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Chelate vs monodentate amine effects. Direct comparison of bis(acetato)amminedichloro(cyclohexylamine)platinum(IV) (JM216) with its *N*-cyclohexyl-1,3-propanediamine analogue☆

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Abstract

In order to investigate the chelate effects on physicochemical properties including antitumor activity, new *cis*,*trans*,*cis*,-[$Pt^{IV}Cl_2L_2$(chpda)] complexes (L = OH, $OCOCH_3$; chpda = *N*-cyclohexyl-1,3-propanediamine) have been synthesized and characterized. The crystal structure of *cis*,*trans*,*cis*-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chpda)] (monoclinic $P2_1/a$, $a = 7.947(1)$, $b = 22.753(11)$, and $c = 10.581(3)$ Å, $\beta = 110.70(2)°$, $V = 1790(1)$ Å^3, $Z = 4$, $R = 0.0534$) shows that the platinum(IV) center adopts a typical octahedral arrangement with two acetate groups in a *trans* position. The pattern and strength of the intramolecular hydrogen bonds are delicately different from those of JM216. Both in vitro and in vivo (oral) cytotoxicities on mouse leukemia L1210 cell line indicate that the activity of chpda chelate analogue is not better than that of the corresponding compound with two monodentate amines (JM216).

Keywords: Chelate effects; Antitumor activity; Crystal structure; *N*-Cyclohexyl-1,3-propanediamine

1. Introduction

A desirable alternative approach to reduce side effects and to enhance the quality of life in the treatment of cancer patients is to develop orally active antitumor drugs. Six-coordinate (diamine)platinum(IV) complexes have been considered as potential oral anticancer agents [1–6]. Among them, *cis*,*trans*,*cis*-[$Pt^{IV}Cl_2(OCOCH_3)_2NH_3$(*cyclo*-$C_6H_{11}NH_2$)] (JM216) shows selective cytotoxicity toward cisplatin-resistant human ovarian tumor cell lines, and is currently in clinical trials [7,8]. Thus, efforts have been directed towards modifying the structure and pharmacokinetics of JM216 [6]. To date, the modified platinum(IV) complexes suitable for oral administration should be neutral, lipophilic, water-soluble, and stable enough to exist in the gastric environment. In particular, the asymmetric amine ligands of the orally active compounds have been known to have profound effects on the formation of orientational isomers and the selectivity for DNA binding sites [9].

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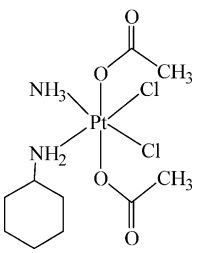
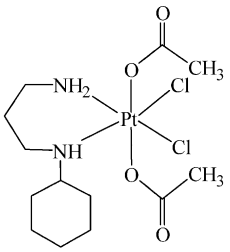
In this context, unique JM216 analogues with an asymmetric chelate amine sustaining a cyclohexyl moiety have been synthesized in order to investigate the chelate effects on antitumor activity. This article reports delicate structural differences between *cis*,-*trans*,*cis*-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chpda)] (chpda = *N*-cyclohexyl-1,3-propanediamine) and JM216. The geometry and functional groups of the present compound are very similar to those of JM216.



JM216



cis,trans,cis-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chpda)]

2. Experimental

2.1. Materials and instrumentation

Reagent grade potassium tetrachloroplatinate(II) (Kojima) and *N*-cyclohexyl-1,3-propanediamine (Aldrich) were used as received. Fresh *cis*-[$Pt^{II}Cl_2$(chpda)] was prepared by a routine procedure [10]. ^{1}H NMR spectra were recorded on a Varian Gemini 300 instrument. The chemical shifts are reported relative to internal Me_4Si. The infrared spectra in the 5000–400 cm^{-1} region were measured as potassium bromide pellets on a Perkin Elmer 16F PC model FT-IR spectrometer. Elemental analysis was performed at the Advanced Analysis Center at KIST.

2.2. Preparation

2.2.1. *cis,trans,cis-[$Pt^{IV}Cl_2(OH)_2$(chpda)]*

To a suspension of *cis*-[$Pt^{II}Cl_2$(chpda)] (2.0 g, 4.7 mmol) in water (100 ml) was added a 30% aqueous solution of H_2O_2 (2.4 ml). The reaction mixture was stirred at 70 °C for 2 h. After the resultant solution was filtered off, the filtrate was reduced to 30 ml. The solution stood overnight to obtain the solid product in 65% yield. m.p. 156 °C (dec.). Anal. Calcd for $C_9H_{22}N_2O_2Cl_2Pt{\cdot}2H_2O$: C, 22.00; H, 5.32; N, 5.69. Found: C, 21.50; H, 5.22; N, 5.70. IR (KBr, cm^{-1}): ν(OH), 3452.

2.2.2. *cis,trans,cis-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chpda)]*

An aqueous suspension of *cis*,*trans*,*cis*-[$PtCl_2$-$(OH)_2$(chpda)] (1,0 g, 2.65 mmol) was stirred with acetic anhydride (20 ml, 156 mmol) at room temperature for 5 h. After the resultant solution was filtered off, the filtrate was evaporated to obtain a yellow solid. The crude product was recrystallized from a mixture of water and acetone. The colorless crystals were obtained in 62% yield. m.p. 132 °C (dec.). Anal. Calcd for $C_{13}H_{26}N_2O_4Cl_2Pt$: C, 25.60; H, 4.77; N, 4.63. Found: C, 25.50; H, 4.87; N, 4.56. IR (KBr, cm^{-1}): *$\nu(COO)_{asym}$, 1630; $\nu(COO)_{sym}$, 1360. ^{1}H NMR (Me_2SO-d_6, δ): 9.3 (NH_2), 7.2 (NH), 1.93 (OCH_3), 1.90 (OCH_3), 3.5 1.0 (chpda 16H).*

2.3. X-ray crystallography of *cis,trans,cis-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chpda)]*

The X-ray data were collected on an Enraf–Nonius CAD4 automatic diffractometer with graphite-monochromated Mo Kα (λ = 0.71073 Å) at ambient temperature (20(2) °C). The unit cell dimensions were based on 25 well-centered reflections by using a least-squares procedure. During the data collection, three standard reflections monitored every hour did not show any significant intensity variation. The data were corrected for Lorentz and polarization effects, and empirically for absorption (azimuthal ψ-scans of six reflections). The structure was solved by the Patterson method (SHELXS-97), and was refined by full-matrix least squares techniques (SHELXL-97) [11]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed at the calculated positions. Crystal parameters and procedural information corresponding to data collection and a structure refinement are given in Table 1.

3. Results

3.1. Synthesis

cis-[$Pt^{II}Cl_2$(chpda)] was oxidized in the presence of H_2O_2 to yield *cis*,*trans*,*cis*-[$Pt^{IV}Cl_2(OH)_2$(chpda)] as shown in Scheme 1. Further carboxylation of

Table 1
Crystallographic data for *cis,trans,cis*-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chpda)]

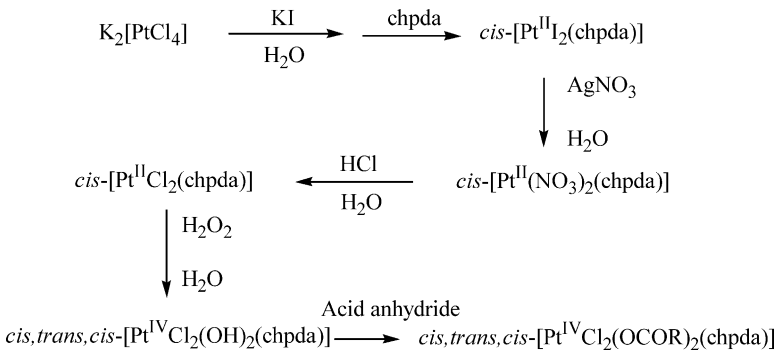
Formula	$C_{13}H_{26}Cl_2N_2O_4Pt{\cdot}2H_2O$
Formular weight	540.35
T (°C)	20(2)
λ (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1/a$ (No. 14)
a (Å)	7.947(1)
b (Å)	22.753(11)
c (Å)	10.581(3)
β (deg)	110.70(2)
V (Å^3)	1790(1)
Z	4
d_{calcd} (g/cm^3)	2.006
Abs. coeff (mm^{-1})	8.156
F(000)	1048
Crystal size (mm^3)	0.05 × 0.10 × 0.20
θ_{max} (deg)	1.79–24.98
Index ranges	$0 \le h \le 9$, $0 \le k \le 26$, $12 \le l \le 11$
Reflections collected	1634
Independent reflections	1532 [$R_{(int)} = 0.0570$]
Parameters refined	199
GOF on F^2	1.057
Final $R[I > 2\sigma(I)]$	$R1 = 0.0534$, $wR2 = 0.0955$
Largest diff. peak (e Å^{-3})	+0.991 and −1.060

$R1 = \sum||F_o| - |F_c||/\sum|F_o|$, $wR2 = \sum w(F_o2 - F_c2)2/\sum w(F_o4)$ 1/2, where $w = 1/\{\sigma2F_o2 + (aP)2 + bP\}$ where $P = \{\max(F_o2, o) + 2F_c2\}/3$.

the hydroxide coordinated to the platinum(IV) produces *cis,trans,cis*-[$Pt^{IV}Cl_2(OCOR)_2$(chpda)]. Composition was in each case determined by elemental analysis, IR, and ^{1}H NMR data. The final platinum(IV) complex is recrystallized in a mixture of water and acetone to give colorless crystalline solids. The products are solids that decompose prior to melting. They are soluble in common organic solvents, and are slightly soluble in water.

3.2. Crystal structure of *cis,trans,cis*-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chpda)]

The molecular structure is depicted in Fig. 1, and selected bond distances and angles are listed in Table 2. The local geometry around the platinum(IV) approximates to a typical octahedral arrangement with two acetate groups in a *trans* position (O(1)–Pt–O(3) = 174.9(6)°). Two chlorides are retained in a *cis* position (Cl(1)–Pt–Cl(2) = 89.3(2)°). Concomitantly, the chpda is bonded to the platinum(IV) in a chelate fashion. For the acetate groups, the bond lengths of C(1)–O(2) (1.18(2) Å) and C(3)–O(4) (1.21(3) Å) are shorter than those of C(1)–O(1) (1.31(3) Å) and C(3)–O(3) (1.31(2) Å), indicating that both acetate groups act as monodentate ligands (Pt–O(1) = 2.00(1) Å; Pt–O(2) = 2.02(1) Å). The N(1)–Pt–N(2) bond angle (96.1(6)°) is slightly splayed to sustain the 6-membered ring in contrast to the corresponding angle of JM216 (94.3(4)°) [8]. There exist intramolecular hydrogen bonds between the dangling oxygens of the acetate groups and the amine groups (N(1)···O(4) = 2.72 and N(2)···O(2) = 2.68 Å). These intramolecular hydrogen bonds may give rise to additional stability in the solid state. The hydrogen bonds are slightly stronger than those of JM216 (2.84–2.86 Å), presumably due to the electronic effect of chpda ligand. Moreover, the pattern of the hydrogen bonds is slightly different from that of JM216, presumably due to the chelate effects of the chpda ligand. For the present compound,



Scheme 1.

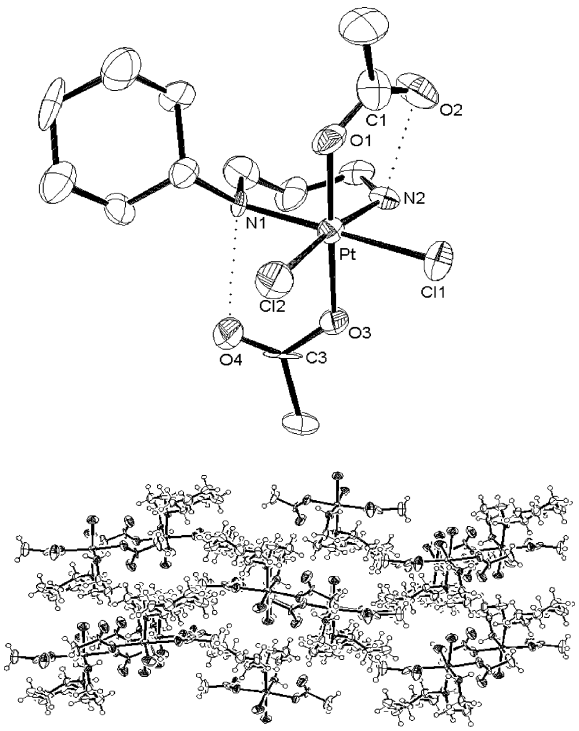


Fig. 1. ORTEP view (top) and packing diagram (bottom) of *cis*,*trans*,*cis*-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chpda)]. For the ORTEP view, hydrogen atoms are omitted for clarity.

a one-to-one interaction exists (N(1)···O(4) and N(2)···O(2)). For JM216, N(1) interacts with two oxygen donors (O(5)···N(1)···O(3)) while N(2) interacts with only one oxygen (N(2)···O(5)) donor

Table 2
Selected bond lengths (Å) and angles (deg) for *cis*,*trans*,*cis*-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chpda)]

Pt–O(1)	2.00(1)	Pt–O(3)	2.02(1)
Pt–N(2)	2.05(1)	Pt–N(1)	2.08(1)
Pt–Cl(2)	2.312(5)	Pt–Cl(1)	2.324(5)
O(1)–C(1)	1.31(3)	O(2)–C(1)	1.18(2)
O(3)–C(3)	1.31(2)	O(4)–C(3)	1.21(2)
O(1)–Pt–O(3)	175.0(6)	O(1)–Pt–N(2)	96.0(6)
O(3)–Pt–N(2)	87.3(5)	O(1)–Pt–N(1)	87.4(6)
O(3)–Pt–N(1)	96.1(6)	N(2)–Pt–N(1)	96.1(6)
O(1)–Pt–Cl(2)	87.6(4)	O(3)–Pt–Cl(2)	88.8(4)
N(2)–Pt–Cl(2)	172.9(4)	N(1)–Pt–Cl(2)	90.2(4)
O(1)–Pt–Cl(1)	92.2(4)	O(3)–Pt–Cl(1)	84.3(4)
N(2)–Pt–Cl(1)	84.4(4)	N(1)–Pt–Cl(1)	179.4(5)
Cl(2)–Pt–Cl(1)	89.4(2)	C(1)–O(1)–Pt	125(2)
C(3)–O(3)–Pt	125(1)		

[8]. The packing diagram of the present compound shows that the hydrophilic groups are arranged in an assembly that is surrounded by the hydrophobic moieties.

3.3. Spectroscopic data and antitumor activity

The ^{1}H NMR spectrum of *cis*,*trans*,*cis*-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chdpa)] exhibits apparently crowded features owing to the presence of the rigid chelating chpda. However, from the characteristic signals, the basic configuration of the X-ray crystal structure is retained and stable in solution for a few days even though the weak and delicate hydrogen bonds may be changed. The two axial acetate moieties give signals at 1.88 and 1.92 ppm. The two chemical shifts seem to originate from the presence of the asymmetric chelating chpda. The acetylation of *cis*,*trans*,*cis*-[$Pt^{IV}Cl_2(OH)_2$(chpda)] is readily identified by the prominent change in the IR spectrum. The dihydroxoplatinum(IV) compound showed the characteristic O–H stretching frequency at 3452 cm^{-1}. Upon acetylation, the O–H band disappears, replaced by strong C=O bands (1630, 1282 cm^{-1}).

Preliminary antitumor activities of the present compound (ED_{50} = 1.1 μM; T/C (%) = 113.4 (oral); ED_{50} = effective dosage concentration that inhibit cell growth to 50% of the control; T/C(%) = Treat/Control × 100) are inferior to JM216 (ED_{50} = 0.6 μM; T/C (%) = 160.0 (oral)). The difference in antitumor activities of JM216 and *cis*,*trans*,*cis*-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chdpa)] may be ascribed to the difference between the monodentate amines in the former and the rigid chelating chpda in the latter; the amine-core of both compounds is retained. The activity difference may also be due to the delicate change of intramolecular hydrogen bonds. Besides the weak interactions, solubility can affect the antitumor activity. Water-solubility of *cis*,*trans*,*cis*-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chpda)] is lower than JM216. On the other hand, anticancer activities (ED_{50} = 2.0 μM; T/C (%) = 100 (oral)) of *cis*,*trans*,*cis*-[$Pt^{IV}Cl_2(OH)_2$(chdpa)] explains the importance of anions as well as the chelate effects. That is, the hydroxo analogue is ineffective compared with *cis*,*trans*,*cis*-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chdpa)] in anticancer activity.

4. Conclusion

A new JM216 analogue, *cis*,*trans*,*cis*-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chpda)] was synthesized and characterized. The chelate effects of neutral amine have been observed on the in vitro and in vivo activities. Understanding the features that can be used to control the physicochemical properties may be a key to the development of platinum complexes that exhibit desirable biological activity.

5. Supporting information available

A listing of refinement details, atomic coordinates, thermal parameters, and bond lengths and angles for *cis*,*trans*,*cis*-[$Pt^{IV}Cl_2(OCOCH_3)_2$(chpda)] are available. Ordering information is given on any current masthead page.

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