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Syntheses and Solution Behavior of Antitumor Active Platinum Blue Compounds with Glutarimidate or 3,3-Dimethylglutarimidate Bridging Ligand

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Two antitumor active platinum blue compounds have been synthesized and the crystal structure is reported. The solution behavior as studied with NMR spectroscopy is discussed in relation to the antitumor activities.

Although several reports have appeared on the antitumor activities of platinum blue compounds,1,2) none of them has been structurally clarified and even the chemical formulas seem to be ambiguous due to possible existence of impurities. In this paper, syntheses and a crystal structure of a new antitumor active platinum blue compound are reported and their solution behavior is discussed in terms of their NMR data.

A platinum blue compound with glutarimidate (GI) ligand, $[Pt_4(NH_3)_8(GI)_4](NO_3)_5\cdot 2H_2O$ (1), was prepared as follows. To a solution of cis-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ (1 mmol in 10 cm^3 of H_2O), which was prepared by adding 2 equiv of $AgNO_3$ to cis-$[PtCl_2(NH_3)_2]$ and filtering off AgCl, was added 1 mmol of glutarimide, and the pH of the solution was adjusted to 7 with 0.1 M (1 M = 1 mol/dm^3) NaOH. After the solution was heated at 90 ℃ for 2 h, it was cooled with ice and was filtered. To the filtrate 1 cm^3 of conc. HNO_3 was added and the solution was left at room temperature for several days to produce blue-black crystals.3) The platinum blue compound with 3,3-dimethylglutarimidate (DMGI) ligand, $[Pt_4(NH_3)_8(DMGI)_4](NO_3)_5\cdot 2H_2O$ (2), was prepared in the same way as for 1, except that 4 mmol of 3,3-dimethylglutarimide was added instead of glutarimide.4) The head-to-head (HH) isomer of $[Pt(II)_2(NH_3)_4(DMGI)_2](NO_3)_2\cdot H_2O$ (3) was obtained as pale green crystals after the filtrate of head-to-tail (HT) $[Pt(II)_2(NH_3)_4(DMGI)_2](NO_3)_2\cdot H_2O$ (4)5) was allowed to stand at room temperature for several days.6) cis-$[Pt(NH_3)_2(DMGI)_2]$ (5) was prepared as follows. To a solution of cis-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ (1 mmol in 10 cm^3 of H_2O) was added 2 mmol of 3,3-dimethylglutarimide, and the pH of the solution was adjusted to 5 with 0.1 M NaOH. After the solution was heated at 80 ℃ for 2.5 h in the dark, it was cooled to room temperature and was evaporated to give yellow precipitate of **5**. It was filtered and was recrystallized from water.7)

The antitumor activities of **1** and **2** were examined on mice bearing L1210. The mice were treated intraperitoneally with the compounds on days 1, 5, and 9. Mean survival times (MST) of treated mice and control tumor-bearing mice were calculated and the %T/C (= MST(treated)/MST(control)) values are summarized in Table 1, which shows that both **1** and **2** are antitumor active.

Table 1. Antitumor Activities of Platinum Compounds against L1210 Leukemia in Vivo

Complex	Dose (mg/kg)	%T/C
Glutarimide blue, **1** $[Pt_4(NH_3)_8(GI)_4](NO_3)_5 \cdot 2H_2O$	50	102
	25	164
	12.5	139
3,3-Dimethylglutarimide blue, **2** $[Pt_4(NH_3)_8(DMGI)_4](NO_3)_5 \cdot 2H_2O$	50	131
	25	156
	12.5	200
	6.25	132
	3.12	114

The structure of the complex cation of **2**8) is shown in Fig. 1. The structure is the same with those of the previously reported platinum blues;9,10) however, the Pt-Pt distances in **2** are the longest among the corresponding ones in α-pyridonate blue9) (Pt-Pt(outer), 2.7745(4) and Pt-Pt(inner), 2.8770(9) Å) and in 1-methyluracilate blue (Pt-Pt(outer), 2.793(2) and 2.810(2), and Pt-Pt(inner), 2.866(2) Å).10) The structure of **3** was confirmed by ^{195}Pt NMR spectroscopy. The structures of **1** to **5** are schematically shown in Scheme 1.

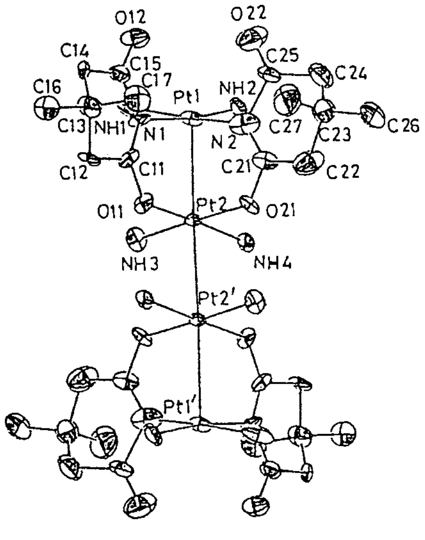
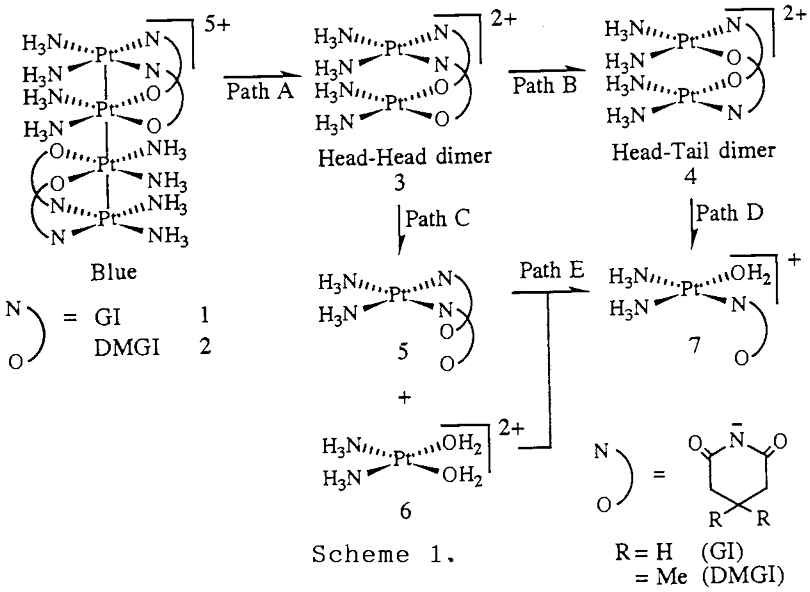


Fig. 1. Structure of **2**.



Scheme 1.

Our previous study on the α-pyrrolidonate-bridged tetranuclear platinum blue complex $[Pt_4(NH_3)_8(C_4H_6NO)_4]^{5+}$ 11,12) has proved that the complex is reduced by water to HH$-[Pt(II)_2(NH_3)_4(C_4H_6NO)_2]^{2+}$. The HH isomer isomerizes to the HT isomer and the solution finally contains HH and HT isomers in equilibrium. In order to know the solution behavior of **2**, chemical species in aqueous solution were examined by NMR spectroscopy. Since ^{195}Pt NMR spectrum of **2** could not be obtained due to its low solubility in H_2O, ^{195}Pt NMR spectrum of its water-reduced form **3** (shown in Fig. 2) was measured. Figure 2 shows that **3** produces dimeric and monomeric species even just after dissolution. After 3 days, only 5 and cis-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ are observed, which then gradually react to form cis-$[Pt(DMGI)(NH_3)_2(OH_2)]^+$ (^{195}Pt, -1988 ppm, not shown in Fig. 2) after a few days.

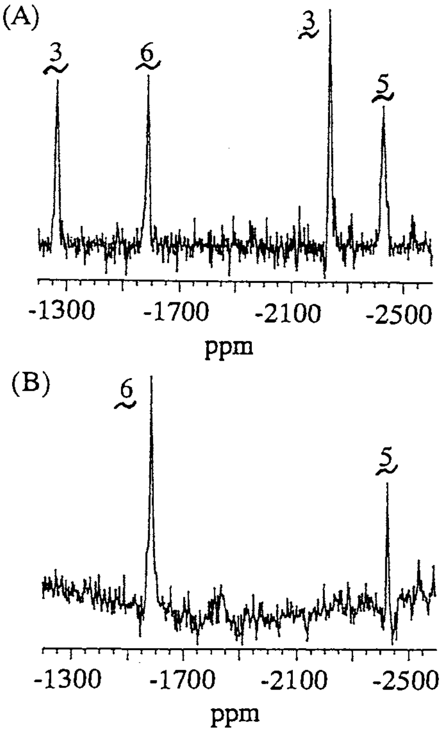


Fig. 2. ^{195}Pt NMR Spectra of 3 in H_2O. (A)After dissolution,(B) After 3 days. (3) -1259, -2233 ppm; (5) -2423 ppm; (6) -1581 ppm relative to K_2PtCl_4 in D_2O.

Figure 2 shows that some of the diamagnetic **3** isomerizes to the HT isomer **4** (path B), while some HH isomer undergoes solvolysis to give **5** and cis-$[Pt(II)(NH_3)_2(OH_2)_2]^{2+}$ (path C). The HT isomer undergoes solvolysis to produce cis-$[Pt(II)(DMGI)(NH_3)_2(OH_2)]$ (path D). The monomers **5** and cis-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ gradually react to give cis-$[Pt(II)(DMGI)(NH_3)_2(OH_2)]^+$ (path E) and therefore the solution contains only cis-$[Pt(DMGI)(NH_3)_2(OH_2)]^+$ after sufficient time. The interim spectral change during the 3 days, although not shown in Fig. 2, has confirmed the reactions mentioned above. The NMR assignment is based on the measurement of each synthesized compound and also on the reported chemical shifts of analogous compounds.13) Compound **1** was confirmed by ^{195}Pt NMR spectroscopy to behave similarly in solution as **2**.

It is probable from these results that the antitumor activities of compounds **1** and **2** are due to decomposition of the compounds to produce cis-$[Pt(NH_3)_2(OH_2)_2]^{2+}$. This compound is also produced from the well-established antitumor drug cis-$[PtCl_2(NH_3)_2]$ and is the real origin of the activity.14)

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3) Anal. Found: C, 13.84; H, 2.91; N, 13.62%. Calcd for $Pt_4C_{20}H_{52}N_{17}O_{25}$: C, 14.04; H, 3.06; N, 13.92%.

4) Anal. Found: C, 18.64; H, 3.76; N, 12.96%. Calcd for $Pt_4C_{28}H_{68}N_{17}O_{25}$: C, 18.44; H, 3.73; N, 13.06%.

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6) Anal. Found: C, 18.90; H, 3.87; N, 12.60%. Calcd for $Pt_2C_{14}H_{34}N_8O_{11}$: C, 19.09; H, 3.89; N, 12.73%.

7) Anal. Found: C, 33.25; H, 5.12; N, 10.89%. Calcd for $PtC_{14}H_{26}N_4O_4$: C, 33.00; H, 5.15; N, 11.00%.

8) Crystal data for $[Pt_4(NH_3)_8(DMGI)_4](NO_3)_5 \cdot 2H_2O$ at 23 C: F.W. = 1823.45, triclinic, space group $P\bar{1}$, a = 10.660(4) Å, b = 13.877(4) Å, c = 9.839(5) Å, α = 103.66(3)°, β = 104.30(3)°, γ = 71.39(3)°, V = 1316.4(9) $Å^3$, Z = 1, ρ_{calcd} = 2.30 g cm^{-1}, ρ_{obsd} = 2.29 g cm^{-1}, μ = 107.93 cm^{-1}. A total of 6572 reflections in the range of $3° < 2\theta < 55°$ ($\pm h, \pm k, l$) were collected on a Rigaku automatic four circle diffractometer AFC-5R with Mo Kα radiation (λ = 0.71073 Å). The program UNICS-III and 4001 unique data with Fo > 4σ(Fo) were used for the structure solution. R = 0.058, R_w = 0.055 ($w = 1/\sigma^2(F)$). All non-hydrogen atoms were located and were anisotropically refined. Selected bond distances (Å) and angles (deg): Pt1-Pt2, 2.860(2); Pt2-Pt2', 3.020(2); Pt1-N1, 1.97(3); Pt1-N2, 1.98(3); Pt1-NH1, 2.03(3); Pt1-NH2, 2.02(4); Pt2-O11, 2.00(2); Pt2-O21, 2.01(2); Pt2-NH3, 2.00(2); Pt(2)-NH4, 2.00(2); Pt2-Pt1-N1 82.9(9); Pt2-Pt1-N2, 82.5(8); Pt2-Pt1-1-NH1, 102.4(1); Pt2-Pt1-NH2, 100.2(9); Pt1-Pt2-Pt2', 161.74(5). The tilt angle between the adjacent Pt coordination planes is 27.1°. The torsion angle about the Pt-Pt vector is 0.5°.

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