# Structures of Platinum(II) Complexes of 2-Aminomethylaziridine and *S*-2-Aminomethylazetidine and Correlation of Anticancer Activities of (2-Aminomethylazacycloalkane)platinum(II) Complexes with the Geometry of the Chelate Rings Formed with Platinum(II)

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**The spectroscopic properties of platinum(II) complexes with 2-aminomethyl-derivatives of small-membered 1-aza-cycloalkane, *i.e.*, =2-aminomethylaziridine=azida and *S*-2-aminomethylazetidine=*S*-azeda, and the crystal structures of their dichloro complexes demonstrate that the conformation of the fused three- (azida) or four- (*S*-azeda) and five-membered chelate ring formed by the coordination of *S*-azida and *S*-azeda to platinum(II) has an *S*(*N*) absolute configuration at the secondary amine site and that the two alkyl groups extend axially from the five-membered chelate ring. The chelate ring of the azida is more planar than the *S*-azeda or other 2-aminomethyl-1-azacycloalkanes. The anticancer activity reported for azeda and 2-aminomethylpyrrolidine appears to be related to their coordination structure, namely the presence of *cis*-fused successive rings.**

**Key words** chelate; X-ray crystallography; platinum(II) complex; small-membered ring; anticancer activity

A series of 2-aminomethylazacycloalkanes was investigated as carrier ligands of platinum(II) to improve the efficacy of *cis*-diamminedichloroplatinum, CDDP, which is currently used to treat several forms of cancer.[1—3] Morikawa *et al.* reported that the efficacy was dependent on the size and absolute configuration of the azacycloalkane and the leaving ligands.[4] The structure and the abbreviations of the 2-aminomethylazacycloalkanes are shown in Fig. 1, as well as that of *N*-methyl-(*S*)-propane-1,2-diamine (Me-*S*-pn). The efficacy was good for platinum(II) complexes of 2-aminomethylazetidine (azeda) and 2-aminomethylpyrrolidine (pyrda) and that of 2-aminomethylpiperidine (pipda) was next most effective while 2-aminomethylaziridine (azida) was ineffective for Colon 26 carcinoma (sc-ip) screen. They also have reported that *R*-2-aminomethylpyrrolidine (*R*-pyrda) has superior properties as carrier ligand for anticancer agents than *S*-2-aminomethylpyrrolidine (*S*-pyrda).[5] The difference in the absolute configuration of pyrda also has an effect on its efficacy, the *R*-isomer, especially [Pt(CBDCA=cyclobutane-1,1-dicarboxylato)(*R*-pyrda)] performed more favorable clinical tests.[5—11]

This prompted us to determine the precise structure of the title compounds. The conformation of chelate rings has been a subject of interest, as it relates to the stereochemistry of coordination compounds for 30 years.[12] However, a precise analysis of chelate rings with a diamine has not been established when one coordinated atom is provided by a heterocyclic diamine and the other coordinated atom is provided by the side chain of a heteroalkane.[13] The formation of a chelate ring on coordination of 2-aminomethylaziridine (azida) or *S*-2-aminomethylazetidine (*S*-azeda) to a metal ion yields fused ring structures between the five-membered chelate ring and the three-membered aziridine or four-membered azetidine rings. In azida and *S*-azeda, two alkyl groups are attached to 1,2-ethanediamine at one of the amine terminals and at the carbon atom next to the amine and this two sites are connected by the common carbon atom for azida and by two methylene groups for azeda. If the five-membered

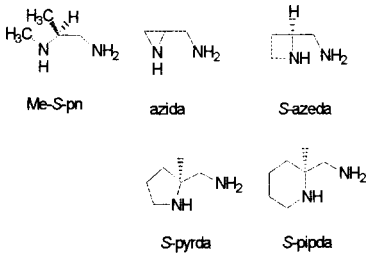


Fig. 1. Chemical Structures of 2-Aminomethyl-1-azacycloalkane and Me-*S*-pn

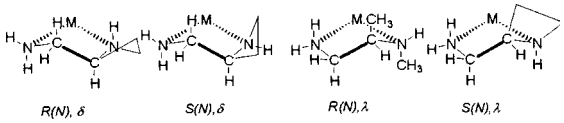


Fig. 2. Possible Conformations of *S*-Azeda on Coordination and *N*-Methyl-(*S*)-propanediamine for the *R*(*N*), λ Conformer

chelate ring has a *gauche* conformation, four conformations are possible for *N*-methyl-(*S*)-propanediamine (Me-*S*-pn). By analogy with Me-*S*-pn,[14] three possible conformations of *S*-azeda, on coordination to a metal ion, are depicted in Fig. 2. One remaining isomer cannot be formed with *S*-azeda because of steric hindrance and is shown using Me-*S*-pn as an example. These confomations are characterized by the absolute configuration of the coordinated secondary amine (*R*(*N*) or *S*(*N*)) and the conformation of the five-membered chelate ring ($\delta$ or $\lambda$). The restriction of the conformations due to the connection of two alkyl groups has a significant influence and one of the possible conformation cannot be formed.

## Experimental

**Materials** Potassium tetrachloroplatinate(II) was purchased from Nacalai. *S*-2-Azetidine-2-caboxylic acid was purchased from Tokyo Kasei. Other chemicals were obtained commercially and were used without further purification. Dichloro(bipyridine)platinum(II), $Pt(bpy)Cl_2$, was prepared according to the method of Morgan and Burstall.[16] Azida was prepared from

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1,3-diamino-2-hydroxypropane by dehydration with 15% fuming sulfuric acid according the method described by Spivack.[17] *S*-Azeda was prepared from *S*-azetidine-2-carboxylic acid by the method described by Philips and Cromwell.[18]

**[$PtCl_2$(azida)]** An aqueous solution of azida (72 mg/5 ml) was added to 1 mmol of potassium tetrachloroplatinate in 20 ml of water and the mixture was allowed to stand at room temperature overnight. The separated yellow crystals were collected on a filter. Yield, 48.2 mg (14.3%). Ethanol (10 ml) was added to the filtrate and the mixture was allowed to stand overnight. The resulting orange crystals were collected (143.67 mg). This was dissolved in 2 ml of water and 2 eq of aqueous silver nitrate solution was added. The white precipitate was removed by centrifugation and decantation. Hydrochloric acid (1 M, 10 ml) was added to the resulting yellow solution and the separated yellow crystals were collected. Yield, 86.3 mg (62.4%). *Anal.* Found: C, 10.73; H, 2.48; N, 8.22%. Calcd for [Pt(azida)$Cl_2$]: C, 10.73; H, 2.38; N, 8.22%.

**[Pt(bpy)(azida)]$(ClO_4)_2$** Pt(bpy)$Cl_2$ (211 mg, 0.5 mmol) was suspended in 2 ml of water. After the addition of 144 mg (2 mmol) of azida, the mixture was stirred for 30 min to give pale yellow solution. This solution was cooled to room temperature and 4 ml of aqueous sodium perchlorate (2 g/5 ml) was added. The separated crystals were collected on a filter. Yield, 917 mg (73.7%). This material was recrystallized by dissolution in 10 ml of water at 75 °C followed by filtration, which was then allowed to stand at room temperature. Yield, 432 mg (34.7%). *Anal.* Found: C, 25.03; H, 2.53; N, 9.00%. Calcd for [Pt(bpy)(azida)]$(ClO_4)_2$: C, 25.09; H, 2.59; N, 9.00%. Azida region of $^1$H-NMR (270 MHz, $D_2O$): $\delta$=3.22 ppm ($H_4$, m, $J(H_4H_5)$=5.7 Hz, $J(H_4H_6)$=7.3 Hz, $J(H_4H_7)$=<1 Hz, $J(H_4H_8)$=5.3 Hz), 2.53 ($H_5$, m, $J(H_5H_6)$=2.8 Hz, $J(PtH_5)$=30 Hz), 3.00 ($H_6$, m), 3.02 ($H_{7'}$, dd, $J(H_7H_8)$=14.2 Hz), 3.70 ($H_8$, dd, $J(PtH_8)$=37.5 Hz). Bpy region of $^1$H-NMR (270 MHz, $D_2O$): $\delta$=8.90 ppm ($H_6$, d), 8.63 ($H_{6'}$, d), *ca.* 8.4 (4H), *ca.* 7.8 (2H).

**[$PtCl_2$(*S*-azeda)]** This compound was prepared using 1 mmol of potassium tetrachloroplatinate using the method described by Morikawa *et al.*[4]

**[Pt(bpy)(*S*-azeda)]$(NO_3)_2$** Into a suspension of Pt(bpy)$Cl_2$ (211 mg, 0.5 mmol) in 2 ml of water, an aqueous solution of *S*-azeda (43 mg, 0.5 mmol) was added. The mixture was stirred for 40 min at 70—75 °C. The resulting pale yellow solution was filtered to remove small amounts of undissolved materials. To the filtrate, 2 ml of saturated aqueous solution of $NaClO_4$ was added and pale yellow precipitates were collected on a filter and washed with a small portion of water. The crude products were recrystallized from 10 ml of water. Yield, 90 mg (31%). *S*-Azeda region of $^1$H-NMR (270 MHz, $D_2O$): $\delta$=4.57 ppm ($H_4$, m $J(H_4H_5)$=7.3 Hz, $J(H_4H_6)$=10 Hz, $J(H_4H_9)$=5.3 Hz, $J(H_4H_{10})$=1.3 Hz), 2.46 ($H_5$, m, $J(H_5H_6)$=12 Hz, $J(H_5H_7)$=7.5 Hz, $J(H_5H_8)$=3.8 Hz), 2.82 ($H_6$, m, $J(H_6H_7)$=10 Hz, $J(H_6H_8)$=10 Hz), 4.47 ($H_7$, ddd, $J(H_7H_8)$=10 Hz), 3.82 ($H_8$, ddd, $J(PtH_8)$=50 Hz), 3.07 ($H_9$, $J(H_9H_{10})$=13.8 Hz. 2.89 ($H_{10}$, dd). Bpy region of $^1$H-NMR (270 MHz, $D_2O$): $\delta$=8.67 ppm ($H_6$, d), *ca.* 8.4 (5H), *ca.* 7.8 (2H).

**Crystal Structure Determination of [$PtCl_2$(azida)] and [$PtCl_2$(*S*-azeda)]** Suitable crystals for X-ray crystallography were obtained by the slow evaporation of an aqueous solution of the complex. A crystal was mounted on a glass capillary and intensity measurements were carried out with a Rigaku AFC 7R diffractometer. The crystal data and a brief summary of the measurements and analysis are shown in Table 1. The structure was solved with the teXsan package[19] using the direct method and was refined on a Silicon Graphics Indigo EWS.

**Physical Measurements** An aqueous solution of [$PtCl_2$(*S*-azeda)] was employed to obtain a CD spectrum with a Jasco J-20 spectropolarimeter. $^1$H-NMR spectra of perchlorate salts was obtained after treatment of a $D_2O$ solution with tetraphenylarsonium chloride using JEOL GX-400 and EX-270 spectrometers, with TSP as an internal standard.

## Results

**Crystal Structures of [$PtCl_2$(azida)] and [$PtCl_2$(*S*-azeda)]** Crystals suitable for X-ray crystallography were mounted on a glass capillary.

Two crystallographically independent molecules (A and B) were found for both and have the essentially same structures for each crystal. The absolute configuration of [$PtCl_2$(*S*-azeda)] was verified by the *R*-values method. The *R* and $R_w$ values after convergence are: 0.0415 and 0.0354 for *R* and 0.0275 and 0.0279 for *S* at the $C_2$ at the stage of near final refinement using nonisotropic thermal factors for nonhydrogen atoms. Views of the structures of molecules A of [$PtCl_2$(azida)] and [$PtCl_2$(*S*-azeda)] are given in Fig. 3. Both compounds have common features: the two nitrogen atoms of the diamine and two chloride ions coordinate to platinum(II) to form a square planer complex in each system. Azida and *S*-azeda act as a bidentate ligand and the five-membered chelate ring has a distorted *gauche* conformation with an absolute conformation of $\lambda$ and the absolute configuration of the coordinated secondary amine is *S* for the latter. The three-membered aziridine ring and four-membered azetidine ring is fused with the chelate ring in a *cis*-orientation. The three-membered aziridine ring is almost a regular triangle but the four-membered azetidine ring is slightly folded: the dihedral angles between the plane defined by $N_1$, $C_1$, and $C_3$ and the plane defined by $C_1$, $C_2$, and $C_3$ are 21.9 and 20.6° for molecules, A and B, respectively.

Table 1. Summary of Crystallographic Data for [$PtCl_2$(azida)] (**1**) and [$PtCl_2$(*S*-azeda)] (**2**)

| Complex | **1** | **2** |
|---|---|---|
| Formula | $C_6H_{16}N_4Cl_4Pt_2$ | $C_8H_{20}N_4Cl_4Pt_2$ |
| F. weight | 676.21 | 704.26 |
| Cry. size/mm | 0.15, 0.09, 0.06 | 0.30, 0.09, 0.06 |
| Space group | $P2_1/n$ | $P2_12_12_1$ |
| *a*/Å | 8.011 (3) | 8.070 (3) |
| *b*/Å | 11.464 (2) | 25.569 (4) |
| *c*/Å | 15.599 (2) | 8.012 (3) |
| $\beta$/° | 103.66 | — |
| *U*/Å$^3$ | 1392.1 (5) | 1653.1 (9) |
| *Z* | 4 | 4 |
| *D*c/g cm$^{-3}$ | 3.26 | 2.83 |
| $\mu$/mm$^{-1}$ | 20.7 | 17.5 |
| Total data | 3597 | 2235 |
| Observed | 2531 [$I>3\sigma(I)$] | 1932 [$I>3\sigma(I)$] |
| Least-squares | 146 | 163 |
| Refinement method | Full-matrix | Full-matrix |
| $R^{b)}$ | 0.032 [$I>3\sigma(I)$] | 0.024 [$I>3\sigma(I)$] |
| $R_w^{c)}$ | 0.030 [$I>3\sigma(I)$] | 0.018 [$I>3\sigma(I)$] |

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

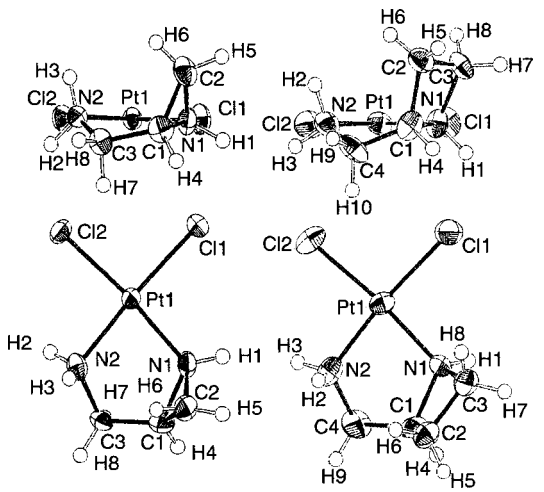


Fig. 3. Molecular Structures of Molecule A of the [$PtCl_2$(azida)] (Left) and [$PtCl_2$(*S*-azeda)] (Right) Complex Viewed along the Bisector of the N–Pt–N Angle and Perpendicular to the Coordination Plane

**NMR study** $^1$H-NMR spectra of [Pt(bpy)(azida)]$Cl_2$ and

[Pt(bpy)(*S*-azeda)]$(NO_3)_2$ were assigned by means of $^1H$–$^1H$ COSY spectra. The protons are designated as shown in Fig. 3. The methylene protons of the 2-aminomethyl group appear as a double doublet and a doublet at 3.70 ($H_8$) and 3.02 ppm ($H_7$) for [Pt(bpy)(azida)]$^{2+}$ and at 3.07 ($H_9$) and 2.89 ppm ($H_{10}$) for [Pt(bpy)(*S*-azeda)]$^{2+}$, respectively. $H_4$ (4.57 ppm) and $H_7$ and $H_8$ of *S*-azeda was shifted down-field, while $H_5$ (2.53 ppm) and $H_6$ (3.00 ppm) of the azida complex was shifted higher field. The appearance of the upfield signals for aziridine ring has been reported for 1-aziridine propionitrile.[20] The azida complex showed characteristic coupling constants due to the presence of the aziridine ring. The geminal coupling constant, $^2J_{H5,H6}$, was very small, 2.8 Hz. The vicinal couplings, $^3J_{H4,H5}$ and $^3J_{H4,H6}$, were 5.7 and 7.3 Hz. These small coupling constants are characteristic of the presence of an aziridine ring. The coupling constants between $H_4$ and $H_7$ or $H_8$ are small: $^3J_{H4,H7}<1$ Hz and $^3J_{H4,H8}=5.3$ Hz. The coupling constants for the azeda complex between $H_4$ and $H_9$ or $H_{10}$ were also small: 5.3 Hz and 1.3 Hz, respectively. This coupling behavior is consistent with the structure of *S*(*N*), $\lambda$ in Fig. 2, where the bridge head proton assumes an equatorial orientation with respect to the five-membered chelate ring.

By employing a 270 MHz spectrometer, the coupling between $^{195}Pt$ was observed for $H_5$ (30 Hz) and $H_8$ (37.5 Hz) for the azida complex but only for $H_8$ (50 Hz) in the case of the *S*-azeda complex.

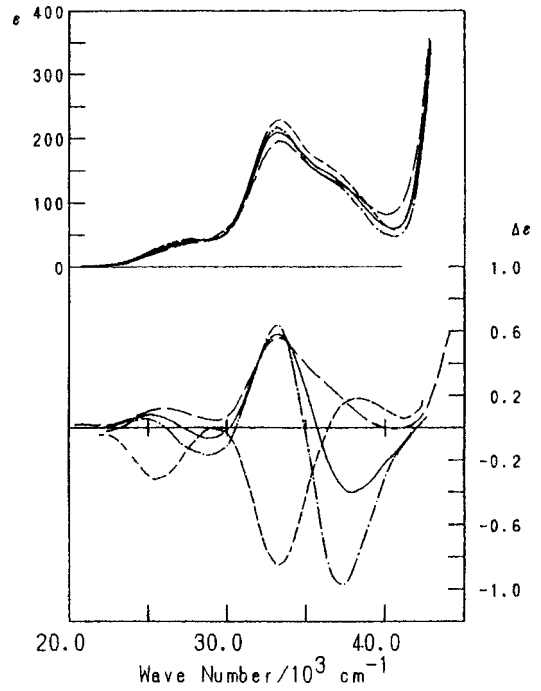


Fig. 4. Electronic and CD Spctra of [$PtCl_2$(*S*-pyrda)] (———); [$PtCl_2$(*S*-azeda)] (— — —); *R*(*N*)-[$PtCl_2$(Me-*S*-pn)] (– – – – –); *S*(*N*)-[$PtCl_2$(Me-*S*-pn)] (— · — · —)

**Electronic and CD Spectral Study** The electronic and CD spectra of [$PtCl_2$(*S*-azeda)] are shown in Fig. 4 along with those of *R*(*N*)- and *S*(*N*)-[$PtCl_2$(Me-*S*-pn)][14] and [$PtCl_2$(*S*-pyrda)].[21] The electronic spectra of these compounds resemble each other but the CD spectra showed a positive Cotton effect around 33000 cm$^{-1}$ for *S*(*N*)-[$PtCl_2$(Me-*S*-pn)], [$PtCl_2$(*S*-pyrda)], and [$PtCl_2$(*S*-azeda)]. The sign of the Cotton effect in this region was reported to reflect the absolute configuration of the coordinated secondary amine.[14] Therefore the absolute configuration of the secondary amine of these complexes can be assigned as *S*. Both the secondary amine and the conformation of the chelate ring contribute to the Cotton effect in the region between 37000 and 38000 cm$^{-1}$. In this region the magnitude of the Cotton effect is reduced in the order *S*(*N*)-[$PtCl_2$(Me-*S*-pn)], [$PtCl_2$(*S*-pyrda)], and [$PtCl_2$(*S*-azeda)]. It should be noted that the alkyl group attached to the carbon ($C_2$) next to nitrogen atom is located exclusively equatorial, axial or equatorial,[22] and exclusively axial for *S*(*N*)-[$PtCl_2$(Me-*S*-pn)], [$PtCl_2$(*S*-pyrda)], and [$PtCl_2$(*S*-azeda)] respectively.

## Discussion

The structural parameters shown in Chart 1 of the chelate ring spanned by 2-aminomethyl-1-azacycloalkanes on coordination to Pt(II) are tabulated for azida, azeda, pyrda, and pipda in Table 2. Though bond lengths do not change significantly and bond angles ($\theta_2$–$\theta_5$) have a tendency to become wide as the number of member of azacycloalkane become smaller, the absolute value of the torsion angle, $\omega$, become significantly smaller.

Projections of [Pt(CBDCA)(*S*-pyrda)], [Pt(bpy)(pipda)]$^{2+}$, and [Pt(CBDCA)(pipda)] are shown in Fig. 5 for comparison, where the other ligands present are removed for the sake of simplicity (CBDCA for [Pt(CBDCA)(pyrda)], bpy for *cis*-fused-[Pt(bpy)(pipda)]$^{2+}$ and CBDCA for *trans*-fused-[Pt(CBDCA)(pipda)] respectively. Details of these structures have already been reported.[15,23] The pyrda complex falls in the *S*(*N*)$\lambda$ type with the pyrrolidine ring fused with the

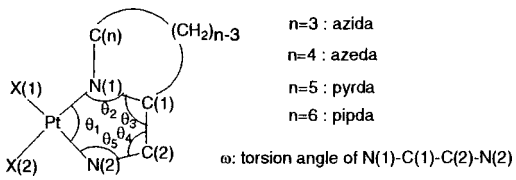


Chart 1

Table 2. Comparisons of Stereochemistry of Chelate Rings Formed by 2-Aminomethyl-1-azacycloalkane on Coordination to Pt(II)

| *n* | X(1), X(2) | Pt–N(1) | N(1)–C(1) | C(1)–C(2) | C(2)–N(2) | N(2)–Pt | $\theta_1$ | $\theta_2$ | $\theta_3$ | $\theta_4$ | $\theta_5$ | $\omega$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | Cl | 2.013 (9) | 1.49 (1) | 1.48 (2) | 1.49 (1) | 2.036 (9) | 83.0 (4) | 113.4 (7) | 113.3 (9) | 110.4 (9) | 111.3 (7) | −26 (1) |
| | | 2.026 (9) | 1.47 (1) | 1.48 (2) | 1.47 (1) | 2.049 (9) | 82.5 (4) | 113.5 (7) | 113.5 (9) | 112 (1) | 111.2 (7) | −25 (1) |
| 4 | Cl | 2.013 (8) | 1.54 (1) | 1.49 (1) | 1.49 (1) | 2.013 (9) | 84.7 (3) | 110.1 (5) | 111.1 (8) | 108.6(8) | 109.7 (6) | −41 (1) |
| | | 2.026 (8) | 1.52 (1) | 1.51 (1) | 1.50 (1) | 2.026 (8) | 84.2 (3) | 111.7 (6) | 111.6 (8) | 109.0 (9) | 110.4 (6) | −37 (1) |
| 5 | CBDCA | 2.019 (4) | 1.475 (7) | 1.512 (8) | 1.486 (8) | 1.998 (4) | 84.4 (2) | 112.6 (3) | 107.6 (4) | 111.1 (5) | 108.1 (4) | −43.4 (6) |
| 6 | 0.5 bpy | 2.039 (6) | 1.54 (1) | 1.46 (1) | 1.48 (1) | 2.030 (6) | 82.5 (2) | 105.9 (5) | 107.4 (5) | 108.6 (3) | 112.4 (5) | 50.1 (8) |
| 6 | CBDCA | 2.044 (3) | 1.504 (5) | 1.502 (5) | 1.485 (5) | 2.034 (3) | 83.4 (1) | 108.2 (2) | 105.8 (3) | 108.6 (3) | 109.5 (2) | 53.8 (4) |

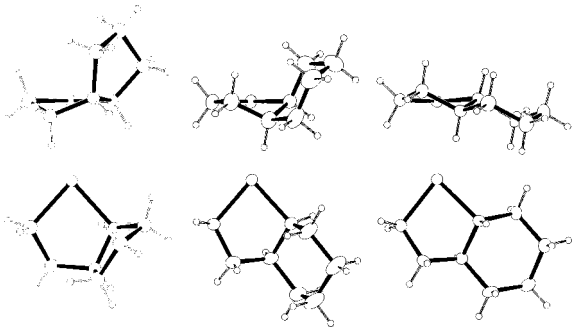

Fig. 5. Diamine–Pt(II) Chelate Ring Structures Viewed along the Bisector of the N–Pt–N Angle and Perpendicular to the Coordination Plane

Left, [Pt(CBDCA)(*S*-pyrda)]; center, $[Pt(bpy)(pipda)]^{2+}$; right, [Pt(CBDCA)(pipda)].

chelate ring is *cis*. However, the pipda complex can exist in either the *cis* and *trans*-fused forms. The former structure is adopted because of 2,2′-bipyridine or 1,10-orthophenanthroline and the stable structure would be the *trans*-fused type. The *cis*-fused structure shows that the absolute configuration of the asymmetric nitrogen is *S* but the conformation of the chelate ring is $\delta$.

**Relation of Structures and the Anti-tumor Efficacy of (2-Aminomethylazacycloalkane)platinum Complexes**

Morikawa *et al.* extensively examined the antitumor activity of these compounds.[4] The most effective compound is [Pt(CBDCA)(*R*-pyrda)].[5—11] [Pt(CBDCA)(azeda)] is also effective, and [Pt(CBDCA)(pipda)] was reported to be effective for p388 leukomia (*ip–ip*) but the latter has extremely low solubility.[4] From these data and present results, the active compounds seems to have *cis*-fused bicylic structures, the pipda complex can form a *cis*-fused structure but this structure would be expected to be less stable than the *trans*-fused structure. The binding of platinum compounds to double stranded DNA contains many stages, including aquation of the complex, preassociation with the DNA, monofunctional adduct formation, closure to a bifunctional adduct, and distortion of the DNA.[24] Dichloro(1,4-diazacycloheptane)platinum(II) has been reported to form two-fold fewer GpG and ApG intrastrand adduct than [$PtCl_2$(1,2-ethanediamine)] because of steric hindrance with DNA.[25] Present study shows that 2-aminomethyl-1-azacycloalkane-platinum(II) unit may be allowed to bind DNA when the additional ring is extended in the perpendicular direction, which is accomplished by *cis*-fusion of the chelate ring and the azacycloalkane. It has also been reported [$PtCl_2$(azida)] is ineffective.[4] Though we cannot give a precise reason for this, azida forms a rather special chelate ring with a small $N_1$–$C_1$–$C_2$–$N_2$ torsion angle and, as a result, the orientation of the N–H bond to the DNA main chain P–$O^-$ will be distorted and the formation of a three-membered aziridine ring requires a reduction in bond length and the total strain energy would be higher than that for homologues although the low p$K_a$ value of the aziridine nitrogen has been pointed.[4]

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**References and Notes**

1) Reedijk J., *Chem. Commun.*, **1996**, 801—806 (1996).
2) Rosenberg B., "Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug," ed. by Lippert B., Wiley-VCH, Weinheim, 1999, pp. 3—27.
3) O'Dwyer P. J., P. Stevenson J., W. Johnson S., "Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug," ed. by Lippert B., Wiley-VCH, Weinheim, 1999, pp. 31—69.
4) Morikawa K., Honda M., Endoh K., Matsumoto T., Akamatsu K., Mitsui H., Koizumi M., *J. Pharm. Sci.*, **79**, 750—753 (1990).
5) Matsumoto T., Endoh K., Akamatsu K., Kamisango K., Mitsui H., Koizumi K., Morikawa K., Koizumi M., Matsuno T., *Br. J. Cancer*, **64**, 41—46 (1991).
6) Endoh K., Akamatsu K., Matsumoto T., Morikawa K., Honda M., Mitsui H., Koizumi M., Koizumi K., Matsuno T., *Anticancer Res.*, **9**, 987—992 (1989).
7) Tamura K., Makino S., Araki Y., *Cancer*, **66**, 2059—2063 (1990).
8) Iwata M., Izuta S., Suzuki M., Kojima K., Furuhasi Y., Tomoda Y., Yoshida S., *Jpn. J. Cancer Res.*, **82**, 433—439 (1991).
9) Kobayashi H., Takemura Y., Miyachi H., Ogawa T., *Investigational New Drugs*, **9**, 313—319 (1991).
10) Morikawa K., Honda M., Endoh K., Matsumoto T., Akamatsu K., Mitsui H., Koizumi M., *J. Pharm. Sci.*, **80**, 837—842 (1991).
11) Morikawa K., Honda M., Endoh K., Matsumoto T., Akamatsu K., Mitsui H., Koizumi K., *Chem. Pharm. Bull.*, **38**, 930—935 (1990).
12) Hawkins C. J., Palmer J. A., *Coord. Chem. Rev.*, **44**, 1—60 (1982).
13) Goto M., Tsuruda N., Fujioka S., Kurosaki H., *Bull. Chem. Soc. Jpn.*, **72**, 1803—1806 (1999).
14) Bosnich B., Sullivan E. A., *Inorg. Chem.*, **14**, 2768—2773 (1975).
15) Goto M., Yamamoto Y., Sumimoto M., Tsuruda N., Kurosaki H., *Chem. Pharm. Bull.*, **51**, 1157—1162 (2003).
16) Morgan G. T., Burstall F. H., *J. Chem. Soc.*, **1934**, 965—971 (1934).
17) Spivack J. D., U.S. Patent, 2931804 (1960) [*Chem. Abstr.*, **55**, 1651 (1961)].
18) Philips B. A., Cromwell N. H., *J. Heterocyclic Chem.*, **10**, 795—799 (1973).
19) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation, Houston, TX, 1985 and 1999.
20) Saito H., Nukada T., Morito K., *J. Am. Chem. Soc.*, **89**, 6605—6611 (1965).
21) Preparation of [$PtCl_2$(*S*-pyrda)] was described in ref. 15. CD spectrum of an aqueous solution was measured.
22) Goto M., Tsuruda N., Fujioka S., Kurosaki H., *Bull. Chem. Soc. Jpn.*, **72**, 1803—1806 (1999).
23) Yonei M., Murata H., Itoh M., Watanabe Y., Ochi K., Honda N., Nawata Y., *Acta Cryst.*, **C46**, 137—138 (1990).
24) Hambley T. W., *J. Chem. Soc., Dalton Trans.*, **2001**, 2711—2718 (2001).
25) Hambley T. W., Ling E. C. H., Munk V. P., Davies M. S., *J. Biol. Inorg. Chem.*, **6**, 534—542 (2001).