The bridging, C-shaped $(CPh)_4$ unit is essentially identical in both anion and cation, as are the positions of the two terminal chlorine atoms. In the cation the chlorine atoms that occur as bridges between the halves of the anion are replaced by THF molecules.

Structural Relationship of Cation to Anion. From a formal point of view there is a very simple and direct relationship between the structure and bonding in the cations and the same features of the anion in this compound. This is shown schematically in Scheme I. To go from the tetranuclear anion to a pair of the dinuclear cations requires (1) extrusion of the bridging oxide ion and two of the bridging chloride ions, (2) movement of one chloride ion into a bridging position between two of the strongly bonded niobium atoms, and (3) entry of four THF molecules into each dinuclear fragment.

Concluding Remarks. The isolation of a compound containing the $[Nb_2Cl_3(CPh)_4(THF)_4]^+$ ion fulfills an earlier suggestion[2,4] that half of the oxo-centered anion, with appropriate adjustments, should be a stable entity. The fact that this cation has actually been obtained in combination with the anion leads an esthetic touch to the structure that is as welcome as it was unanticipated.

Acknowledgment. We thank the Robert A. Welch Foundation, Grant No. A-494, for support.

Supplementary Material Available: Tables of detailed crystal data, general displacement parameters, and complete bond distances and angles (12 pages); a table of observed and calculated structure factors (33 pages). Ordering information is given on any current masthead page.

Contribution from the Department of Synthetic Chemistry, Faculty of Engineering, The University of Tokyo, Hongo, Tokyo 113, Japan

Highly Active Antitumor Platinum(II) Complexes of Amino Sugars

Taro Tsubomura,*,† Masumi Ogawa, Shigenobu Yano,*,‡ Kimiko Kobayashi,§ Tosio Sakurai,§ and Sadao Yoshikawa∥

Received August 15, 1989

The syntheses, structures, spectroscopic properties, and antitumor activities of a series of platinum(II) diamino sugar complexes, $[PtCl_2(\text{diamino sugar})]$, have been studied. The molecular structure of one of these is described. Crystal data for $[PtCl_2(\text{Me-ManNN})]\cdot H_2O$ (Me-ManNN = methyl 2,3-diamino-2,3-dideoxy-α-D-mannopyranoside) are as follows: $C_7H_{18}N_2O_5Cl_2Pt$; fw = 476.2 monoclinic, $P2_1$, a = 10.048 (2) Å, b = 8.725 (2) Å, c = 7.584 (2) Å, β = 90.67 (2)°, V = 664.8 (3) Å^3, D_c = 2.39 g cm^{-3}, D_o = 2.37 g cm^{-3}, Z = 2, and μ = 110.8 cm^{-1} (Mo Kα). Antitumor activity was investigated against S180 and L1210 tumors. In the S180 study, the life span of mice treated with $[PtCl_2(\text{GlcNN})]\cdot H_2O$ (GlcNN = 2,3-diamino-2,3-dideoxy-D-glucose) increased, and the T/C value was up to 410%. Other compounds also showed high activities (T/C = 200–380%) against S180. The correlation between the chelate conformation of diamino sugar ligands and the antitumor activity is discussed.

Since the antitumor activity of cisplatin, *cis*-$[PtCl_2(NH_3)_2]$, was discovered by Rosenberg et al.,[1] many platinum-group metal complexes have been prepared, and their activities were examined.[2-4] Besides platinum complexes, ruthenium, rhodium, palladium, and other metal complexes such as *cis*-$[Ru^{II}Cl_2(dmso)_4]$, $[Ru^{III}(NH_3)_5(H_2O)]^{3+}$, $[Rh^{I}(pyR)(cod)]^+$, and $[Ti(Cp)_2Cl_2]$, where pyR = *N*-(3-pyridinylmethylene)alkylamine, cod = 1,5-cyclooctadiene, and Cp = cyclopentadienyl, were found to show antitumor activity.[2,3] Among these metal complexes, platinum(II) complexes have been most extensively studied in both preparation and clinical test. Chargeless platinum(II) complexes of the *cis*-$[PtX_2L_2]$ type generally show antitumor activity, where X_2 represents anionic monodentate or bidentate "leaving group" ligands and L_2 represents monodentate or bidentate neutral ligands. Cisplatin is effective against the tumors of bladder, testicle, ovary, etc., but it has high toxicity including nephrotoxicity, nausea, and ototoxicity.[2] In particular, kidney toxicity is the most serious problem.[5] To attain lowered toxocity and enhanced solubility, much work has been devoted to the preparation of new platinum complexes having various anionic "leaving group" ligands instead of chloride ions. These complexes include "second-generation drugs", for example, *cis*-(cyclobutanedicarboxylato)diammineplatinum(II), and (malonato)(1,2-diaminocyclohexane)platinum(II), but in almost all complexes, ammonia or simple alkylamines, which are toxic themselves, have been used as the neutral ligands.[2,3,6]

Many anticancer reagents having sugar residues such as bleomycine, adriamycin, and many antibiotics are now widely used clinically. The former two form metal complexes containing a sugar residue and have peculiar physiological activity.[7] It is therefore very interesting to examine the activity of platinum complexes having sugar residues in vivo.

As a significant part of our program to clarify the nature of sugar-transition-metal interactions,[8] we have synthesized and fully characterized several cisplatin-type complexes of diamino sugars. These platinum diamino sugar complexes show high antitumor activity against sarcoma S180. In this paper, the syntheses, structures, physical properties, and antitumor screening data of a series of platinum diamino sugar complexes are described in detail.

† Present address: Department of Industrial Chemistry, Faculty of Engineering, Seikei University, Musashino, Tokyo 180, Japan.
‡ Present address: Department of Chemistry, Faculty of Science, Nara Women's University, Nara 630, Japan.
§ Present address: The Institute of Physical and Chemical Research (RIKEN), Wako, Saitama 351, Japan.
∥ Present address: Applied Chemistry, Faculty of Science and Technology, Keio University, Kouhoku, Yokohama 223, Japan.

(1) Rosenberg, B.; VanCamp, L.; Trosco, J. E.; Mansour, V. H. *Nature* **1969**, *222*, 385.
(2) Umapathy, P. *Coord. Chem. Rev.* **1989**, *95*, 129.
(3) *Platinum, Gold, and other Metal Chemotherapeutic Agents*; Lippard, S. J., Ed.; ACS Symposium Series 209; American Chemical Society: Washington, DC, 1983.
(4) *Platinum Coordination Complexes in Cancer Chemotherapy*; Hacker, M. P., Douple, E. B., Krakoff, I. H., Eds., Multinus Nijhoff: Boston, MA, 1984.
(5) Borch, R. F.; Dedon, P. C.; Montine, T. J. *Dev. Oncol.* **1988**, *53*, 190.
(6) Hollis, L. S.; Amundsen, A. R.; Stern, E. M. *J. Am. Chem. Soc.* **1985**, *107*, 274.
(7) *Inorganic Chemistry in Biology and Medicine*; Martel, A. E., Ed.; ACS Symposium Series 140; American Chemical Society: Washington, DC, 1980.
(8) Yano, S.; Takizawa, S.; Sugita, H.; Takahashi, K.; Tsubomura, T.; Shioi, H.; Yoshikawa, S. *Carbohydr. Res.* **1985**, *142*, 179. Shioi, H.; Yano, S.; Toriumi, K.; Ito, T.; Yoshikawa, S. *J. Chem. Soc., Chem. Commun.* **1983**, 201. Tsubomura, T.; Yano, S.; Toriumi, K.; Ito, T.; Yoshikawa, S. *Polyhedron* **1983**, *2*, 123. Tsubomura, T.; Yano, S.; Toriumi, K.; Ito, T.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1833. Tsubomura, T.; Yano, S.; Toriumi, K.; Ito, T.; Yoshikawa, S. *Inorg. Chem.* **1985**, *24*, 3218. Tsubomura, T.; Yano, S.; Toriumi, K.; Ito, T.; Yoshikawa, S. *Inorg. Chem.* **1986**, *25*, 392.

0020-1669/90/1329-2622$02.50/0

Experimental Section

2,3-Diamino-2,3-dideoxy-D-glucose Dihydrochloride (GlcNN·2HCl). This was prepared from benzyl 2-*N*-acetyl-4,6-*O*-benzylidene-D-glucosaminide by the method of Meyer zu Reckendorf.[9]

Methyl 2,3-Diamino-2,3-dideoxy-β-D-glucopyranoside Dihydrochloride (Me-GlcNN·2HCl). This compound was prepared according to the method of Baer[10,12,13] with a slight modification. Methyl 3-nitro-3-deoxy-β-D-glucopyranoside (**1**) was prepared from methyl β-D-glucopyranoside (Sigma Co.) by the method of Baer.[10] The acetal exchange method[11] was adopted to prepare the 4,6-*O*-benzylidene derivative of **1**. A mixture of **1** (11.1 g), dimethoxytoluene (7.6 g), dry DMF (35 mL), and *p*-toluenesulfonic acid (0.030 g) was placed in a rotary evaporator and heated at 60 °C under reduced pressure with a water aspirator for 40 min. Then the mixture was heated at 90 °C to remove the solvent. Aqueous $NaHCO_3$ solution (0.05 M, 80 mL) was added to the resultant solution, and on filtration, 10 g of methyl 4,6-*O*-benzylidene-3-nitro-β-D-glucopyranoside was obtained. It was treated with mesyl chloride and triethylamine in ether[12] to give methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-erythrohexo-2-enopyranoside (**2**). Me-GlcNN·2HCl was synthesized from **2** by a three-step reaction as described by Baer.[13]

Methyl 2,3-Diamino-2,3-dideoxy-α-D-mannopyranoside Dihydrochloride (Me-ManNN·HCl). Methyl 2-acetamido-3-amino-2,3-dideoxy-α-D-mannopyranoside (**3**) was prepared by the reported method.[14] The starting material for **3** was methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-erythrohexo-2-enopyranoside, which was synthesized in a manner described by the same group.[15] A solution of 1.0 g of **3** dissolved in 60 mL of 1 N hydrochloric acid was heated at 90 °C for 1 h. The mixture was evaporated to a small volume, and a small amount of water was added. It was then evaporated again. This procedure was repeated twice more to remove hydrogen chloride. Finally, ethanol was added, and the solution was evaporated to a syrup. It was dissolved in a small amount of methanol, and ethyl acetate was added to give a white powder (0.6 g). Proton NMR revealed that one-fourth of the amount of **3** used remained unhydrolyzed. The mixture was, however, used in the preparation of platinum complexes without further purification.

Benzyl 3,4-Diamino-3,4-dideoxy-β-D-arabinopyranoside Dihydrochloride (Bn-D-AraNN·2HCl). Benzyl 3,4-diazido-3,4-dideoxy-β-D-arabinopyranoside (2.3 g), which was prepared by the method of Janairo,[16] was hydrogenated at atmospheric pressure in the presence of 0.5 g of 10% palladium–charcoal for 3.5 h. Hydrochloric acid (1 N, 15 mL) was then added, and the solution was evaporated under reduced pressure to a syrup. Workup with methanol and ether gave a white precipitate (1.4 g). ^{1}H NMR (D_2O): δ 4.67 (d, 1 H, J = 7.3 Hz, 1-C*H*), 3.91 (dd, 1 H, J = 7.3, 11.0 Hz, 2-C*H*), 3.83 (dd, 1 H, J = 11.0, 3.7 Hz, 3-C*H*), 4.07 (ddd, 1 H, J = 3.7, 1.7, 2.1 Hz, 4-C*H*), 4.02 (dd, 1 H, J = 1.7, 13.7 Hz, 5-C*H*H'), 4.22 (dd, 1 H, J = 2.1, 13.7 Hz, 5-CH*H'*), 4.83 (d, 1 H, J = 11.6 Hz, CH*H'*-Ph), 5.01 (d, 1 H, J = 11.6 Hz, C*H*H'-Ph), 7.52 (m, 5 H, Ph).

Benzyl 3,4-Diamino-3,4-dideoxy-β-L-arabinopyranoside Dihydrochloride (Bn-L-AraNN·2HCl). This was prepared from 3,4-diazido-3,4-dideoxy-β-L-arabinopyranoside by the same method as that used for benzyl 3,4-diamino-3,4-dideoxy-β-D-arabinopyranoside dihydrochloride described above.

[$PtCl_2$(GlcNN)]·H_2O. This complex was prepared by a method analogous to that used in the preparation of the platinum diamine complexes reported by Appleton and Hall.[17] Commercial dipotassium tetrachloroplatinate (0.5 mmol, 207 mg) was dissolved in 1 mL of water. If there were yellow insoluble crystals, which might be potassium hexachloroplatinate(IV), they were filtered off. To the solution was added 0.5 mmol of GlcNN·2HCl and concentrated KOH solution containing 0.75 mmol of KOH, and the mixture was stirred until yellow crystals formed. The mixture was kept in a refrigerator for 2 days. The yellow crystals were filtered, washed with a small amount of methanol and then with ether, and dried in vacuo (90 mg, 39%). They were recrystallized from 1 N hydrochloric acid. Anal. Calcd for $PtCl_2C_6H_{16}N_2O_5$: C, 15.6; H, 3.5; N, 6.1; Cl, 15.3. Found: C, 15.5; H, 3.4; N, 5.9; Cl, 15.3. Solubility in 35 °C water was >20 mg/mL. ^{1}H NMR (D_2O, mixture of α and β anomer): for α anomer, δ 5.40 (d, 1 H, J = 3.3 Hz, 1-C*H*), 2.95 (dd, 1 H, J = 3.3, 12.6 Hz, 2-C*H*), 3.04 (dd, 1 H, J = 12.6, 9.7 Hz, 3-C*H*), 3.63 (dd, 1 H, J = 9.7, 9.5 Hz, 4-C*H*), 3.76 (ddd, 1 H, J = 9.5, 4.9, 2.1 Hz, 5-C*H*), 3.83 (dd, 1 H, J = 4.9, 12.2 Hz, 6-C*H*H'), 3.92 (dd, 1 H, J = 2.1, 12.2 Hz, 6-CH*H'*); for β anomer, δ 4.88 (d, 1 H, J = 7.9 Hz, 1-C*H*), 2.66 (dd, 1 H, J = 7.9, 12.3 Hz, 2-C*H*), 2.89 (dd, 1 H, J = 12.3, 10 Hz, 3-C*H*), 3.62 (dd, 1 H, J = 10, 9.5 Hz, 4-C*H*), 3.45 (ddd, 1 H, J = 9.5, 5.2, 2.1 Hz, 5-C*H*), 3.79 (dd, 1 H, J = 5.2, 12.2 Hz, 6-C*H*H'), 3.97 (dd, 1 H, J = 2.1, 12.2 Hz, 6-CH*H'*).

[$PtCl_2$(Me-GlcNN)]·$^3/_2H_2O$. Commercial $K_2[PtCl_4]$ (0.5 mmol, 207 mg) was dissolved in 1 mL of water, and the insoluble impurity was filtered off. To the solution was added 1 mmol of Me-GlcNN·2HCl (140 mg) and 1 mmol of Na_2CO_3, and the solution was stirred until a yellow precipitate appeared. After the mixture was kept in a refrigerator for 2 days, yellow crystals were collected by filtration. A further crop of crystals was obtained as follows. The yellow-orange filtrate was passed through a glass column filled with Sephadex G-10 gel (2 × 30 cm). A yellow fraction was collected and concentrated to a small volume under reduced pressure to give yellow crystals. The combined crystals were recrystallized from a minimum amount of hot water; yield 55 mg (23%). Anal. Calcd for $PtCl_2C_7H_{19}N_2O_{5.5}$: C, 17.3; H, 4.0; N, 5.8; Cl, 14.6. Found: C, 17.0 H, 3.5; N, 5.8; Cl, 15.0. Solubility in 35 °C water was >25 mg/mL. ^{1}H NMR (D_2O): δ 4.60 (d, 1 H, J = 7.8 Hz, 1-C*H*), 2.66 (dd, 1 H, J = 7.8, 12.0 Hz, 2-C*H*), 2.87 (dd, 1 H, J = 12.0, 9.7 Hz, 3-C*H*), 3.61 (dd, 1 H, J = 9.7, 10 Hz, 4-C*H*), 3.45 (ddd, 1 H, J = 10, 5.6, 2.3 Hz, 5-C*H*), 3.80 (dd, 1 H, J = 5.6, 12.4 Hz, 6-C*H*H'), 4.00 (dd, 1 H, J = 2.3, 12.4 Hz, 6-CH*H'*), 3.62 (s, 3 H, O-CH_3).

[$PtCl_2$(Me-ManNN)]·H_2O. This complex was prepared from $K_2[PtCl_4]$ and Me-ManNN·2HCl by the same method as that used for [$PtCl_2$(Me-GlcNN)]·$^3/_2H_2O$; yield 33%. Anal. Calcd for $PtCl_2C_7H_{18}N_2O_5$: C, 17.7; H, 3.8; N, 5.9; Cl, 14.9. Found: C, 17.4; H, 3.7; N, 5.8; Cl, 14.6. Solubility in 35 °C water was >2.5 mg/mL. ^{1}H NMR (D_2O): δ 4.86 (d, 1 H, J = ~0 Hz, 1-C*H*), 3.33 (dd, 1 H, J = ~0, 4.7 Hz, 2-C*H*), 3.01 (dd, 1 H, J = 4.7, 10.1 Hz, 3-C*H*), 4.09 (dd, 1 H, J = 10.1, 10 Hz, 4-C*H*), 3.74 (ddd, 1 H, J = 10, 5.2, 2.4 Hz, 5-C*H*), 3.89 (dd, 1 H, J = 5.2, 12.5 Hz, 6-C*H*H'), 3.96 (dd, 1 H, J = 2.4, 12.5 Hz, 6-CH*H'*), 3.46 (s, 3 H, O-CH_3).

[$PtCl_2$(Bn-D-AraNN)]. Commercial $K_2[PtCl_4]$ (0.5 mmol, 207 mg) was dissolved in 2 mL of water, and the insoluble impurity was filtered off. To the solution was added 0.5 mmol (155 mg) of Bn-D-AraNN·2HCl and $NaHCO_3$ solution (1 mmol in 3 mL), and the mixture was stirred until a yellow precipitate appeared. The mixture was kept in a refrigerator for 2 days. The crystals obtained were recrystallized from a minimum amount of hot water; yield 90 mg (35%). Anal. Calcd for $PtCl_2C_{12}H_{18}N_2O_3$: C, 28.6 H, 3.6; N, 5.6; Cl, 14.1. Found: C, 28.3; H, 3.5; N, 5.4; Cl, 13.9. Solubility in 35 °C water was 1.6 mg/mL. ^{1}H NMR (D_2O): δ 4.51 (d, 1 H, J = 7.3 Hz, 1-C*H*), 3.93 (dd, 1 H, J = 7.3, 10.0 Hz, 2-C*H*), 2.92 (dd, 1 H, J = 10.0, 5.4 Hz, 3-C*H*), 3.33 (m, 1 H), 4.02 (m, 2 H), 7.52 (m, 5 H, *Ph*); some peaks are hidden behind the solvent (D_2O) peak.

[$PtCl_2$(Bn-L-AraNN)]. This was prepared from $K_2[PtCl_4]$ and Bn-L-AraNN·2HCl by the same procedure as that for [$PtCl_2$(Bn-D-AraNN)]. Anal. Calcd for $PtCl_2C_{12}H_{18}N_2O_3$: C, 28.6; H, 3.6; N, 5.6; Cl, 14.1. Found: C, 28.4, H, 3.5; N, 5.4; Cl, 13.7.

X-ray Crystal Structure Determination of [$PtCl_2$(Me-ManNN)]·H_2O. Crystal Data. $C_7H_{18}N_2O_5Cl_2Pt$, yellow prism, fw = 476.2, monoclinic, $P2_1$, a = 10.048 (2) Å, b = 8.725 (2) Å, c = 7.584 (2) Å, β = 90.67 (2)°, V = 664.8 (3) Å^3, D_c = 2.39 g cm^{-3}, D_o = 2.37 g cm^{-3}, Z = 2, μ = 110.8 cm^{-1} (Mo Kα), transmission range = 0.032–0.116.

Crystallographic Measurements. The crystal used had dimensions of 0.21 × 0.22 × 0.25 mm^3. It was mounted on a Rigaku AFC-4 four-circle diffractometer equipped with graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å). Cell parameters were determined from 20 reflections with 23° < 2θ < 29°. The agreement of the equivalent reflections (hkl and $h\bar{k}l$) was tested in the range $-3 < hkl < 3$. Intensity data were collected by ω scan (2θ < 30°) and ω–2θ scan methods (2θ > 30°), where scan speed = 4°/min, and scan width = (1.2 + tan θ)°. The intensities of three standard reflections monitored in every 100 reflections gradually decreased over the course of measurements by 4%, so that all the intensity data were corrected for the decay. A set of 1736 reflections within a sphere limited by 2θ = 55° was measured, and 1510 measurements with $I > 3\sigma(I)$ were used for the structure determination. These data were corrected for the Lorentz-polarization effect and for absorption (Gaussian integration,[18] grid 6 × 6 × 6).

Crystal Structure Determination. Calculations were performed with a universal crystallographic program, UNICS III.[19] Atomic scattering

(9) Meyer zu Reckendorf, W. *Methods Carbohydr. Chem.* **1972**, *6*, 266.
(10) Baer, H. H. *Methods Carbohydr. Chem.* **1972**, *6*, 245.
(11) Evans, M. E. *Methods Carbohydr. Chem.* **1980**, *8*, 313.
(12) Baer, H. H.; Georges, F. F. Z. *J. Org. Chem.* **1976**, *41*, 3474.
(13) Baer, H. H.; Kienzle, F. *J. Org. Chem.* **1969**, *34*, 3848.
(14) Baer, H. H.; Rank, W. *Can. J. Chem.* **1974**, *52*, 2257.
(15) Baer, H. H.; Rajabalee, F.; Kienzle, F. *J. Org. Chem.* **1969**, *34*, 4204; see footnote 9. Baer, H. H. Kienzle, F. *Can. J. Chem.* **1967**, *45*, 983.
(16) Janairo, G.; Malik, A.; Voelter, W. *Liebigs Ann. Chem.* **1985**, 653.
(17) Appleton, T. G.; Hall, J. R. *Inorg. Chem.* **1970**, *9*, 1800.
(18) Busing, W. R.; Lavy, H. A. *Acta Crystallogr.* **1957**, *10*, 180.
(19) Sakurai, T.; Kobayashi, K. *Rikagaku Kenkyuusho Houkoku* **1979**, *55*, 69.

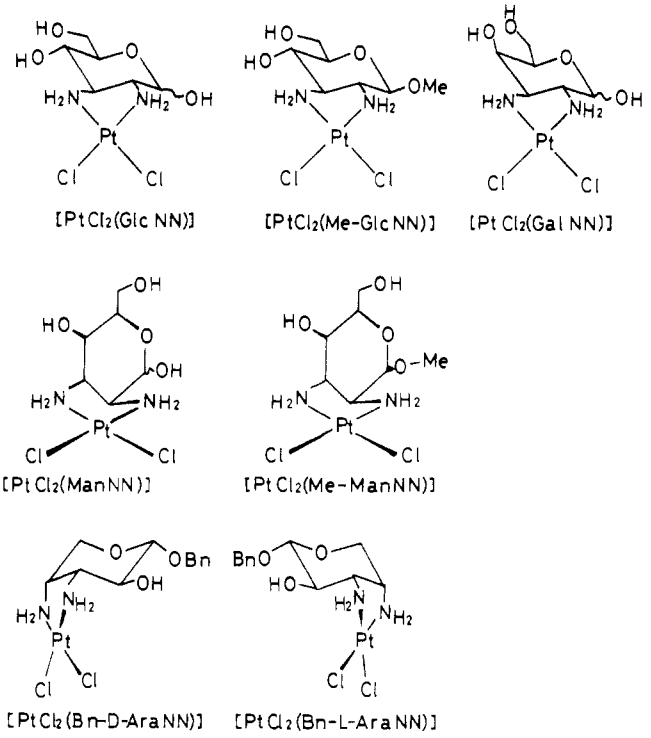

Figure 1. Structures of platinum diamino sugar complexes.

factors are taken from ref 20. The location of the platinum atom was determined from the three-dimensional Patterson map. The remaining non-hydrogen atoms were progressively found by a standard Fourier synthesis and a block-diagonal least-squares technique. Least-squares refinement of the positional and anisotropic thermal parameters of the non-hydrogen atoms gave convergence at $R = 0.046$. At this stage, when the signs of f'' parameters were reversed to test the absolute chirality, the convergence reached $R = 0.049$, which is significantly larger than the former value. The initial values of the parameters of hydrogen atoms, except H-O2 and H-O4, were calculated at idealized positions, and these positional and isotropic thermal parameters were also refined. At this point, convergence reached $R = 0.036$, but some observed diffraction intensities of the reflections with low 2θ were found to be very small compared to the calculated values. Further refinement of the positional and anisotropic thermal parameters of non-hydrogen atoms, positional parameters of hydrogen atoms, and an extinction coefficient by the full-matrix least-squares method,[21] converged at $R = 0.028$ and $R_w = 0.030$. In this refinement, the weighting scheme $1/w = \sigma(F_o)^2$ was employed, and $\sum w(F_o - F_c)^2$ was minimized. The anisotropic type-I extinction effect, which was introduced by Coppens and Hamilton,[22] was taken into account in this calculation.

Spectroscopic Measurements. Electronic absorption spectra of 10^{-3} M aqueous solutions of the platinum complexes were recorded at room temperature on a Hitachi Model 340 spectrophotometer just after dissolution. CD spectra of the same solutions were measured on a JASCO J-500 spectropolarimeter at room temperature. ^{1}H NMR spectra of D_2O solutions ($(1-3) \times 10^{-3}$ M) were obtained with a JEOL JNM-GX400 spectrometer at room temperature, ^{t}BuOH being used as the internal reference.

Antitumor Activity Test. Antitumor activity was tested by Ajinomoto Co., Inc.

Sarcoma 180. 10^6 sarcoma S180 cells were intraperitoneally (ip) transplated into female ICR/CRJ mice, whose ages were 5–7 weeks. Then the mice were divided into several groups consisting of five or seven animals each. The first group served as control. Physiological saline solutions of the platinum complexes were given by the ip method into each of the groups the next day soon after the dissolution. The mean survival time of the treated animals (T) was compared with that of untreated control animals (C).

(20) *International Tables for X-ray Crystallography* Kynoch Press: Birmingham, England 1962; Vol. III.
(21) Coppens, P.; Guru Row, T. N.; Leung, p.; Stevens, E. D.; Becker, P. J.; Yang, Y. W. *Acta Crystallogr., Sect. A* **1979**, *35*, 63.
(22) Coppens, P. J.; Hamilton, W. C. *Acta Crystallogr., Sect. A* **1970**, *26*, 71.

Table I. Atomic Parameters for Non-Hydrogen Atoms[a]

Atom	x	y	z	B_{eqv}
Pt	361.02 (4)	0 (0)	124.58 (5)	1.6
Cl1	357.0 (4)	−62.9 (4)	−170.6 (5)	2.9
Cl2	382.2 (4)	−252.8 (4)	210.9 (5)	3.0
O1	347.6 (8)	459.2 (9)	567 (1)	2.5
O2	99 (1)	387 (1)	89 (1)	2.6
O3	168.9 (7)	287 (1)	555 (1)	1.8
O4	−85 (1)	425 (1)	594 (1)	3.7
N1	354.4 (9)	72 (1)	378 (1)	2.0
N2	353 (1)	227 (1)	69 (2)	2.4
C1	309 (1)	306 (2)	556 (2)	1.9
C2	370 (1)	241 (1)	391 (2)	1.7
C3	301 (1)	313 (1)	226 (2)	1.4
C4	152 (1)	302 (2)	235 (2)	1.7
C5	104 (1)	372 (2)	408 (2)	2.2
C6	−44 (1)	352 (2)	436 (2)	3.1
C7	298 (1)	536 (2)	720 (2)	3.2
OC	922 (1)	212 (1)	917 (2)	4.1

[a] Positional parameters are multiplied by 10^3. Thermal parameters are given by equivalent temperature factors (Å^2).

Table II. Bond Distances (Å) for $[PtCl_2(Me\text{-}ManNN)]$[a]

Pt–Cl1	2.305 (4)	Pt–Cl2	2.310 (4)
Pt–N1	2.02 (1)	Pt–N2	2.03 (1)
O1–C1	1.39 (2)	O1–C7	1.43 (2)
O2–C4	1.43 (2)	O3–C1	1.42 (1)
O3–C5	1.48 (2)	O4–C6	1.43 (2)
N1–C2	1.49 (2)	N2–C3	1.51 (2)
C1–C2	1.51 (2)	C2–C3	1.55 (2)
C3–C4	1.50 (2)	C4–C5	1.53 (2)
C5–C6	1.51 (2)		

[a] Standard deviations are given in parentheses.

Table III. Bond Angles (deg) for $[PtCl_2(Me\text{-}ManNN)]$[a]

Cl1–Pt–Cl2	92.8 (1)	Cl1–Pt–N1	174.8 (3)
Cl1–Pt–N2	91.8 (3)	Cl2–Pt–N1	91.8 (3)
Cl2–Pt–N2	174.7 (3)	N1–Pt–N2	83.8 (5)
C1–O1–C7	114 (1)	C1–O3–C5	111.9 (9)
Pt–N1–C2	111.4 (8)	Pt–N2–C3	109.6 (8)
O1–C1–O3	113 (1)	O1–C1–C2	107 (1)
O3–C1–C2	111 (1)	N1–C2–C1	113 (1)
N1–C2–C3	108 (1)	C1–C2–C3	110 (1)
N2–C3–C2	106.3 (9)	N2–C3–C4	111 (1)
C2–C3–C4	112 (1)	O2–C4–C3	107 (1)
O2–C4–C5	110 (1)	C3–C4–C5	109 (1)
O3–C5–C4	108 (1)	O3–C5–C6	105 (1)
C4–C5–C6	113 (1)	O4–C6–C5	111 (1)

[a] Standard deviations are given in parentheses.

L1210. 10^5 L1210 cells were ip transplanted into female BDF_1 mice, whose ages were 5–6 weeks. Physiological saline solutions of the platinum complexes were ip given next day into a group consisting of five mice. T/C values were evaluated as described above.

Results and Discussion

2,3-Diamino- or 3,4-diaminoaldoses, which are regarded as substituted ethylenediamine ligands, were used in this study. They are expected to coordinate to the platinum ion and form stable five-membered chelates. Although some difficulties were anticipated in the isolation of these complexes because of the general sugar properties of high solubility and reducing ability, crystals of (diamino sugar)platinum metal complexes were easily isolated. The structures of a series of the platinum complexes prepared in this study are shown in Figure 1. The structures of the two platinum complexes $[PtCl_2(GalNN)]$ and $[PtCl_2(ManNN)]$ (ManNN = 2,3-diamino-2,3-dideoxymannose and GalNN = 2,3-diamino-2,3-dideoxygalactose) synthesized by Suami et al. are included in the figure.

Many of these complexes, especially those containing Me-GlcNN and GlcNN, showed high solubility in water in comparison with cisplatin.

Molecular and Crystal Structure of $[PtCl_2(Me\text{-}ManNN)]\cdot H_2O$. Atomic coordinates of non-hydrogen atoms, bond lengths, and

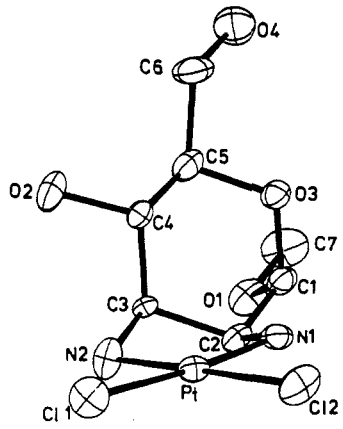

Figure 2. ORTEP drawing of $[PtCl_2(Me\text{-}ManNN)]$.

bond angles are listed in Tables I–III, respectively. An ORTEP drawing of the complex is shown in Figure 2. A diamino sugar, Me-ManNN, is bound to platinum through N1 and N2 atoms. The pyranose ring of Me-ManNN has the normal α-$^4C_1$ chair conformation. The dihedral angles within the pyranose skeleton range from 51 to 69°, which does not show much deviation from the gauche angle, 60°, although in solution a distortion around C1 was observed as described later. The pyranose ring is in nearly perpendicular orientation with respect to the coordination square plane around the platinum atom. Amino groups N1 and N2 are axial and equatorial, respectively, with respect to the pyranose ring. Pt–N1–C2–C3–N2 chelate adopts the λ-gauche conformation. Two chloride anions and a bidentate Me-ManNN ligand complete the square-planar coordination around the platinum atom. The distances between the best fitted plane and each atom around the platinum atom are smaller than 10 pm, as follows: Pt, 0.001 (4) pm; Cl1, 0.7 (1) pm; Cl2, 1.0 (1) pm; N1, 8 (1) pm; N2, 9 (1) pm.

In the crystal of $[PtCl_2(meso\text{-dach})]$ (dach = 1,2-diaminocyclohexane), a significantly short platinum–platinum distance was found.[23] It was reported to be caused by hydrogen bonding between the amino and chloride groups. The molecular structure of $[PtCl_2(Me\text{-}ManNN)]$ resembles that of $[PtCl_2(meso\text{-dach})]$, but the platinum–platinum distance is long (>5 Å) in this platinum Me-ManNN complex.

Spectroscopic Results of Platinum Complexes. Pyranose conformations in the platinum complexes containing GlcNN, Me-GlcNN, and Me-ManNN ligands were clarified by ^1H NMR data, especially by vicinal proton–proton coupling constants. For GlcNN and Me-GlcNN complexes, coupling constants J_{HH} are as follows: J_{H2H3} = 12.0–12.6 Hz; J_{H3H4} and J_{H4H5} = 9.5–10.0 Hz. These data support the all trans conformation; i.e., pyranose rings adopt the $^4C_1$ conformation. For the Me-ManNN complex, J_{H2H3} = 4.7 Hz and J_{H3H4} and J_{H4H5} = 10–10.1 Hz. These data also show that the pyranose ring of Me-ManNN ligands has the same conformation. However, the J_{H1H2} value of $[PtCl_2(Me\text{-}ManNN)]$ is almost 0, implying that the conformation around C1 of the mannopyranose ring is somewhat distorted. The conformation of Bn-D-Ara ligand was determined to $^1C_4$ in the platinum complex. In the $[PtCl_2(GlcNN)]$ complex, both α- and β-GlcNN are present in aqueous solution. The ratio of α to β anomers in D_2O at room temperature was determined to be 65:35.

Absorption and circular dichroism spectra of these platinum complexes are shown in Figure 3. Three peaks are observed in these absorption spectra. They are ascribable to the spin-allowed and spin-forbidden d–d transitions $^1A_{1g} \rightarrow {}^3E_g$ (27×10^3 cm^{-1}), $^1A_{1g} \rightarrow {}^1A_{2g}$ (33×10^3 cm^{-1}), and $^1A_{1g} \rightarrow {}^1E_g$ (38×10^3 cm^{-1}), respectively.[24]

Circular dichroism spectra of these platinum complexes can be classified into two groups. The first group consisting of GlcNN and Me-GlcNN complexes shows only two positive peaks in the

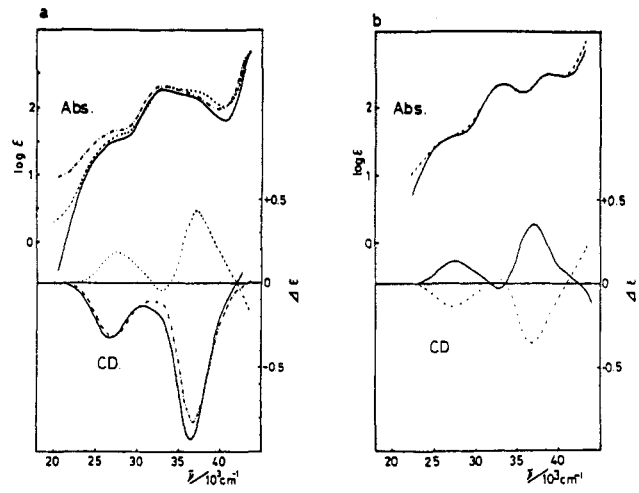

Figure 3. Absorption and CD spectra of platinum complexes: (a) (—) $[PtCl_2(GlcNN)]$ (–·–) $[PtCl_2(Me\text{-}GlcNN)]$, (--) $[PtCl_2(Me\text{-}ManNN)]$; (b) (—) $[PtCl_2(Bn\text{-}D\text{-}AraNN)]$, (--) $[PtCl_2(Bn\text{-}L\text{-}AraNN)]$.

CD spectra, each of which corresponds to the first and third absorption bands described above. The CD spectra of the second group consisting of other complexes have three peaks. Two of them corresponding to the first and third absorption bands have the same sign, and the remaining peak has the opposite sign. These features of the CD spectra are associated with the structure of the complexes. The pyranose ring in the first group lies in the same plane as that of the platinum coordination square. The five-membered chelate ring in the diamino sugar has the δ conformation. The structures of these complexes are considered to be an analogue of those of $[PtCl_2((+)\text{-}trans\text{-}1,2\text{-diaminocyclohexane})]$ complexes. Actually, the CD spectra of these platinum GlcNN and Me-GlcNN complexes resemble that of the (+)-*trans*-1,2-diaminocyclohexane complex.[25] On the other hand, in the second group of complexes, two amino groups, N1 and N2, have axial and equatorial orientation with respect to the pyranose ring, respectively. Therefore, the pyranose ring has a nearly perpendicular orientation with respect to the coordination square plane around the platinum atom. The structures of the ligands of the second group correspond to that of the configuration of *cis*-1,2-diaminocyclohexane, which is an achiral molecule. These diamino sugar complexes are the first example of chiral platinum complexes having a *meso*-diaminocyclohexane-type ligand. In the second group of complexes, Me-ManNN and Bn-D-AraNN complexes have the λ conformation chelate and have a positive CD band in the first absorption region, whereas the Bn-L-AraNN complex has the δ conformation chelate and has a negative CD band in the region.

Solution Stability of Platinum Complexes. *cis*-$[PtCl_2(NH_3)_2]$, *cis*-DDP, is known to lose its chloride ions, hydrolyze, and form reactive aquo complexes in aqueous media. Equilibrium was reported for substitution of Cl^- by H_2O in *cis*-DDP in detail.[26] At pH 7, the *cis*-$[PtCl_2(NH_3)]$ molecule predominates in the presence of 0.1 M Cl^-, as occurs in blood plasma. But at low Cl^- concentration (4 mM), as might occur within a cell, and pH 7, the chloro–hydroxo complex becomes dominant. Therefore *cis*-DDP loses its reactivity in blood because of high Cl^- concentration, but after diffusion into a cell, reactions with biological targets can take place.

According to the above described aquation process, the absorption spectra of an aqueous solution of *cis*-DDP undergo changes. We obtained the first-order kinetic constant of aquation as 1.4×10^{-4} s^{-1} from the absorption change at 300 nm of the initial state of the reaction (reported value = 8×10^{-5} s^{-1}).[27] We found that the absorption spectra of the aqueous solution of platinum sugar complexes also demonstrate a change similar to

(23) Lock, C. J. L.; Pilon, P. *Acta Crystallogr., Sect. B* **1981**, *37*, 45.
(24) Ito, H.; Fujita, J.; Saito, K. *Bull Chem. Soc. Jpn.* **1967**, *40*, 2584.
(25) Noji, M.; Okamoto, K.; Kidani, Y. *J. Med. Chem.* **1981**, *24*, 508.
(26) Martin, R. B. In ref 3, p 231.
(27) Reishus, J. W.; Martin, D. S., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 2457.

Table IV. Antitumor Activities of Platinum Complexes[d]

	dose, mg/kg	mean lifetime,[a] days T	C	T/C, %	n[c]
	(1) S180				
$[PtCl_2(GlcNN)]\cdot H_2O$	5	13 (2)	10 (2)	120	7
	10	23 (11)	10 (2)	220	7
	20	29 (11)	10 (2)	280	7
	50	42 (11)	10 (2)	410	7
$[PtCl_2(Me\text{-}GlcNN)]\cdot{}^3/_2H_2O$	5	23 (12)	12 (2)	190	5
	10	34 (15)	12 (2)	290	5
	20	33 (11)	12 (2)	280	5
$[PtCl_2(ManNN)]$[b]	5	13 (2)	10 (2)	130	7
	10	28 (17)	10 (2)	270	7
	20	34 (10)	10 (2)	330	7
	50	25 (4)	10 (2)	240	7
$[PtCl_2(Me\text{-}ManNN)]\cdot H_2O$	5	12 (4)	10 (2)	120	7
	10	15 (2)	10 (2)	140	7
	50	24 (15)	10 (2)	230	7
$[PtCl_2(GalNN)]$[b]	5	22 (16)	12 (2)	190	5
	10	22 (7)	12 (2)	190	5
	20	33 (15)	12 (2)	280	5
$[PtCl_2(Bn\text{-}D\text{-}AraNN)]$	5	24 (10)	12 (2)	200	5
	10	27 (9)	12 (2)	230	5
	20	38 (14)	12 (2)	330	5
$[PtCl_2(Bn\text{-}L\text{-}AraNN)]$	5	31 (13)	12 (2)	260	5
	10	46 (7)	12 (2)	390	5
	20	27 (14)	12 (2)	230	5
	(2) L1210				
$[PtCl_2(GlcNN)]\cdot H_2O$	8	10 (1)	10 (1)	100	5
	32	12 (1)	10 (1)	120	5
	64	12 (5)	10 (1)	120	5
$[PtCl_2(Me\text{-}GlcNN)]\cdot{}^3/_2H_2O$	8	13 (1)	11 (1)	120	5
	16	16 (4)	11 (1)	150	5
	32	13 (4)	11 (1)	120	5
$[PtCl_2(ManNN)]$[b]	32	12 (2)	10 (1)	120	5
	64	12 (3)	10 (1)	120	5
$[PtCl_2(Me\text{-}ManNN)]\cdot H_2O$	8	10 (2)	10 (1)	100	5
	32	11 (1)	10 (1)	110	5
$[PtCl_2(GalNN)]$[b]	8	11 (2)	11 (1)	100	5
	16	11 (1)	11 (1)	100	5
	32	12 (1)	11 (1)	110	5
$[PtCl_2(Bn\text{-}D\text{-}AraNN)]$	8	15 (7)	11 (2)	140	5
	16	17 (6)	11 (2)	150	5
	32	15 (4)	11 (2)	130	5
$[PtCl_2(Bn\text{-}L\text{-}AraNN)]$	8	19 (7)	11 (2)	170	5
	16	28 (18)	11 (2)	250	5
	32	24 (23)	11 (2)	210	5

[a] Standard deviations are given in parentheses. [b] Reference 30. [c] Number of mice used in the group. [d] Each value (T, C, and T/C) was rounded off to two significant figures.

that of *cis*-DDP. Preliminary experiments showed that the kinetic constants of the aquation are $(1-2) \times 10^{-4}$ s^{-1}. However in 0.1 M NaCl solution, a very small spectral change was observed for these platinum complexes. Consequently, these platinum sugar complexes are also not reactive in blood, but the reaction with biological targets can occur in the cell after the hydrolysis.

Antitumor Activity. The results of the activity of our compounds against sarcoma S180 and L1210 are tabulated in Table IV. In addition to our preliminary results for GlcNN and Me-ManNN complexes,[28] further results are included. Some test data[30] for the complexes $[PtCl_2(ManNN)]$ and $[PtCl_2(GalNN)]$, which were synthesized by Suami et al., are also included in the table. In general, these complexes show high antitumor activity against S180. The T/C value of cisplatin, $[PtCl_2(NH_3)_2]$, is reported to be 237 (dose 8 mg/kg), which is comparable to our data at the same dose. However, it should be noted that the best effect was observed with our $[PtCl_2(GlcNN)]$ complex at a dose of 50 mg/kg. Since the LD_{50} of cisplatin was 13 mg/kg, such high T/C in high dosage is not expected for cisplatin. These complexes that contain the sugar moieties seemed to be of low toxicity.

Kidani et al. reported an interesting fact that the *trans*-1,2-diaminocyclohexane (dach) complexes are more effective than the cis isomers.[29] The order of the antitumor activity was as follows: 1(*R*),2(*R*)-dach > 1(*S*),2(*S*)-dach > *meso*-dach. When these diamine ligands coordinate to a platinum atom, the former two chelate rings adopt the chiral conformations, δ and λ, respectively. In our diamino sugar complexes, a difference in the antitumor activity is also clearly observed for the isomers of the diamino sugar ligands. Since the small number (five to seven) of mice were used, statistical discussion may be difficult. But some evident differences were observed in these platinum drugs. For example, the best survival time for $[PtCl_2(Bn\text{-}L\text{-}AraNN)]$ was 46 ± 7 days at a dose of 10 mg/kg, whereas the result for the enantiomer, $[PtCl_2(Bn\text{-}D\text{-}AraNN)]$, was 27 ± 9 days at the same dose. Furthermore, the best result for $[PtCl_2(GlcNN)]$ was 42 ± 11 days, but the result for $[PtCl_2(ManNN)]$, where ManNN is a C-2 epimer of GlcNN, was 25 ± 4 days. It is interesting that the complexes of δ-gauche chelates are more effective than those of λ-gauche chelates in both cases.

Almost all complexes do not have high antitumor activity against L1210, but two Bn-AraNN complexes, especially the Bn-L-AraNN complex, showed high T/C values against the L1210 tumor. It is notable that the Bn-L-AraNN complex including the δ-gauche chelate also shows better results than the Bn-D-AraNN complex.

All complexes tested have shown antitumor activity at least against S180, and some show much higher T/C values than cisplatin. Furthermore, it is of interest that some correlation is found between the chelate structures of these diamino sugar complexes and their antitumor activities. Although chemotherapeutic effects against various tumor models were insufficient for these (diamino sugar)platinum complexes at this time, these complexes are expected to be new drugs having high activity and low toxicity.

Acknowledgment. We wish to thank Professor K. Kurita of Seikei University for his helpful comments. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education of Japan (63470035), a grant from Iwatani Naoji Foundation, and by a grant from the Naito Foundation.

Supplementary Material Available: Tables of anisotropic thermal parameters of non-hydrogen atoms and hydrogen positional parameters (2 pages); a table of observed and calculated structure factors (8 pages). Ordering information is given on any current masthead page.

(28) Tsubomura, T.; Yano, S.; Kobayashi, K.; Sakurai, T.; Yoshikawa, S., *J. Chem. Soc., Chem. Commun.* **1986**, 459.
(29) Kidani, Y.; Inagaki, K.; Tsukagoshi, S. *Gann* **1976**, *67*, 921.
(30) Suami, T. Private communication.