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Synthesis and Antitumor Activity of Pt(II) Complexes containing 2,3-Diaminopropanol Isomers

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Halogeno, sulfato, and nitrato Pt(II) complexes of 2,3-diaminopropanol (pnOH) isomers were synthesized and their antitumor activities against leukemia L1210 were tested. The conformations of their chelate rings were determined to be λ- and δ-gauche forms for *R*- and *S*-pnOH, respectively, by ^{13}C-nuclear magnetic resonance and circular dichroism spectral analyses. Among the pnOH isomers, Pt(II) complexes containing *R*-pnOH showed higher antitumor activity than those containing *S*- or racemic pnOH. It seems that there may be a relationship between the conformations of the chelate rings and antitumor activity in the case of five-membered chelate rings.

Keywords——platinum(II) complex; antitumor activity; 2,3-diaminopropanol; optically active diamine; conformation of chelate ring

Many antitumor platinum complexes containing various amines and diamines have been synthesized and tested in various tumor systems, but most of them are hardly soluble in H_2O. Solubilization of these platinum complexes has been tried by introducing leaving groups such as nitrate and sulfate ions.[1-3] It is desirable to introduce leaving groups, which have a suitable coordination strength to the central platinum ions, but usually it is difficult to find such leaving groups and the substitution leads to instability and/or a decrease of the antitumor activity. For example, even *cis*-DDP, *cis*-dichlorodiammineplatinum(II), which was first found to be antitumor-active by Rosenberg *et al.*,[4] is hydrolyzed to yield toxic hydroxy-bridged polymers.[5]

These facts led us to investigate the solubilization of antitumor platinum complexes by modifying carrier ligands instead of leaving groups. This could lead to the development of more effective antitumor-active platinum complexes.

As a carrier ligand, we adopted 2,3-diaminopropanol(pnOH), which is a derivative of the simplest optically active diamine, 1,2-propanediamine, because we have been interested in the relationship between optical activity of platinum(II) complexes and antitumor activity. A series of Pt(II) complexes containing racemic pnOH and optical isomers of pnOH was synthesized and the antitumor activities of the compounds against leuckemia L1210 were tested.

Experimental

Dihydrochloride of 2,3-diaminopropanol was synthesized by the reaction of 3,4-dihydropyran and 2,3-dibromopropanol according to the method described in the literature.[6] Resolution of the racemic 2,3-diaminopropanol was achieved by a modification of the method used in the case of 1,2-propanediamine.[7]

Resolution of Racemic 2,3-Diaminopropanol Dihydrochloride——2,3-Diaminopropanol dihydrochloride (8 g, 0.047 mol) was converted to the free form by passing through a column containing 35 g of Amberlite IRA-410 resin. To 300 ml of the eluate was added 15 g (0.094 mol) of L(+)-tartaric acid, and the resultant solution was concentrated to 20 ml under reduced pressure. The concentrate was left overnight in a refrigerator and the crystals that deposited were collected by filtration. They were recrystallized three times from H_2O, giving (*R*)-2,3-diaminopropanol·H_2{H(+)tart}$_2$. *Anal.* Calcd for: C; 31.68, H; 6.04, N; 6.72.

Found: C; 31.89, H; 6.12, N; 6.63. $[\alpha]_D=23.55$ (1% aqueous solution).

The di(dydrogen tartrate) of 2,3-diaminopropanol was passed through an IRA-410 column to liberate the free amine, which was obtained as its dihydrochloride salt by the addition of conc. HCl to the eluate and evaporation of the solution to dryness. (*Anal.* Calcd for : C; 22.09, H; 7.43, N; 17.18. Found: C; 21.94, H; 7.71, N; 17.04. $[\alpha]_D=7.1$ (1% aqueous solution).

(*S*)-2,3-Diaminopropanol dihydrochloride was obtained by the same method as described for the resolution of the *R*-isomer except that D(−)-tartaric acid was used. *Anal.* Calcd for: C; 22.09, H; 7.43, N; 17.18. Found: C; 21.76, H; 7.56, N; 16.92. $[\alpha]_D=-24.87$ for (*S*)-pnOH·H_2 {H(−)tart}$_2$ and $[\alpha]_D=-6.3$ for (*S*)-pnOH $(HCl)_2$ (1% aqueous solutions).

Platinum(II) complexes of pnOH isomers were prepared according to the methods described in the literature.[8-11] The results of elemental analyses are shown in Table I.

TABLE I. Elemental Analyses of Pt(II) Complexes containing 2, 3-Diaminopropanol Isomers

Complexes	Found (%)			Calcd (%)		
	C	H	N	C	H	N
$PtCl_2$ (*R,S*-pnOH)	10.21	2.27	7.78			
$PtCl_2$ (*R*-pnOH)	9.89	2.70	7.64	10.12	2.83	7.87
$PtCl_2$ (*S*-pnOH)	10.22	2.85	7.85			
$PtBr_2$ (*R,S*-pnOH)	8.06	2.20	6.36			
$PtBr_2$ (*R*-pnOH)	8.23	2.39	6.44	8.10	2.27	6.29
$PtBr_2$ (*S*-pnOH)	8.15	2.32	6.32			
PtI_2 (*R,S*-pnOH)	6.80	1.85	5.26	6.89	1.93	5.36
Pt (SO_4) (*R,S*-pnOH)·1/2 H_2O	9.22	2.95	6.97	9.24	2.84	7.19
Pt (SO_4) (*R*-pnOH)·H_2O	9.05	3.14	7.09	9.02	3.03	7.01
Pt (SO_4) (*S*-pnOH)·H_2O	8.98	3.00	6.93			
Pt (SO_4) (*R,S*-pnOH)·H_2O	8.90	2.50	13.62	8.81	2.46	13.69

Measurements——A FT ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectrum was obtained at 25 MHz with broad-band proton decoupling on a JEOL JNM-FX-100 spectrometer employing the solvent deuterium as an internal lock. A total of 20200—25800 FID's (8192 points) was averaged to provide the desired signal-to-noise ratio in the 2.5 kHz frequency spectrum. Pulse angles of 45° were employed with no pulse delay. The ambient temperature was room temperature. Tetramethylsilane sealed in a capillary was used as an external reference. The spectrum was measured in D_2O solution. Absorption spectra (AB) were measured in H_2O with a Shimadzu UV200 recording spectrometer. Circular dichroism (CD) spectra were measured in H_2O with a JASCO J-40 spectropolarimeter. All measurements were performed at room temperature.

Antitumor Activity——Leukemia L1210 cells (10^5) were transplanted intraperitoneally into CDF_1 mice on day 0, and the samples were given intraperitoneally on days 1, 5, and 9. From the mean survival time of both treated (*T*) and control (*C*) mice, *T*/*C* % values were calculated. Compounds with *T*/*C* % values that exceeded 125 were evaluated as antitumor-active.

Results and Discussion

By introducing a hydroxyl group into 1,2-propanediamine(pn), the solubility of $PtCl_2$(pnOH) was increased to about twice that of $PtCl_2$(pn). The solubility of the former complex was determined to be 173 mg/100 ml of H_2O (4.87×10^{-3} M), while that of the latter was 70 mg/100 ml of H_2O (2.26×10^{-3} M) as determined by atomic absorption spectrometry.

^{13}C-NMR Spectroscopy

Since the halogeno Pt(II) complexes of pnOH isomers are not soluble enough in H_2O and the soluble sulfato(or nitrato) complexes are too unstable in H_2O for ^{13}C-NMR measurements, a new stable and soluble complex, $Pt(NH_3)_2$(pnOH), was synthesized for ^{13}C-NMR measurement. Its ^{13}C-NMR spectrum is illustrated in Fig. 1; three signals were observed at 51.07, 49.85, and 38.64 ppm. The signal at 51.07 ppm was a doublet and the rest of the signals showed triplets in the off-resonance spectrum, indicating that the lowest field signal was assignable to the methine, *i.e.*, C_2, carbon atom.

The signal at 49.85 ppm was accompanied by a pair of satellite signals with a coupling constant of 36.6 Hz, and was assigned to C_1. No coupling between the ^{13}C nuclei, *i.e.*, C_2 and C_3, and ^{195}Pt was observed in $[Pt(NH_3)_2(pnOH)]Cl_2$.

The coupling, denoted as $^{2,3}J_{Pt-C}$, is assumed to be the sum of coupling *via* two-bond and three-bond paths. In a σ-bond network, ^2J and ^3J are expected to possess opposite signs, and thus observations of small or zero coupling constant values of $^{2,3}J$ can be explained by the multipath mechanism suggested by Erickson *et al.*[12] On the other hand, ^3J coupling constants usually give very important information for determining the orientation of the objective carbon atom. Erickson *et al.* reported a large ^3J value of 52 Hz between ^{195}Pt and the β carbon atom in Pt(bpy)(dach)(dach=1,2-diaminocyclohexane) and concluded that the carbon atom is necessarily equatorial with a dihedral angle of *ca.* 160° for Pt–N–Cα–C$_\beta$. Similarly, a pure axial orientation(dihedral angle of 90°) would be expected to have a very small ^3J value, perhaps approaching zero according to the Karplus equation.[12]

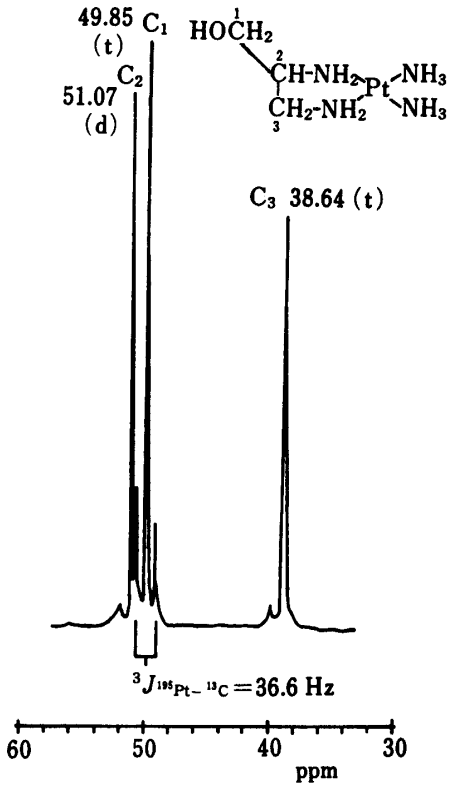


Fig. 1. ^{13}C-NMR Spectrum of $Pt(NH_3)_2(pnOH)$

Therefore, the signal at 49.85 ppm was assigned to C_1, and the ^3J coupling constant of 36.6 Hz between ^{195}Pt and $^{13}C_1$ coincides with that of $Pt(pn)_2$ reported by Yano *et al.*[13] This value may mean that the chelate ring

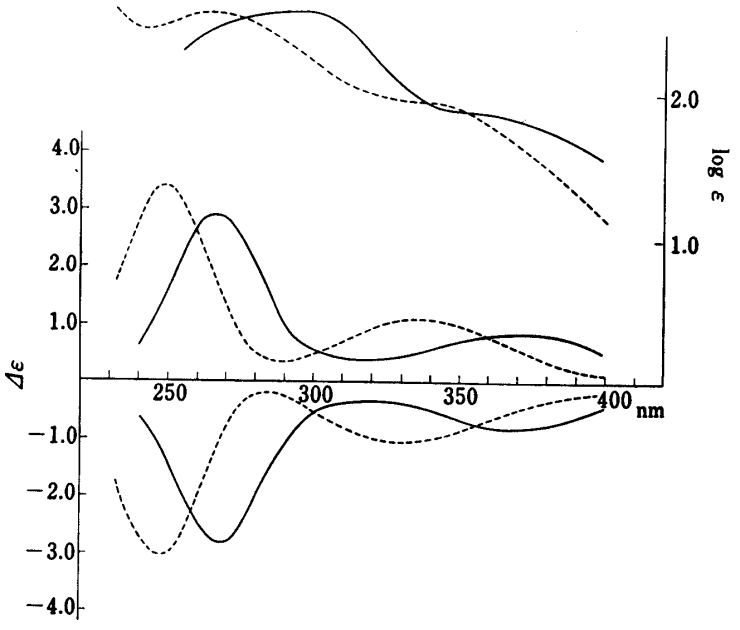


Fig. 2. Absorption and Circular Dichroism Spectra of Pt(II) Complexes containing 2,3-Diaminopropanol Optical Isomers

·····: sulfato Pt(II) complexes of (*R*) and (*S*) pnOH.
——: dichloro Pt(II) complexes of (*R*) and (*S*) pnOH.

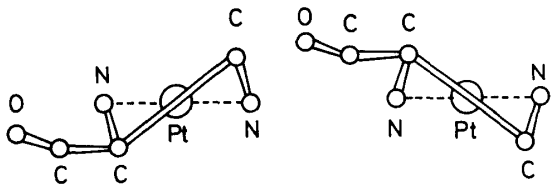
preferentially takes λ or δ gauche form with an equatorial C_1 atom depending upon whether the *R*- or *S*-isomer is involved, respectively.

AB and CD Spectra

The AB and CD spectra of dichloro and sulfato Pt(II) complexes containing pnOH isomers in H_2O are illustrated in Fig. 2. The Pt(II) complexes showed medium intensity absorption bands in the region of 200—400 nm, indicating d-d transitions. The AB spectrum of $PtCl_2$(pnOH) resembles that of $PtCl_2$(pn)[14] and showed bands around 370, 290, and 270 nm, the last of which was observed only as a shoulder. They can be assigned to bands II($^1A_{1g}\rightarrow{}^3E_g$), III($^1A_{1g}\rightarrow{}^1A_{2g}$), and IV($^1A_{1g}\rightarrow{}^1E_g$), respectively, from the longer wavelength region according to the assignments reported by Ito *et al.*[14]

$Pt(SO_4)$(pnOH) gave an AB spectrum similar to that of $PtCl_2$(pnOH), although the bands were shifted toward the shorter wavelength region, since the sulfato complex is considered to exist as aquo species in H_2O and water occupies a higher position in the spectrochemical series than Cl^-.[15,16] The bands around 340 and 260 nm can be assigned to bands II and III, but band IV was obscured due to the overlapping with the charge transfer transitions.

It is well known that *R*-pn and *R*,*R*-dach coordinate to Pt(II) ions in a λ-gauche form.[14] The CD data which have been reported so far indicate that the conformational effects of the diamines in a λ-gauche form exhibit a positive CD sign for the band corresponding to a transition $^1A\rightarrow{}^1E$, irrespective of the kind of metal ion.[17—20] Actually, Pt(II) complexes containing *R*-pn and R,R-dach were reported to give two positive CD bands in the bands II and IV regions.[14]



λ-gauche form σ-gauche form

Fig. 3. Conformations of Pt(II) Complexes containing *R*- and *S*-pnOH

$PtCl_2$(*R*-pnOH) showed two positive bands at 368 and 267 nm with $\Delta\varepsilon$ values of 0.09 and 0.29, respectively. $Pt(SO_4)$(pnOH) also exhibited two positive bands at 335 and 249 nm with $\Delta\varepsilon$ values of 0.11 and 0.34, respectively. The dichloro and sulfato Pt (II) complexes containing the optical isomer, *S*-pnOH, gave mirror-image spectra with respect to those of the corresponding Pt(II) complexes of *R*-pnOH. The bands were assigned to band II ($^1A\rightarrow{}^3E$) and band IV($^1A\rightarrow{}^1E$) from the longer wavelength region. The signs of these CD bands indicate that a λ-gauche form is predominant in *R*-pnOH Pt(II) complexes and a δ-gauche form in *S*-pnOH Pt(II) complexes, as illustrated in Fig. 3.

TABLE II. Antitumor Activity of Pt(II) Complexes of Racemic 2,3-Diaminopropanol

Leaving groups	Dose(mg/kg) 25	12.5 (*T/C* %)	6.25
Cl_2	130	125	115
Br_2	169	142	130
I_2	121	115	130
$(NO_3)_2$	158	170	139
SO_4	103	166	130

Administered on days 1, 5, and 9.
Underlined figures represent a positive result ($T/C\% \geqq 125$).
L1210 : 10^5 cells/mouse, *i.p.*-*i.p.* CDF_1 mice (6 mice/group).

Antitumor Activity

Table II shows the antitumor activities of Pt(II) complexes of racemic pnOH against leukemia L1210. Among the halogeno complexes, the dibromo complex had the highest activity, while the most insoluble diiodo complex had no effect. The water-soluble sulfato

TABLE III. Antitumor Activity of Pt(II) Complexes of Optical Isomers of 2,3-Diaminopropanol against Leukemia L1210

Optical isomers	Leaving groups	Dose (mg/kg) 50	25	12.5 (*T/C* %)	6.25
R	Cl_2	0	85	231 (1/6)	—
S	Cl_2	0	142	173	—
R	Br_2	—	213	140	123
S	Br_2	—	168	146	121
R	SO_4	—	0	100	143
S	SO_4	—	107	135	125

Administered on days 1, 5, and 9.
Underlined figures represent a positive result (T/C % ≧ 125).
L1210 : 10^5 cells/mouse, *i.p.-i.p.*, CDF_1 mice (6 mice/group).
The number in parenthesis indicates one 30-d survivor out of 6 mice.

and nitrato complexes were both effective. As shown in Table III, Pt(II) complexes of *R*- and *S*-pnOH exhibited remarkably different activities as compared to the racemic ones. That is, $PtCl_2$(*R*-pnOH) exhibited the highest activity with a T/C % value of 231, and one mice survived out of six. Among the Pt(II) complexes examined, those containing *R*-pnOH have a superior effect to those containing *S*-pnOH or racemic pnOH. This tendency has been found among Pt(II) complexes of optically active dach, perhaps due to effects on the interaction with deoxyribonucleic acid (DNA).[2,3]

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