Conformation of 2-Aminomethylpyrrolidine and 2-Aminomethylpiperidine in Ternary Platinum(II) Complexes: Regulation of Conformation of the Diamine by the Coexisting Ligand

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Square-planar complexes with the formula $[Pt(L_2)(L_1)](X)_2 \cdot nH_2O$, where L_1 is *S*-2-aminomethylpyrrolidine (*S*-pyrda) or 2-aminomethylpiperidine (pipda) and L_2 is diammine (X=Cl), cyclobutane-1,1-dicarboxylato (cbdca) (X=none), 2,2′-bipyridine (bpy) ($X=NO_3$), or 1,10-phenanthroline (phen) (X=Cl), were prepared and the nature of the coordination of L_1 was examined by ^{1}H-NMR spectroscopy and X-ray crystallography. These 2-aminomethylazacycloalkane derivatives form five-membered chelate rings condensed with an azacycloalkane ring in *cis*- or *trans*-configurations. The ^{1}H-NMR spectrum of complexes with *S*-pyrda as L_1 were consistent with *cis*-condensed rings in an *S*(*N*) conformation with any of L_2 group. However, ^{1}H-NMR spectra of the complexes with pipda as L_1 indicated *trans*-fused successive rings for the diammine and cbdca as L_2, but spectra for bpy and phen as L_2 were consistent with a conformation having *cis*-fused successive rings. X-Ray crystallography data for the two complexes with pipda as L_1 and cbdca (1) and bpy (2) as L_2 confirms the different coordination behavior in the solid state.

Key words chelate; conformation; geometrical isomerism; X-ray crystallography; platinum(II) complex; NMR

A series of 2-aminomethylazacycloalkanes was investigated as carrier ligands of platinum(II) to improve the efficacy of *cis*-diamminedichloroplatinum, CDDP, which is used in cancer treatment.[1—3] The efficacy was found to depend on the size and absolute configuration of the azacycloalkane and the leaving ligands. In particular, platinum(II) complexes of *R*-2-aminomethylpyrrolidine (*R*-pyrda) and its *S*-isomer are superior anticancer agents than that of 2-aminomethylpiperidine (pipda).[4—10] The structure and numbering scheme of these diamines is shown in Fig. 1. The difference in the absolute configuration of pyrda also affects its efficacy, the *R*-isomer is more efficacous in clinical tests.[10]

In a previous report, we described the stereochemistry of coordinated *S*-pyrda and pipda coordinated to tetracyano Fe(II) and Co(III), which form regular octahedral complexes and reported that these two diamines assume different stereochemistries, when fused in two consecutive rings: *cis*- and *trans*-fusion for *R*-pyrda and pipda respectively.[11] Using NMR spectroscopy, a conformational study of platinum(II) complexes with pipda was undertaken two decades ago[12] and several studies using derivatives of its enantiomeric form have been reported recently in conjunction with the orientations of nucleosides that coordinate as the ligands.[13—16] For the platinum(II) complex with pyrda, several X-ray studies have also been reported.[17,18] However, the conformations of these diamines in metal complexes in solution and in the crystal state may not be the same. Therefore we initiated a study of the conformations of chelates of these amines with platinum(II) and found that the pipda has the ability to assume two distinctly different conformations depending on the structure of the intramolecular ligand which is simultaneously coordinated to Pt(II).

Experimental

Material Potassium tetrachloroplatinate(II) was obtained from Wako. *S*-2-aminomethylpyrrolidine (*S*-pyrda) and 2-aminomethylpiperidine (pipda) were prepared according to a previously described method.[11] Dichloro(2,2′-bipyridine)platinum(II) and dichloro(1,10-phenanthroline)platinum(II) were prepared according to the methods of Morgan and Burstall[19] and Hall and Plowman[20] respectively.

Preparation of Platinum(II) Complexes. (2,2′-Bipyridine)(*S*-2-aminomethylpyrrolidine)platinum(II) Nitrate $[Pt(bpy)(S\text{-pyrda})](NO_3)_2$ and (2,2′-Bipyridine)(2-aminomethylpiperidine)platinum(II) Nitrate Hydrate $[Pt(bpy)(pipda)](NO_3)_2 \cdot H_2O$ To a suspension of $[PtCl_2(bpy)]$ (422 mg, 1 mmol in 5 cm^3 water), a slight excess of the diamine (for *S*-pyrda, 110 mg (1.10 mmol) and for pipda 120 mg (1.05 mmol)) was added. The mixture was heated at 75 °C until the color of the solution turned yellow.

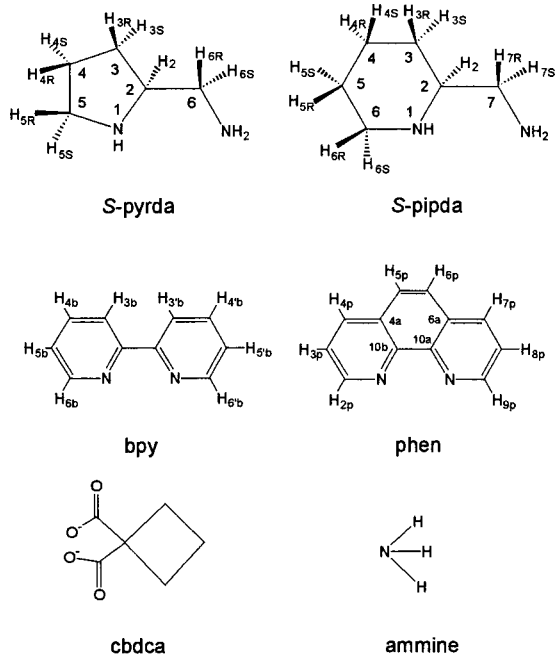

Fig. 1. Structure and Numbering of *S*-2-Aminomethylpyrrolidine (*S*-pyrda), *S*-2-Aminomethylpiperidine (*S*-pipda), 2,2′-Bipyridine (bpy), and 1,10-Phenanthroline (phen), and the Structure of Cyclobutane-1,1-dicarboxylate (cbdca), and Ammine

The Pt(II) complexes prepared in this study has a square planar structure with four coordinating atoms provided by these ligands.

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After filtering the mixture, an equal volume of saturated aqueous sodium nitrate was added to the filtrate and the mixture was allowed to stand overnight. The separated yellow crystals were collected on a filter and washed successively with cold 0.1 M nitric acid and water. Yield, 413 (71.7%) and 580 mg (95.4%) for *S*-pyrda and pipda complex respectively. *Anal.* Found: C, 31.19; H, 3.24; N, 14.67 for *S*-pyrda complex. Calcd for $[Pt(C_{10}H_8N_2)(C_5H_{12}N_2)](NO_3)_2$: C, 31.31; H, 3.50; N, 14.60. Found: C, 31.78; H, 3.74; N, 13.89 for pipda complex. Calcd for $[Pt(C_{10}H_8N_2)(C_6H_{14}N_2)](NO_3)_2\cdot H_2O$: C, 31.63; H, 3.98; N, 13.83. ^{1}H-NMR (D_2O) of the *S*-pyrda complex: δ=8.78 (H_{6b}, d, $J(H_{6b}H_{5b})$=5.7 Hz), 8.63 ($H_{6'b}$, d, $J(H_{6'b}H_{5'b})$=5.7 Hz), 8.40—8.52 (H_{4b}, $H_{4'b}$, H_{3b}, $H_{3'b}$, m), 7.88 (H_{5b}, dd, $J(H_{5b}H_{6b})$=7.3 Hz, $J(H_{5b}H_{4b})$=5.7 Hz), 7.84 ($H_{5'b}$, dd, $J(H_{5'b}H_{6'b})$=7.3 Hz, $J(H_{5'b}H_{4'b})$=8.5 Hz), 3.94 (H_2, m, $J(H_2H_{6R})$=11.7 Hz, $J(H_2H_{6S})$=5.2 Hz, $J(H_2H_{3R})$=3.0 Hz, $J(H_2H_{3R})$=5.5 Hz), 3.74 (H_{5S}, m, J=11.9, <3 Hz), 3.49 (H_{5R}, m, J=11.9, 8.0 Hz), 3.12 (H_{6S}, dd, $J(H_{6S}H_{6R})$=12.9 Hz, $J(H_{6S}H_2)$=5.2 Hz), 2.94 (H_{6R}, t, $J(H_{6R}H_{6S})$=12.4 Hz), 2.3—2.1 (H_{3S}, H_{4R}, H_{4S}), 2.03 (H_{3R}, m). ^{13}C-NMR (270 MHz, D_2O) of the *S*-pyrda complex: δ=157.8 (C_{2b}, C_{2b}, J_{195PtC}=31 Hz), {151.3 (J_{195PtC}=33 Hz), 150.9 (J_{195PtC}=32 Hz) (C_{6b}, $C_{6'b}$)}, 142.7 (C_{4b}, $C_{4'b}$), {129.2 (J_{195PtC}=37 Hz), 129.0 (J_{195PtC}=33 Hz) (C_{5b}, $C_{5'b}$)}, {125.0 (J_{195PtC}=27 Hz), 124.9 (J_{195PtC}=27 Hz), (C_{3b}, $C_{3'b}$)}, 66.8 (C_2, J_{195PtC}=12 Hz), 51.6 (C_5, J_{195PtC}=9 Hz), 49.3 (C_6, J_{195PtC}=6 Hz), 24.8 (C_3, J_{195PtC}=31 Hz), 24.6 (C_4, J_{195PtC}=38 Hz). ^{1}H-NMR (400 MHz, D_2O) of pipda complex: δ=8.71 (H_{6b}, d, J=5.9 Hz), 8.56 ($H_{6b'}$, d, J=5.9 Hz), 8.4—8.5 (H_{3b}, $H_{3'b}$, H_{4b}, $H_{4'b}$, m), 7.88 (H_{5b}, m, $J(H_{5b}H_{4b})$=7.3 Hz, $J(H_{5b}H_{6b})$=5.9 Hz), 7.82 ($H_{5b'}$, m, $J(H_{5b'}H_{4b'})$=6.1 Hz, $J(H_{5b'}H_{4b'})$=5.5 Hz), 3.72 (H_2, d, $J(H_2H_{3R})$=3.0 Hz, $J(H_2H_{3R})$=5.5 Hz), 3.60 (H_{7R}, t, J=12.8 Hz), 3.58 (H_{6R}, t, J=13 Hz), 3.40 (H_{6S}, d, J=13.7 Hz), 2.95 (H_{7S}, dd, J=12.6, 4.4 Hz), 2.1—1.65 (H_3, H_4, H_5, m). ^{13}C-NMR (D_2O) of the pipda complex: δ=157.4 (C_{2b}, $C_{2'b}$), 150.7 (C_{6b}, $C_{6'b}$), 142.7 (C_{4b}, $C_{4'b}$), {129.2, 128.8 (C_{5b}, $C_{5'b}$)}, {125.0, 124.9, (C_{3b}, $C_{3'b}$)}, 63.2 (C_2), 48.1 (C_6), 44.8 (C_7), 26.3 (C_5), 24.1 (C_3), 18.5 (C_4).

(1,10-Phenanthroline)(*S*-2-aminomethylpyrrolidine)platinum(II) Chloride, [Pt(phen)(*S*-pyrda)]$Cl_2\cdot H_2O$ To a suspension of $[PtCl_2(phen)]$ (300 mg, 0.67 mmol in 5 cm^3 water), 151 mg (1.35 mmol) of *S*-pyrda was added. The mixture was heated at 100 °C until all the components were dissolved. After filtering the mixture, the filtrate was concentrated to near dryness. The separated pale yellow crystals were collected on a filter and washed with diethyl ether. Yield, 122 mg (37.3%). *Anal.* Found: C, 35.98; H, 3.74; N, 9.88. Calcd for $[Pt(C_{12}H_8N_2)(C_5H_{12}N_2)]Cl_2\cdot H_2O$: C, 36.18; H, 3.93; N, 9.93. ^{1}H-NMR (400 MHz, D_2O): δ={9.07 (J=5.0 Hz), 8.93 (J=4.8 Hz) (H_{2p}, H_{9p}, d)}, 8.86 (H_{4p}, H_{7p}, d, J=8.3 Hz), {8.12, 8.11 (H_3, H_8, dd)}, 7.99 (H_{5p}, H_{6p}, s), 4.10 (H_2, m), 3.89 (H_{5S}, m), 3.62 (H_{5R}, m), 3.24 (H_{6S}, J=13.1 Hz, J=4.8 Hz), 3.09 (H_{6R}, t, J=13.1 Hz), 2.34 (H_{3R}, H_{3S}, H_{4R}, m), 2.15 (H_{4S}, m). ^{13}C-NMR (D_2O): δ={152.1, 151.7 (C_{2p}, C_{9p})}, 147.4 (C_{10ap}, C_{10bp}), 141.7 (C_{4p}, C_{7p}), 131.4 (C_{4ap}, C_{6ap}), 128.7 (C_{5p}, C_{6p}), {127.4, 127.1 (C_{3p}, C_{8p})}, 67.0 (C_2), 52.0 (C_5). 49.6 (C_6), {24.8, 24.7 (C_3, C_4)}.

(1,10-Phenanthroline)(2-aminomethylpiperidine)platinum(II) Perchlorate, [Pt(phen)(pipda)]$(ClO_4)_2$ To a suspension of $[PtCl_2(phen)]$ (150 mg, 0.336 mmol in 2.5 cm^3 water), 80 mg (0.70 mmol) of pipda was added. The mixture was heated at 100 °C until all the components dissolved. After filtering the mixture, lithium perchlorate (1.0 g) in 3 cm^3 of water was added. The separated pale yellow crystals were collected on a filter and washed successively with ethanol and diethyl ether. Yield, 212 mg (92%). *Anal.* Found: C, 31.59; H, 3.21; N, 8.10. Calcd for $[Pt(C_{12}H_8N_2)(C_6H_{14}N_2)](ClO_4)_2$: C, 31.41; H, 3.22; N, 8.14. ^{1}H-NMR (The perchlorate salt was converted to the chloride salt with tetraphenylarsonium chloride, 400 MHz, D_2O): δ={9.06 (d, J=5.0 Hz), 8.90 (d, J=4.9 Hz) (H_{2p}, H_{9p})}, {8.90 (d, J=8.9 Hz), 8.88 (d, J=8.9 Hz) (H_{4p}, H_{7p})}, {8.15 (dd, J=8.2, 5.4 Hz), 8.10 (dd, J=8.1, 5.3 Hz) (H_{3p}, H_{8p})}, 8.04 (H_{5p}, H_{6p}, s), 3.88 (H_2, d, J=12.8 Hz), 3.77 (H_{6R}, m, J=12.1 Hz), 3.75 (H_{7R}, t, J=13.4 Hz), 3.52 (H_{6S}, d, J=14 Hz), 3.07 (H_{7S}, dd, J=12.5, 4.4 Hz), 2.2—1.8 (H_3—H_5, m).

Diammine(*S*-2-aminomethylpyrrolidine)platinum(II) Chloride $[Pt(NH_3)_2$(*S*-pyrda)$]Cl_2$ To an aqueous solution of $K_2[PtCl_4]$ (2.564 g, 6.16 mmol in 36 cm^3), *S*-pyrda (0.323 g, 3.2 mmol) in 4 cm^3 of water was added. The mixture was occasionally stirred at room temperature, and the separated pale yellow precipitate was isolated on a filter. This process was repeated several times and after no more precipitate was formed, *S*-pyrda (0.282 g, 2.8 mmol) dissolved in 3.2 cm^3 of water was further added to the filtrate and the separated precipitates were collected several times. The separated *cis*-$PtCl_2$(*S*-pyrda) (1.19 g, 52%) was suspended in concentrated aqueous ammonia in a test tube and the mixture was stoppered tightly and heated in a boiling water until the Pt complex dissolved. The resulting pale yellow solution was concentrated on a rotary evaporator and the residue was dissolved in a hot mixture of water (1 cm^3) and methanol (10 cm^3). The mixture was filtered while still hot and the filtrate was allowed to stand in a refrigerator. The separated crystals were collected and dried *in vacuo*. Yield, 621 mg (13.2%). *Anal.* Found: C, 15.23; H, 4.61; N, 14.21. Calcd for $[Pt(NH_3)_2(C_5H_{12}N_2)]Cl_2$: C, 15.01; H, 4.53; N, 14.00. ^{1}H-NMR (400 MHz, D_2O): δ=3.52 (H_2, $J(H_2H_3)$=10.6 Hz, $J(H_2H_3)$=3.0 Hz), 3.22 (H_{5S}, ddd, J=11.4, 7.7, 4.1 Hz), 3.06 (H_{5R}, dt, J=11.4, 8.2 Hz), 2.85 (H_{6S}, dd, J=12.7, 5.0 Hz), 2.66 (H_{6R}, dd, J=12.1, 11.1 Hz), 2.09 (H_{4S}, m), 2.01 (H_{3R}, m, $J(H_2H_{3R})$=3.5 Hz), 1.86 (H_{4R}, m), 1.72 (H_{3S}, m, $J(H_2H_{3S})$=12.1 Hz). ^{13}C-NMR (D_2O): δ=66.4 (C_2), 51.2 (C_5), 50.7 (C_6), 25.6 (C_4), 24.9 (C_3).

Diammine(2-aminomethylpiperidine)platinum(II) Chloride $[Pt(NH_3)_2$(pipda)$]Cl_2$ A mixture of *cis*-dichlorodiammineplatinum(II) (0.37 g, 0.12 mmol) and pipda (0.14 g, 0.12 mmol) in 2 cm^3 of water was stirred at 70 °C for 20 min. The solution was concentrated to dryness on a rotatory evaporator. The resulting solid was dissolved in a small amount of ethanol, followed by the addition of small amount of acetonitrile. The crystals that separated after 2 months were collected on a filter. Yield, 10 mg (10%). *Anal.* Found: C, 17.26; H, 5.11; N, 13.23. Calcd for $[Pt(NH_3)_2(C_6H_{14}N_2)]Cl_2$: C, 17.40; H, 4.87; N, 13.53. ^{1}H-NMR (400 MHz, D_2O): δ=3.11 (H_{6S}, d, J=12.4 Hz), 2.88—2.83 (H_2 and H_{6R}, m), 2.74 (H_{7S}, dd, J=13.6, 3.8 Hz), 2.43 (H_{7R}, t, J=12.5 Hz), 1.99 (H_{3S}, d, J=15.5 Hz), 1.86 (H_{4R}, d, J=7.3 Hz), 1.67 (H_{5R}, m), 1.55 (H_{4S}, H_{5S}, m), 1.34 (H_{3R}, m). ^{13}C-NMR (D_2O): δ=67.1 (C_2), 50.4 (C_6), 49.8 (C_7), 25.0 (C_3), 24.2 (C_5), 20.7 (C_4).

(Cyclobutane-1,1-dicarboxylato)(2-aminomethylpiperidine)platinum(II), [Pt(cbdca)(pipda)] The above compound was prepared according to the method described by Morikawa *et al.*[9] Yield, 233 mg (62%). *Anal.* Found: C, 31.66; H, 4.48; N, 6.23. Calcd for $[Pt(C_6H_{14}N_2)(C_6H_6O_4)]$: C, 31.93; H, 4.47; N, 6.21. ^{1}H-NMR (400 MHz, D_2O): δ=3.15 (H_{6S}, d, J=12.4 Hz), 2.89 (cbdca, t), 2.86 (cbdca, t), 2.85—2.72 (H_2 and H_{6R}, m), 2.53 (H_{7S}, dd, J=12.2, 4.3 Hz), 2.33 (H_{7R}, t, J=12.2 Hz), 1.95—1.82 (H_{3S}, H_{4R}, m), 1.90 (cbdca, quintet), 1.65—1.50 (H_{5R}, H_{4S}, H_{5S}, m), 1.30 (H_{3R}, m).

X-Ray Crystallography A summary of general experimental procedure and crystal data is listed in Table 1. Single crystals suitable for diffraction studies were grown by the slow cooling of aqueous solutions and were mounted on a thin glass fiber with epoxy resin. Data were collected on a Rigaku AFC-7R diffractometer at 20±1 °C. The final cell parameters were obtained by a least-squares fit to the automatically centered settings for 20 reflections. Three reflections were monitored during the data collection for each crystal. Intensity data were all corrected for absorption (empirically, based on azimuthal scans of several reflections), anomalous dispersion, and Lorentz and polarisation effects.

Table 1. Summary of Crystallographic Data for [Pt(cbcda)(pipda)] (**1**) and [Pt(bpy)(pipda)]$(NO_3)_2\cdot H_2O$ (**2**)

Complex	**1**	**2**
Formula	$C_{12}H_{20}N_2O_4Pt$	$C_{16}H_{24}N_6O_7Pt$
Formula weight	451.39	607.49
Cryst size/mm	0.11, 0.10, 0.10	0.21, 0.18, 0.09
Space group	*Pbcn*	$P2_1/n$
a/Å	17.463(4)	9.187(1)
b/Å	11.551(2)	14.928(1)
c/Å	14.146(4)	15.030(1)
β/°		95.473(9)
U/Å^3	2853(1)	2051.8(3)
Z	8	4
D_c/g cm^{-3}	2.101	1.966
μ/mm^{-1}	9.806	6.863
F(000)	1728	1184
Total data	25974	5189
Unique data	24156 [R_{int}=0.044]	4895 [R_{int}=0.023]
Observed data	13006 [$I>2\sigma(I)$]	3228 [$I>3\sigma(I)$]
Least-squares variables	173	255
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on *F*
R_1 [b]	0.047 [$I>2\sigma(I)$]	0.036 [$I>3\sigma(I)$]
R_w	0.037 [$I>2\sigma(I)$] [c]	0.029 [$I>3\sigma(I)$] [d]

a) Details in common: Rigaku AFC7R diffractometer, λ(Mo$K\alpha$)=0.71069 Å, ω–2θ scan type, T=293(1) K, $2\theta_{max}$=55.0°. *b*) $R=\Sigma||F_o|-|F_c||/\Sigma|F_o|$. *c*) $R_w=[\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2)]^{1/2}$, where $w=1/\sigma^2(F_o^2)=[\sigma c^2F_o^2+(p(\mathrm{Max}(F_o^2,0)+2F_c^2)/3)^2]^{-1}$. *d*) $R_w=[\Sigma w(|F_o|-|F_c|)^2/\Sigma wF_o^2)]^{1/2}$, where $w=1/\sigma^2(F_o)=[\sigma_c^2F_o+p^2F_o^2/4]^{-1}$.

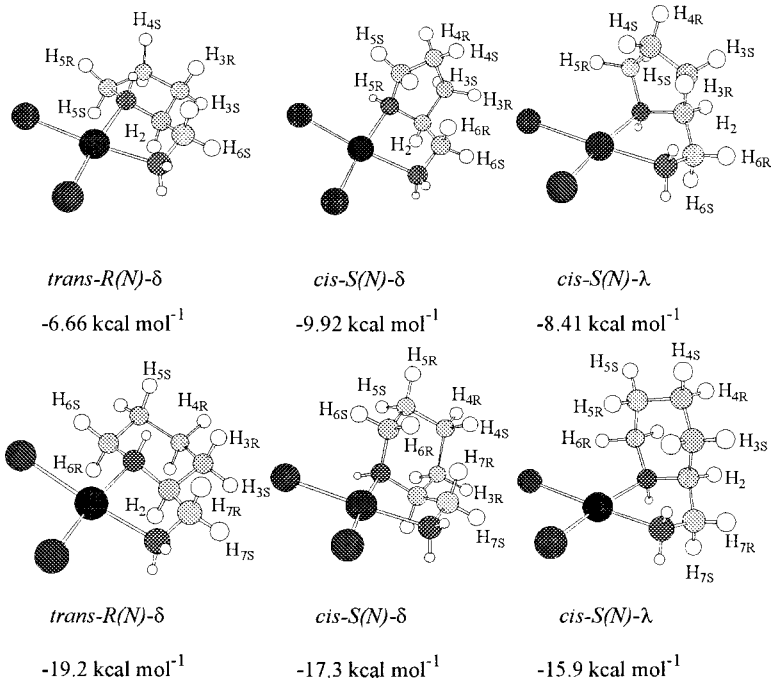

Fig. 2. Possible Coordination Modes of *S*-2-Aminomethylpyrrolidine (*S*-pyrda) in Upper Raw and *S*-2-Aminomethylpiperidine (*S*-pipda) in Lower Raw to $Pt(II)Cl_2$

[Pt(cbdca) (pipda)] (1) The structure was solved by a Patterson orientation/translation search and expanded using Fourier techniques.[21] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms are included but not refined.

[Pt(bpy)(pipda)]$(NO_3)_2\cdot H_2O$ (2) The structure was solved by a direct method and expanded using Fourier techniques.[21] One of the nitrate ions was found to be disordered. The non-hydrogen atoms other than the nitrate ion and water were refined anisotropically. Hydrogen atoms were included but not refined. Two rigid bodies of nitrate with an occupancy of 0.65 and 0.35 modeled the disordered nitrate ion.

Physical Measurements UV–visible absorption spectra were recorded on a Shimadzu UV-2200 spectrophotometer. Infrared spectra were recorded on a JEOL JIW-6500W FT-infrared spectrophotometer with the samples in compressed KBr disks. ^{1}H- and ^{13}C-NMR measurements were carried out using JEOL EX GX-400 and JEOL EX-270 spectrometers in D_2O solutions using sodium 2,2-dimethyl-2-silapropionate-d_2 and dioxane (67.4 ppm), respectively, as references.

Molecular Modeling Calculations The geometries of the conformational isomers of [$PtCl_2$(*S*-pyrda)] and [$PtCl_2$(*S*-pipda)] were optimized by MM3 calculations with supplementary force fields for platinum augmented in CAche.[22] The geometries of [Pt(bpy)(*S*-pipda)]$^{2+}$ were initially optimized as above and were subjected to a MOPAC calculation with AM1 parameters.

Results

The possible conformations of *S*-pyrda and *S*-pipda are shown schematically in Fig. 2, where each hydrogen is labeled as *R* or *S* using the IUPAC convention. In the following sections, the proton assignments are described as complexes with pipda as *R*-pipda for the sake of simplicity, although the prepared complexes were the racemic mixtures of *R*- and *S*-pipda.

Two types of ternary platinum(II) complexes [$Pt(L_2)(L_1)$]$^{n+}$ were prepared by conventional methods using *S*-pyrda and pipda as L_1. Type 1 contains aromatic 1,10-phenanthroline (phen) as L_2 and type 2 contains di(ammine=NH_3) and cyclobutane-1,1-dicarboxylate as L_2.

^{1}H-NMR Spectra The diamine regions of 400 MHz ^{1}H-NMR spectra of [$Pt(NH_3)_2$(*S*-pyrda)]$^{2+}$ and [Pt(bpy)(*S*-pyrda)]$^{2+}$ and those of [$Pt(NH_3)_2$(pipda)]$^{2+}$ and [Pt(bpy)(pipda)]$^{2+}$ are reproduced in Figs. 3 and 4. The bipyridine regions were similar to other [Pt(diamine)(bpy)]$^{2+}$ complexes. The methylene protons, on C_6 and on C_7 for *S*-pyrda and pipda respectively, appeared as an apparent triplet and a double doublet, this shows that the five-membered chelate rings take skew forms. As seen from Figs. 3 and 4, the double doublets for the *S*-pyrda and pipda are flanked with satellites due to $^3J_{195Pt-N-C-H}$. For [$Pt(NH_3)_2$(*S*-pyrda)]$^{2+}$, all the protons appeared separately and the coupling with ^{195}Pt were 63 and 17 Hz for the double doublet (H_{6S}) and the triplet (H_{6R}) respectively. These double doublets are located equatorially with respect to the five-membered chelate ring because the large coupling with ^{195}Pt is consistent with a dihedral angle

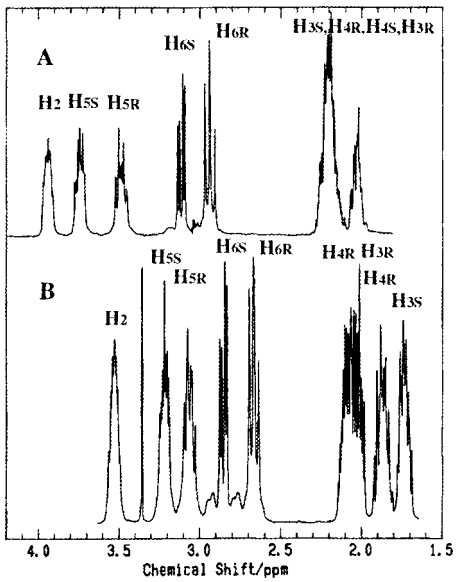

Fig. 3. 400 MHz *S*-pyrda Region ^{1}H-NMR Spectra of [Pt(bpy)(*S*-pyrda)]$^{2+}$ (A) and [$Pt(NH_3)_2$(*S*-pyrda)]$^{2+}$ (B) and Assignments of Signals.

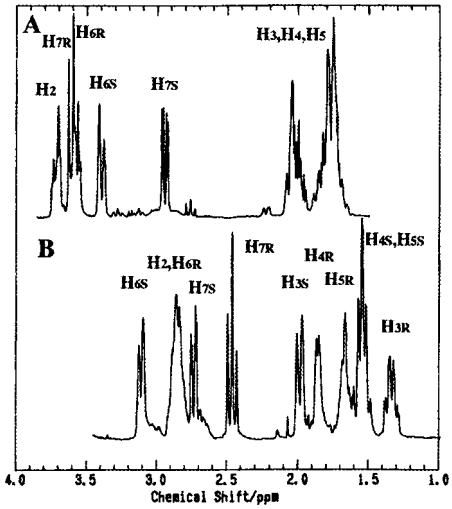

Fig. 4. 400 MHz pipda Region ^{1}H-NMR Spectra of $[Pt(bpy)(pipda)]^{2+}$ (A) and $[Pt(NH_3)_2(pipda)]^{2+}$ B) and Assignments of Signals

of Pt–N–C–H_{6S} near 180°.[23] The apparent triplets assigned to the axial protons arise from vicinal coupling, $^3J(H_{6R}H_2)$ or $^3J(H_{7S}H_2)$, and geminal coupling, $^2J(H_{6R}H_{6S})$ or $^2J(H_{7R}H_{7S})$ for *R*-pyrda and the pipda chelate respectively with almost same absolute values. Other signals were assigned by homonuclear ^{1}H–^{1}H COSY spectra from these assignments. The complex, $[Pt(bpy)(S\text{-pyrda})]^{2+}$, showed H_6 signals at 2.94 and 3.12 ppm as a triplet and a double doublet respctively and $[Pt(NH_3)_2(S\text{-pyrda})]^{2+}$ showed H_6 signals at 2.66 and 2.85 ppm for a triplet and a double doublet respctively. These spectra are similar to those of $[Co(CN)_4(S\text{-pyrda})]^-$ and $[Fe(CN)_4(pipda)]^{2-}$,[11] thus *S*-pyrda forms only *cis*-fused consecutive rings, and the conformation of the coordinated *S*-pyrda has a *cis*-*S*(*N*)-conformation.

On the other hand, the triplet and the double doublet sinals of H_7 signals for $[Pt(L_2)(pipda)]^{n+}$ appeared at 3.60 and 2.95 ppm for L_2=bpy, 3.75 and 3.07 ppm for L_2=phen and 2.43 and 2.74 ppm for the $L_2=(NH_3)_2$, *i.e.* the order of the chemical shifts of the triplet and the doublet were reversed between type 1 and type 2. Similar chemical shifts have been reported for $[Pt(D_2O)_2(pipda)]^{2+}$, 2.25 and 2.30 ppm.[16] The H_2 signals were separated from the other signals for all the complexes examined in this study and each H_2 proton is located in an axial position with respect to the five-membered chelate ring since strong coupling with one of the methylene protons (H_6 and H_7 for *S*-pyrda and pipda) was observed. Based on these data, the coordination mode of *cis*-*S*(*N*)-λ is not populated with *S*-pyrda complexes.

The coupling constants between H_2 and H_3 are different for the *S*-pyrda and pipda complexes for L_2=bpy or phen. The pipda complex with bpy showed ^3J couplings of 4.2 Hz with either one of the H_3 protons but the *S*-pyrda complex showed coupling constants of *ca.* 3.0 and 5.5 Hz. The $^3J(H_2H_3)$ would be considerably smaller for *cis*-fused pipda complexes because H_2 behaves as an equatorial proton in the chair form of the piperidine ring as shown in Fig. 2. An *S*-pipda is coordinated in the *cis*-*S*(*N*)-δ conformation for complexes with bpy and phen. Amino protons were observed for the pD 2.0 (DCl) solution of $[Pt(bpy)(pipda)](NO_3)_2$ at 6.44, 6.59, and 6.83 ppm. Homogated decoupling of these protons showed that the amino protons at 6.83 ppm are the secondary

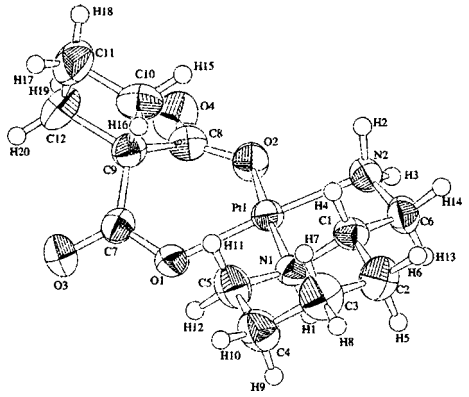

Fig. 5. Perspective View of [Pt(cbdca)(pipda)] (**1**)

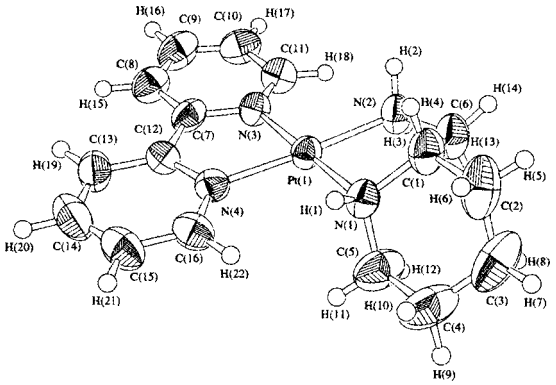

Fig. 6. Perspective View of $[Pt(bpy)(pipda)]^{2+}$ (**2**)

amino protons, which showed a coupling of 4 Hz with H_2. Again, this small coupling is in agreement with a *cis*-fusion, because the dihedral angle would be expected to be around 60° in this structure. In the case of $[Pt(NH_3)_2(pipda)]^{2+}$, however, one of the ^3J between H_2 and H_3 was 10.6 Hz and the other was 3.0 Hz. These values are consistent with a *trans*-fused five- and six-membered ring, *trans*-*R*(*N*)-δ for *S*-pipda. Thus, pipda takes different conformations depending on the nature of L_1 in D_2O.

X-Ray Crystallography of Two Pipda Complexes The difference in ^{1}H-NMR spectra between type 1 and type 2 pipda complexes arises from the difference in the coordination mode of pipda between them.

In order to confirm this, X-ray crystallography was carried out for two representative complexes of type 1 and type 2. The perspective views of [Pt(cbcda)(pipda)] and $[Pt(bpy)(pipda)]^{2+}$ are shown in Figs. 5 and 6. Both the platinum(II) complexes have a typical square planar coordination as shown in Table 2.

The [Pt(cbdca)(pipda)], **1**, takes a characteristic structure of coordinated cbdca common to [Pt(cbdca)(*R*-pyrda)].[17] A derivative of malonato, 1,1-cyclobutanedicarboxylato, coordinates as a bidentate ligand with a bite angle of 89.5(1)° in a pseudo boat form and C(10) and C(12) of the cyclobutane ring are located in axial and equatorial position in the mast head carbon of the boat form leaving the cyclobutane ring unsymmetric with respect to the coordination plane. The C(7), C(8) and C(9) atoms deviate from the coordination plane defined by Pt, O(1), O(2), N(1) and N(2) by 0.629(4), 0.531(5), and 1.434(4) Å. The two carbonyl groups of the

Table 2. Comparisons of the Geometries around Pt(II) between Two Pipda Complexes

Complex	**1**		**2**
Pt–pipda		Pt–pipda	
Pt–N(1)	2.044(3)	Pt–N(1)	2.039(6)
Pt–N(2)	2.034(3)	Pt–N(2)	2.030(6)
Pt-cbcda		Pt-bpy	
Pt–O(1)	2.032(3)	Pt–N(3)	2.007(6)
Pt–O(2)	2.022(3)	Pt–N(4)	2.011(6)
pipda-Pt-cbcda		pipda-Pt-bpy	
N(1)–Pt–N(2)	83.4(5)	N(1)–Pt–N(2)	82.5(2)
N(1)–Pt–O(1)	93.5(1)	N(1)–Pt–N(3)	178.8(3)
N(1)–Pt–O(2)	176.3(1)	N(1)–Pt–N(4)	99.7(2)
N(2)–Pt–O(1)	176.5(1)	N(2)–Pt–N(3)	97.3(3)
N(2)–Pt(1)–O(2)	93.5(1)	N(2)–Pt–N(4)	176.0(2)
O(1)–Pt(1)–O(2)	89.5(1)	N(3)–Pt–N(4)	80.5(2)
pipda		pipda	
N(1)–C(1)	1.504(5)	N(1)–C(1)	1.54(1)
N(1)–C(5)	1.493(4)	N(1)–C(5)	1.44(1)
N(2)–C(6)	1.484(5)	N(2)–C(6)	1.48(1)
C(1)–C(2)	1.518(6)	C(1)–C(2)	1.55(1)
C(1)–C(6)	1.502(5)	C(1)–C(6)	1.46(1)
C(2)–C(3)	1.508(6)	C(2)–C(3)	1.48(1)

carboxylates, O(3) and O(4) atoms force the cyclobutane ring to occupy a region remote from this plane and in an axial orientation. The C(9)–C(10) is almost perpendicular to the plane. Pipda exists in *trans*-fused successive five- and six-membered rings. The six-membered ring is a typical chair form. The five-membered chelate ring has a puckered form with the torsion angle of N(1)–C(1)–C(6)–N(2) is 55(1)°. The C(5) in the piperidine ring is situated on the same side as the cyclobutane ring with respect to the coordination plane.

In contrast, pipda assumes a different condensation mode, *cis*-fusion, in the case of the bpy complex as shown in Fig. 6. In $[Pt(bpy)(pipda)]^{2+}$, **2**, the bpy ring is coplanar to the coordination plane. The pipda coordinates as a bidentate ligand and the five-membered chelate ring has a puckered conformation with a torsion angle, N(1)–C(1)–C(6)–N(2), of 50.1(8)°. The hydrogen at the 6-position protrudes in the direction of the piperidine ring and the N(1)–C(5) bond of the piperidine ring is directed to perpendicular to the coordination plane. C(2) is located in an equatorial position relative to the five-membered chelate ring. Some thermal fluctuation is indicated by the large anisotropic ellipsoids for C(4) and C(5).

The optimized structure and steric energy was calculated for $[PtCl_2(S\text{-pyrda})]$ and $[PtCl_2(S\text{-pipda})]$ as planar Pt(II) compounds free of intramolecular repulsions. $[PtCl_2(S\text{-pyrda})]$ prefer a *cis*-condensation mode to a *trans*-condensation by *ca.* 3 kcal mol^{-1}. On the other hand, $[PtCl_2(S\text{-pipda})]$ prefers a *trans*-condensation to a *cis*-coordination. These differences arise from the steric interaction of the condensation modes of the five-membered chelate ring and five-membered pyrrolidine and six-membered piperidine.

The conformation of pipda in the $[Pt(bpy)(pipda)]^{2+}$ was evaluated by AM1 calculation using the CAChe molecular modeling software package.[22] The *cis*-*S*(*N*)-form is favored over the *trans*-*R*(*N*)-form by 3 kcal mol^{-1}, the repulsion of the hydrogens of bpy and the piperidine ring within the latter form is relaxed, as evidenced by the hydrogen–hydrogen distance of 1.98 Å but this caused a severe distortion in bipy planarity and a square planar coordination plane. The intramolecular steric repulsions of 2.41 and 2.27 Å for the former form are found in the mast-head methylene and piperidine ring as shown in Fig. 7. The H···H distances, estimated based on the X-ray crystal structure, are 2.35 and 2.34 Å.

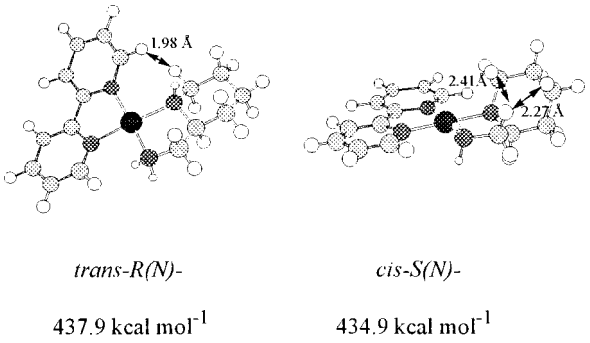

Fig. 7. Energy Optimized Structures of $[Pt(bpy)(pipda)]^{2+}$ and Values Obtained by AM1 Calculation

Discussion

The overall feature of the Pt(II) complexes with L_1=*S*-pyrda is similar to those of corresponding tetracyanocobaltate(III) and tetracyanoferrate(II) complexes,[11] although each signal appeared at lower magnetic field and the difference in chemical shift between H_{6a} and H_{6e} was decreased for the Pt(II) complexes. In the solution state, the predominant species has a conformation where the pyrrolidine ring extends from the five-membered chelate ring with the C_3 carbon extended equatorially and C_5 carbon in a pseudo axial direction. The restriction of the five-membered pyrrolidine ring does not define distinctively an axial direction as does the six-membered piperidine ring.

However, pipda coordinated to Pt(II) can change its condensation mode depending on the adjacent intramolecular ligand. Several studies have been reported on *trans*-1,2-cyclohexanediamine[25,26] and *trans*-1,2-cyclopentanenediamine[27—29] and these have two carbon atoms of definite absolute configuration in the five-membered chelate ring on coordination, but pipda has the characteristic that the configuration of the secondary amine is subject to the effect by neighboring atoms. In the case of the Pt(II) complexes with L_1=pipda, the general feature is similar to those of the octahedral complexes with $L_2=(NH_3)_2$ or cbdca, the chemical shifts of H_{7a} and H_{7e} are reversed for L_2=bpy or phen. Though the ^{13}C-NMR spectrum of $[Pt(bpy)(pipda)]^{2+}$ was reported two decades ago,[12] the resolution of the spectrum at that time was not sufficient to establish the condensation modes of the chelate ring and the piperidine ring. The authors assumed that the *trans*-fused structure for this chelate on the basis of a model.[12] However, an analysis of the ^{1}H-NMR spectrum in this study leads to the conclusion that the *cis*-condensation mode is favoured. This is firmly established by the crystallography of the two platinum complexes. ^{1}H-NMR spectrum shows a characteristic change in the chemical shift of H_{7S} and this chemical shift change provides a clue to the differentiation of the *cis*- and *trans*-fusion of this ligand in solution.

The diamines used here are derivatives of *N*-alkylsubstituted 1,2-ethanediamines. The stereochemistry of these di-

amines is strongly affected by the presence of bpy or phen, because the hydrogens at the 6,6′-positions of the former and the 2,9-positions of the latter are located on the plane of these aromatic diimines. *N*-Methyl-1,2-ethanediamine has been reported to take the structure of the axially located *N*-methyl group in ternary complexes of this amine and the aromatic diimine and square-planar metal centre.[30—32] We have also found that the *N*-arylmethyl groups of *N*-arylmethyl-1,2-ethanediamine (aryl=phenyl, 1-naphtyl, and 9-anthryl) assume an axial orientation in ternary complexes of bpy or phen and platinum(II).[33,34] These findings support the presence of strong repulsive interactions if these *N*-alkyl substituents of 1,2-ethanediamine are in an equatorial orientation. For 2-aminomethylpiperidine, the *trans*-fused structure yields a stable structure as a bidentate ligand itself, but this strong repulsive interaction from the aromatic diimine forces the diamine to assume the next most stable structure in $[Pt(bpy)(pipda)]^{2+}$ and $[Pt(phen)(pipda)]^{2+}$, *i.e.* a *cis*-fused structure with the carbon atom next to the secondary amine in an axial orientation. For 2-aminomethylpyrrolidine, on the other hand, the fused five and five-membered rings formed on coordination to a metal ion yield a *cis*-fused structure where the carbon atoms next to the secondary amine assume an axial orientation itself.

Anticancer activity of Pt(II) diamine copounds correlates to the binding with double-stranded DNA. After removal of leaving groups such as Cl^- ion or cbdca, the two coordination sites of Pt(II) are filled with nucleotide bases such as guanine. Pt(II) complexes containing pipda are less effective in anticancer agent than those containing *R*-pyrda and *S*-pyrda.[4—10] Present study has shown that coordinated pipda presents mainly in *trans*-fusion and takes *cis*-fusion under specific conditions. But coordinated pyrda presents exclusively in the *cis*-fusion structure. The spatial arrangement of the consecutive ring is perpendicular to the chelate rings for the *cis*-fusion but the ring is extended for the *trans*-fusion to the region where the nucleotide base coordinates. Thus steric repulsion between nucleotide base(s) and azacyloalkane ring is smaller for pyrda than for pipda and the difference in the anticancer activity probably arises from this effect, though hydrogen bonding between amino-hydrogen of the coordinated diamine and phosphate group of main chain of DNA cannot be excluded.

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