) was added an aqueous solution of 30% H_2O_2 (20 cm^3) and the reaction mixture was stirred for 2 h. The resulting pale yellow solution was concentrated to 5 cm^3 on a rotavapor at 40°C, to which acetone (100 cm^3) was added. The light yellow precipitate was filtered and washed with ethyl ether. The crude products were recrystallized from water to obtain a crystalline solid.

$(NH_3)_2Pt(ipm)(OH)_2$ (**3**). Yield 75%; m.p. 173°C (dec.). Found (Calc. for $C_6H_{14}N_2O_6Pt$): C, 17.2 (17.8); H, 3.3 (3.5); N, 6.7 (6.9)%. IR (KBr cm^{-1}): ν $(C{=}O)_{asym}$, 1636; ν $(C{=}O)_{sym}$, 1360, 1226; ν (Pt—O), 556. ^1H NMR (D_2O, ppm): 1.95 (s, 6H), ^{13}C NMR (D_2O, ppm): 175, 152, 127, 23.

$(ma)_2Pt(ipm)(OH)_2$ (**4**). Yield 68%; m.p. 170°C(dec.). Found (Calc. for $C_8H_{18}N_2O_6Pt$): C, 22.1 (22.2); H, 4.2 (4.2); N, 6.3 (6.5)%. IR (KBr cm^{-1}): ν $(C{=}O)_{asym}$, 1624; ν $(C{=}O)_{sym}$, 1372; ν (Pt—O), 562. ^1H NMR (D_2O, ppm): 2.18 (s, 6H, $^3J_{Pt-H}$, 30.7), 1.96 (s, 6H).

Synthesis of $A_2Pt((OOC)_2C{=}C(CH_3)_2)(OCOCR)_2$ (A = NH_3, ma; R = CH_3, CF_3, C_2H_5, n-C_3H_7)

To a suspension of $A_2Pt((OOC)_2C{=}C(CH_3)_2)(OH)_2$ (0.7 mmol) in CH_2Cl_2 (50 cm^3) was added acetic anhydride (5 cm^3), the reaction mixture was stirred, until the solution became clear. The solvent was removed by evaporation under reduced pressure and the residue was recrystallized from methanol to obtain crystals suitable for X-ray crystallography.

Trifluoroacetate, propionate, and *n*-butyrate analogs were prepared by the same procedure, using trifluoroacetic, propionic and butyric anhydride instead of acetic anhydride.

$(NH_3)_2Pt(ipm)(OCOCH_3)_2$ (**5**). Yield 72%; m.p. 196°C (dec.). Found (Calc. for $C_{10}H_{18}N_2O_8Pt$): C, 24.1 (24.5); H, 3.2 (3.7); N, 5.3 (5.7)%. IR (KBr cm^{-1}): ν $(C{=}O)_{asym}$, 1636; ν $(C{=}O)_{sym}$, 1360, 1226. ^1H NMR (D_2O, ppm): 1.98 (s, 6H), 1.95 (s, 6H); ^{13}C NMR (D_2O, ppm): 181, 157, 128, 23, 21.

$(ma)_2Pt(ipm)(OCOCH_3)_2$ (**6**). Yield 48%; m.p. 182°C (dec.). Found (Calc. for $C_{12}H_{22}N_2O_8Pt$): C, 28.5 (27.9); H, 4.2 (4.3); N, 4.9 (5.1)%. IR (KBr cm^{-1}): ν $(C{=}O)_{asym}$, 1640; ν $(C{=}O)_{sym}$, 1350, 1321. ^1H NMR (D_2O, ppm): 2.16 (s, 6H, $^3J_{Pt-H}$, 29.1), 2.04 (s, 6H), 1.99 (s, 6H).

$(NH_3)_2Pt(ipm)(OCOCF_3)_2$ (**7**). Yield 78%; m.p. 214°C (dec.). Found (Calc. for $C_{10}H_{12}N_2O_8PtF_6$): C, 19.8 (20.1); H, 2.2 (2.0); N, 4.3 (4.7)%. IR (KBr cm^{-1}): ν $(C{=}O)_{asym}$, 1713, 1636; ν $(C{=}O)_{sym}$, 1360; ν $(C{-}F)_{sym}$, 1168. ^1H NMR (CD_3OD, ppm): 1.98 (s, 6H); ^{13}C NMR (CD_3OD, ppm): 172.4, 163.4, 162.8, 129.2, 114.9, 110.3, 22.7.

$(ma)_2Pt(ipm)(OCOCF_3)_2$ (**8**). Yield 65%; m.p. 177°C (dec.). Found (Calc. for $C_{12}H_{16}N_2O_8PtF_6$): C, 22.1 (23.0); H, 2.5 (2.6); N, 4.3 (4.5)%. IR (KBr cm^{-1}): ν $(C{=}O)_{asym}$, 1741, 1640; ν $(C{=}O)_{sym}$, 1358; ν $(C{-}F)_{sym}$, 1182. ^1H NMR (CD_3OD, ppm): 2.18 (s, 6H, $^3J_{Pt-H}$, 30.4), 2.01 (s, 6H).

$(NH_3)_2Pt(ipm)(OCOC_2H_5)_2$ (**9**). Yield 71%; m.p. 191°C (dec.). Found (Calc. for $C_{12}H_{22}N_2O_8Pt$): C, 26.1 (25.5); H, 4.5 (4.3); N, 5.2 (5.4)%. IR (KBr cm^{-1}): ν $(C{=}O)_{asym}$, 1642; ν $(C{=}O)_{sym}$, 1410, 1338. ^1H NMR (D_2O, ppm): 2.36 (q, 4H), 1.97 (s, 6H), 0.96 (t, 6H).

$(ma)_2Pt(ipm)(OCOC_2H_5)_2$ (**10**). Yield 45%; m.p. 193°C (dec.). Found (Calc. for $C_{14}H_{26}N_2O_8Pt$): C, 31.2 (30.8); H, 5.0 (4.8); N, 4.9 (5.1)%. IR (KBr cm^{-1}): ν $(C{=}O)_{asym}$, 1644; ν $(C{=}O)_{sym}$, 1360, 1325. ^1H NMR (D_2O, ppm): 2.36 (q, 4H), 2.18 (s, 6H, $^3J_{Pt-H}$, 28.9), 1.99 (s, 6H), 0.98 (t, 6H).

$(NH_3)_2Pt(ipm)(OCOC_3H_7)_2$ (**11**). Yield 48%; m.p. 196°C (dec.). Found (Calc. for $C_{14}H_{26}N_2O_8Pt$): C, 29.3 (30.8); H, 4.5 (4.8); N, 4.6 (5.1)%. IR (KBr cm^{-1}): ν $(C{=}O)_{asym}$, 1640; ν $(C{=}O)_{sym}$, 1414, 1348. ^1H NMR (D_2O, ppm): 2.30 (t, 4H), 1.99 (s, 6H), 1.48 (m, 4H), 0.82 (t, 6H).

$(ma)_2Pt(ipm)(OCOC_3H_7)_2$ (**12**). Yield 38%; m.p. 192°C (dec.). Found (Calc. for $C_{16}H_{30}N_2O_8Pt$): C, 32.5 (33.5); H, 5.1 (5.3); N, 4.7 (4.9)%. IR (KBr cm^{-1}): ν $(C{=}O)_{asym}$, 1640; ν $(C{=}O)_{sym}$, 1368, 1330. ^1H NMR (D_2O, ppm): 2.28 (t, 4H), 2.08 (s, 6H, $^3J_{Pt-H}$, 28.3), 1.96 (s, 6H), 1.47 (m, 4H), 0.80 (t, 6H).

X-ray crystallography

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 an ambient temperature of 23 ± 2°C. A prelimary diffractometric investigation indicated orthorhombic and monoclinic systems for **1** and **5**, respectively. Accurate cell dimensions were obtained from the setting angles of 25 well centered reflections by a least-square procedure. During the data collection, three standard reflections monitored after every 1 h did not reveal any systematic variation in intensity. The space group of each crystal was determined uniquely from the systematic absences. The structures were solved by a conventional heavy atom method, followed by successive difference 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 SHELXS-86 and SHELXL-93 programs running on PC. [14] Details of crystallographic data for **1** and **5** are summarized in Table 1.

Reduction of Pt^{IV} *complexes with ascorbic acid*

6×10^{-2} mmol both of a Pt^{IV} complex and ascorbic acid were completely dissolved in 2 cm^3 of a pH 7 buffer solution and the progress of reaction was monitored at room temperature with ^1H NMR spectroscopy.

Stability of Pt^{IV} *complexes in* HCl *aqueous solution*

We examined the rate of decomposition of 6×10^{-2} mmol of a Pt^{IV} complex in 0.01, 0.1, and 1 N HCl aqueous solutions at 37°C in the dark, by monitoring with ^1H NMR spectroscopy.

RESULTS AND DISCUSSION

Synthesis

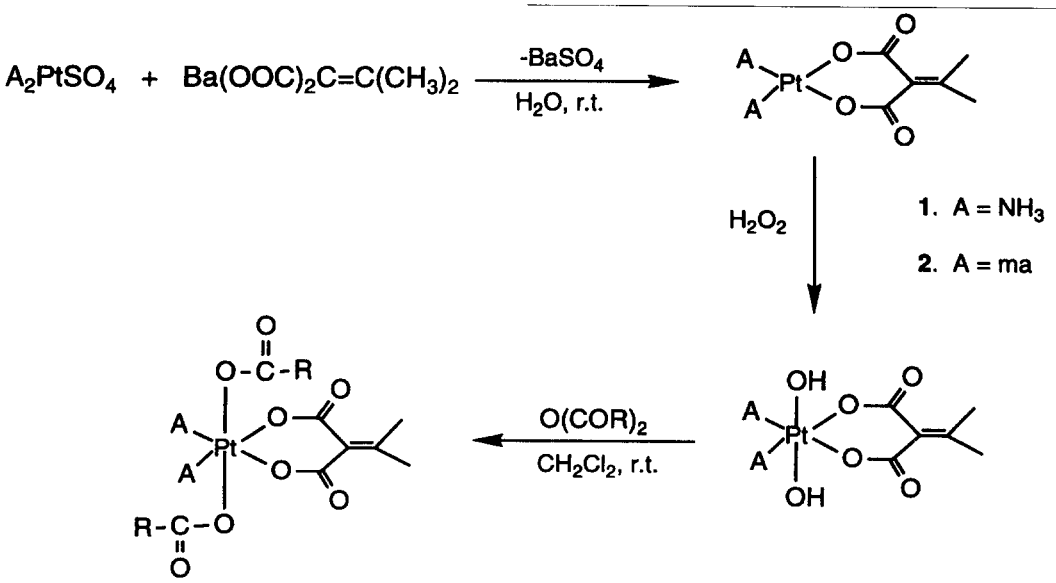
The platinum(II) complexes of isopropylidenemalonate, $A_2Pt(OOC)_2C{=}C(CH_3)_2$ (A = NH_3, ma),

Table 1. Crystal parameters and experimental details for **1** and **5**

Compound	**1**	**5**
Formula	$C_6H_{12}N_2O_4Pt$	$C_{10}H_{20}N_2O_8Pt$
fw	371.27	491.37
Crystal system	Orthorhombic	Monoclinic
Space group	*Pnma* (no. 62)	$P2_1/c$ (no. 14)
a (Å)	7.460(2)	11.518(4)
b (Å)	10.265(3)	10.262(4)
c (Å)	11.877(5)	13.132(6)
α (°)		90
β (°)		103.93(3)
γ (°)		90
V (Å^3)	909.4(5)	1506.6(11)
Z	4	4
$F(000)$	688	944
d_{calcd} (g cm^{-3})	2.712	2.166
Crystal size (mm)	0.15 × 0.15 × 0.35	0.3 × 0.3 × 0.15
μ (cm^{-1})	1.5414	0.9352
Scan method	$\omega/2\theta$	$\omega/2\theta$
Data collected	h, k, l	±h, k, l
No. of unique data > $3\sigma(I)$	777	2070
No. of parameters refined	64	199
R	0.0518	0.0764
wR	0.1838	0.1300
GoF on F^2	1.139	1.029

$R = (\Sigma|F_0 - F_c|)/\Sigma|F_0|$, $wR = (\Sigma|F_0 - F_c|w^{1/2})/\Sigma|F_0|w^{1/2}$.

have been prepared by the reaction of the corresponding diamineplatinum(II) sulfate with barium isopropylidene malonate in water according to the general method [11–13]. The oxidation of the platinum(II) complexes with hydrogen peroxide yielded the octahedral platinum(IV) complexes with two hydroxyl groups in axial positions. These complexes were further reacted with several carboxylic anhydride in dichloromethane to produce the corresponding *trans*-(dicarboxylato)platinum(IV) complexes with high yields. In our previous study, in which anhydride was used as solvent, not only the yield was low, but also longer reaction time was required. The whole synthetic route is shown in Scheme 1.



Scheme 1.

As the reaction progressed, suspension of the dihydroxoplatinum(IV) complexes in CH_2Cl_2 became clear. After filtering off the unreacted reactant, evaporation of the solvent gave the pure dicarboxylatoplatinum(IV) complexes. All the title complexes are air-stable and are obtained as white or yellow crystals. The complexes are soluble and fairly stable in water at room temperature. The water-solubility of the *trans*-dicarboxylatoplatinum(IV) complexes (20 mg cm^{-3} H_2O) is less than that of the *trans*-dihydroxoplatinum(IV) complexes (>50 mg cm^{-3} H_2O).

Crystal structures of **1** *and* **5**

The molecular structure and labeling scheme for **1** are shown in Fig. 1. Bond distances and 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 a slightly distorted square planar: the distances of Pt—N(1) and Pt—O(1) are 2.044(13) and 2.014(9)Å, respectively, and the bond angles of N—Pt—N^1, $O(1)^1$—Pt—N^1, O(1)—Pt—N and $O(1)^1$—Pt—O(1) are 95.8(7), 87.2(5), 87.2(5) and 89.7(6)°, respectively, which are consistant with those of the similar Pt^{II} complexes [15–16]. The ipm ligand chelates to the platinum atom *via* oxygens of two different carboxylate with a bite angle of 89.7(6)°. The ring conformation of the ipm ligand adopts a boat form. This study further confirms an earlier suggestion [15] that the malonate ligand prefers to adopt the boat form rather than any other conformation, such as chair, envelope or skew-boat. The dihedral angle between the $O(1)^1$—Pt—O(1) plane and the plane of O(1), $O(1)^1$, C(1), and C(2) is 34.67(0.68)°, which is similar to those of other platinum(II) analogs [16]. The molecular structure for **5** presented in Fig. 2 shows that the local geometry around the platinum(IV) atom adopts an octahedral

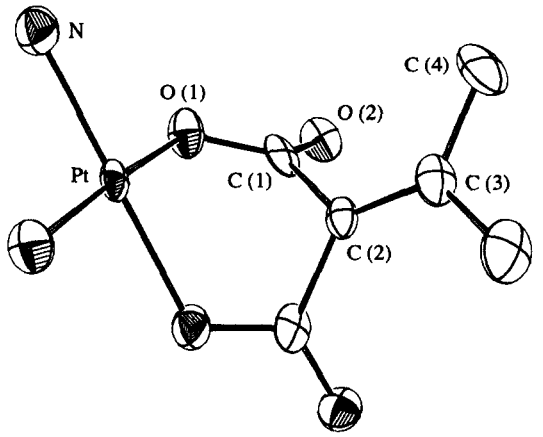


Fig. 1. View of the $(NH_3)_2Pt(ipm)$ (**1**).

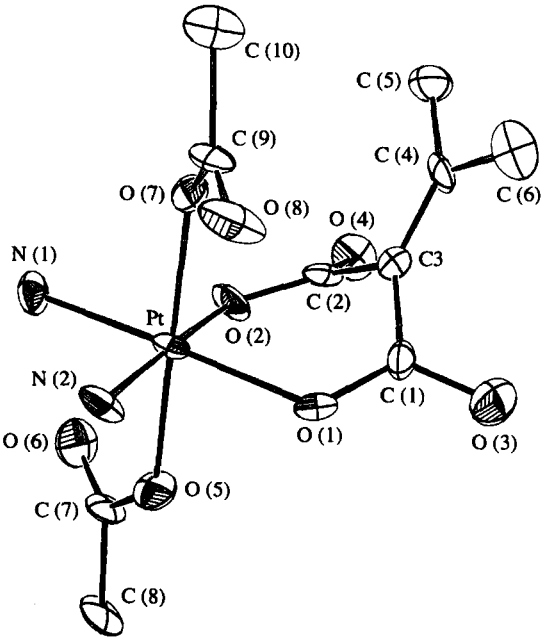


Fig. 2. View of the $(NH_3)_2Pt(ipm)(OCOCH_3)_2$ (**5**).

arrangement with two acetate ligands in the *trans* positions. The average Pt—N (2.01 Å) and Pt—O (2.00 Å) bond lengths are similar to those of complex **1** and within the normal range for other diamine platinum(IV) complexes [15–17]. The four Pt^{IV}—O distances are not significantly different from one another. Comparison of the bond distances between C=O and C—O bonds indicates no significant electronic delocalization of any of the C=O bonds. [18] The dihedral angle between O(1)—Pt^{IV}—O(2) plane and the plane of O(1), O(2), C(1) and C(2) is 25.82(0.92)°, which is much smaller than that of complex **1** due to increased coordination number.

Spectroscopic properties

The title complexes have been characterized also by IR and NMR spectroscopic data. In the IR spectra of all the platinum(II) and platinum(IV) complexes, the difference ($\Delta\nu$) between the asymmetric and symmetric carbonyl stretching frequences is larger than 200 cm^{-1}, suggesting that both of the carboxylate groups in the isopropylidenemalonate ligand act as monodentate ligand as shown in the X-ray structures of **1** and **5**. The oxidation products of the Pt^{II} complexes of **1** and **2**, the dihydroxoplatinum (IV) complexes **3** and **4**, could readily be identified by their characteristic PtO—H stretches at 3450 and 3430 cm^{-1}, respectively, and Pt—O stretches at 556 and 562 cm^{-1}, respectively. After carboxylation, both PtO—H and Pt—O stretches disappeared. One broad carbonyl stretching absorption in the range 1636–1640 cm^{-1} has been observed for the *trans*-diacetatoplatinum(IV) as well as *trans*-dibutyratoplatinum(IV) complexes due to overlapping in the stretching fre-

Table 2. Bond distances (Å) and angles (°) for $(NH_3)_2Pt(ipm)$ (**1**)

Pt—O(1)	2.014(9)	C(1)—C(2)	1.51(2)
Pt—O(1)^1	2.014(9)	C(2)—C(3)	1.36(3)
Pt—N(1)	2.044(13)	C(2)—C(1)^1	1.51(2)
Pt—N(1)^1	2.044(13)	C(3)—C(4)	1.51(2)
O(1)—C(1)	1.29(2)	C(3)—C(4)^1	1.51(2)
O(2)—C(1)	1.22(2)		
O(1)^1—Pt—O(1)	89.7(6)	O(2)—C(1)—C(2)	120.2(11)
O(1)^1—Pt—N	176.4(4)	O(1)—C(1)—C(2)	115.6(11)
O(1)—Pt—N	87.2(5)	C(3)—C(2)—C(1)^1	122.9(7)
O(1)^1—Pt—N^1	87.2(5)	C(3)—C(2)—C(1)	122.9(7)
O(1)—Pt—N^1	176.4(4)	C(1)—C(2)—C(1)	114.2(14)
N—Pt—N^1	95.8(7)	C(2)—C(3)—C(4)	121.3(8)
C(1)—O(1)—Pt	119.3(8)	C(2)—C(3)—C(4)^1	121.3(8)
O(2)—C(1)—O(1)	123.9(12)	C(4)—C(3)—C(4)^1	117(2)

Symmetry transformations used to generate equivalent atoms: $^1x,y,-z+1/2$.

Table 3. Bond distances (Å) and angles (°) for $(NH_3)_2Pt(ipm)(OCOCH_3)_2$ (**5**)

Pt—O(1)	2.028(12)	O(6)—C(7)	1.22(2)
Pt—O(2)	1.988(11)	O(7)—C(9)	1.25(2)
Pt—O(5)	1.996(13)	O(8)—C(9)	1.20(2)
Pt—O(7)	1.988(12)	C(1)—C(3)	1.46(2)
Pt—N(1)	2.024(14)	C(2)—C(3)	1.52(3)
Pt—N(2)	2.001(14)	C(3)—C(4)	1.32(2)
O(1)—C(1)	1.28(2)	C(4)—C(5)	1.45(2)
O(2)—C(2)	1.30(2)	C(4)—C(6)	1.52(2)
O(3)—C(1)	1.26(2)	C(7)—C(8)	1.48(2)
O(4)—C(2)	1.20(2)	C(9)—C(10)	1.49(3)
O(5)—C(7)	1.30(2)		
N(1)—Pt—O(2)	90.0(5)	O(3)—C(1)—O(1)	118(2)
N(1)—Pt—O(5)	96.5(5)	O(3)—C(1)—C(3)	121(2)
O(2)—Pt—O(5)	91.3(5)	O(1)—C(1)—C(3)	121.4(13)
N(1)—Pt—O(7)	83.4(5)	O(4)—C(2)—O(2)	122(2)
O(2)—Pt—O(7)	88.6(5)	O(4)—C(2)—C(3)	119(2)
O(5)—Pt—O(7)	179.8(4)	O(2)—C(2)—C(3)	118.6(12)
N(1)—Pt—N(2)	90.0(6)	C(4)—C(3)—C(1)	125(2)
O(2)—Pt—N(2)	176.7(6)	C(4)—C(3)—C(2)	121(2)
O(5)—Pt—N(2)	85.5(6)	C(1)—C(3)—C(2)	123.9(14)
O(7)—Pt—N(2)	94.7(6)	C(3)—C(4)—C(5)	126(2)
N(1)—Pt—O(1)	177.6(5)	C(3)—C(4)—C(6)	122(2)
O(2)—Pt—O(1)	91.3(5)	C(5)—C(4)—C(6)	113(2)
O(5)—Pt—O(1)	81.4(5)	O(6)—C(7)—O(5)	122(2)
O(7)—Pt—O(1)	98.6(5)	O(6)—C(7)—C(8)	126(2)
N(2)—Pt—O(1)	88.6(6)	O(5)—C(7)—C(8)	112(2)
C(1)—O(1)—Pt	119.8(10)	O(7)—C(9)—O(8)	124(2)
C(2)—O(2)—Pt	121.6(10)	O(7)—C(9)—C(10)	114(2)
O(7)—O(5)—Pt	124.4(11)	O(8)—C(9)—C(10)	122(2)
O(9)—O(7)—Pt	125.2(11)		

quency of the different carboxylate functional groups, while two carbonyl stretching bands are observed for the *trans*-bis(trifluoroacetato)platinum(IV) analogs. The carbonyl stretching frequencies of the trifluoroacetate ligand in complexes **7** and **8** appear, as expected, in the region at 1713 and 1723 cm^{-1} with a blue-shift of approximately 100 cm^{-1} compared with that (1600–1630 cm^{-1}) of other carboxylate ligands [19–22].

The ^1H NMR spectral data of the complexes in D_2O are consistent with the structure in the solid state. For the platinum(II) complexes, the methyl protons of ipm ligand resonate at 1.83 ppm as a singlet, which undergoes downfield shift to 1.95–2.04 ppm in their corresponding octahedral platinum(IV) complexes. The methyl protons of ma ligand in $(ma)_2Pt(ipm)$ appear as a singlet at 2.23 ppm with satellites of $^3J_{Pt-H} = 40.7$ Hz due to coupling with ^{195}Pt ($I = 1/2$). For $(ma)_2Pt(ipm)(OH)_2$, the corresponding protons appear as a singlet at 2.18 ppm with setellites of $^3J_{Pt-H} = 30.7$ Hz. Thus, ^3J(Pt—H) coupling constants of the present complexes are characteristic of oxidation state of the present platinum complexes. For the Pt^{IV} complexes, the *cis* ligands seem to exert only a small effect on the coupling constant. In our system, there is no distinct influence with the axial ligands of Pt^{IV} complexes.

Reduction properties

Since the previous studies [22] suggested that the Pt^{IV} complexes must be activated by reduction to the Pt^{II} complexes for antitumor activity, the reduction properties of the present Pt^{IV} complexes have been examined. Optimal stability occurs at pH values between 5 and 7, where the ascorbic acid molecule exists mostly in the monoanion form. [23] The reaction of the present platinum(IV) complexes with equivalent ascorbic acid in the buffer solution at pH 7 at room temperature was monitored by ^1H NMR spectroscopy (Fig. 3). As the reaction progressed, the resonance peaks corresponding to the Pt^{IV} complexes disappeared with increasing intensity of the peaks for the corresponding Pt^{II} complex. As shown in Table 4, all the platinum(IV) complexes were reduced to the corresponding platinum(II) complexes by ascorbic acid with variable rates. The reduction rate of the Pt^{IV} complexes seems to be nearly independent on the type of the carrier amine ligands, but greatly dependent on

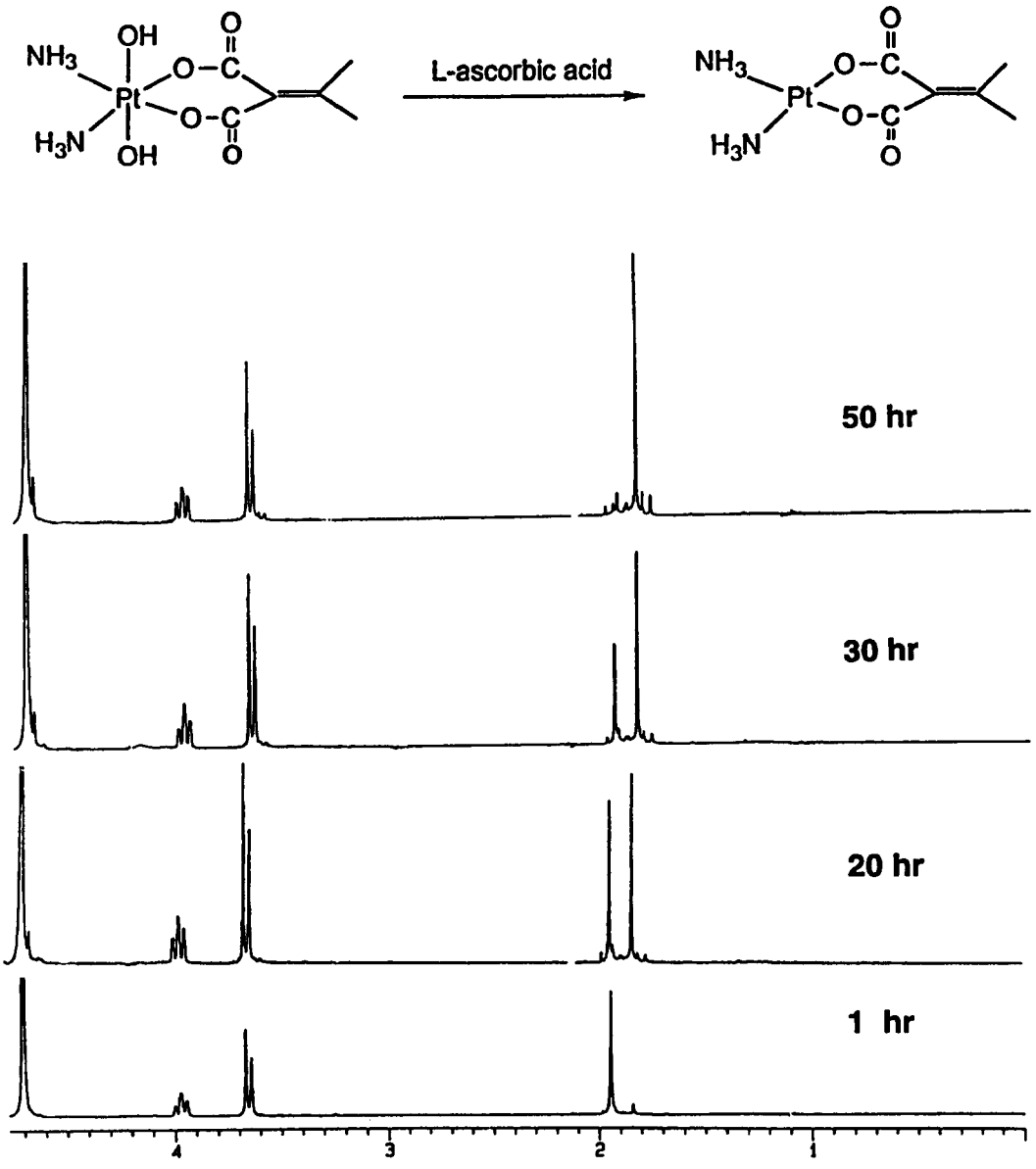


Fig. 3. Reduction of $(NH_3)_2Pt(ipm)(OH)_2$ (3) by ascorbic acid.

the type of their axial ligands. The trifluoroacetato analogs are reduced more readily than any other Pt^{IV} complexes and the ratio of the corresponding Pt^{IV} and Pt^{II} complexes is *ca* 1 before 1 h. It is also seen from the Table 4 that the *trans*-dicarboxylatoplatinum(IV) complexes are more easily reduced than the dihydroxo analogs and also the reduction rate is remarkably enhanced when the axial ligand is changed from acetato to propionato or butyrato group.

Stability of Pt^{IV} *complexes in* HCl *aqueous solution*

Since the orally adminstered compound must pass through the stomach cell membrane, the compound should be stable at low pH. Therefore, we examined the disappearance of the Pt^{IV} complexes in the dark, at 37°C, in 0.01, 0.1 and 1 N HCl aqueous solution, and the loss of compound was monitored by ^1H NMR.

The *trans*-dihydroxoplatinum(IV) complexes were readily decomposed in 1 N HCl aqueous solution and almost half of the original Pt^{IV} compound remained in the solution after 3 h. At lower HCl concentrations, neligible decomposition of these complexes occurred over a 6 h period, but approximately half of the original compound remained after 48 h in 0.01 N HCl aqueous solution. The other Pt^{IV} complexes were stable and neligible decomposition occurred over a 6 h period, and after 72 h, approximately half of the original compound remained in the 0.1 N HCl aqueous solution (Table 5).

Table 4. Reduction rate of $A_2Pt(ipm)X_2$ complexes by ascorbic acid

Compound	$t_{1/2}$ (h) 1 mM	10 mM
3	>50	20
4	>50	25
5	45	12
6	40	10
7	<1	<0.2
8	<1	<0.2
9	3	<1
10	4	1
11	5	<0.5
12	8	2

Ascorbic acid concentration: 1 mM, 10 mM.

Table 5. Stability of $A_2Pt(ipm)X_2$ complexes

Compound	$t_{1/2}$ (h) 1 N	0.01 N
3	2.5	>48
4	3	>48
5	5	>72
6	5	>72
7	10	>72
8	9	>72
9	8	>72
10	9	>72
11	10	>72
12	9	>72

HCl aqueous solution concentration: 1 N, 0.01 N.

In conclusion, the isopropylidenmalonatoplatinum(IV) complexes prepared in this work are readily reduced to the platinum(II) complexes by ascorbic acid and also stable enough in physiological acidic conditions, which indicates that these complexes may be used as an orally administrable drug. Thus, all these complexes are currently in the stage of intensive *in vivo* screening studies.

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