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# Preparation of Platinum(II) Complexes of Diamine Isomers [PtX(1,3-Diamine)] (X=$Cl_2$, $SO_4$, $(NO_3)_2$, Oxalato, D-Glucuronato, and D-Gluconato) and Determination of Their Antitumor Activity against Leukemia L1210

Koji Okamoto,[a,1)] Masahide Noji,[a] Tazuko Tashiro,[b] and Yoshinori Kidani*,[a]

*Faculty of Pharmaceutical Sciences, Nagoya City University,[a] Tanabe-dori, Mizuho-ku, Nagoya 467, Japan and Division of Experimental Chemotherapy, Cancer Chemotherapy Center,[b] 1-37-1, Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan*

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Platinum(II) complexes of the type [PtX(1,3-diamine)] (X=$Cl_2$, $SO_4$, $(NO_3)_2$, oxalato, D-glucuronato, and D-gluconato; 1,3-diamine=2-(aminomethyl)cyclohexylamine, 2,4-pentanediamine, 1,3-butanediamine, and 1,3-diphenyl-1,3-propanediamine isomers) were prepared, and their antitumor activity against leukemia L1210 was tested according to the protocol recommended by the National Cancer Institute for the evaluation of Pt analogs. A large number of long-term survivors was observed with certain analogs, though the therapeutic indices were not large. Among the platinum(II) complexes tested so far, *trans-l-* and *cis-l*-2-(aminomethyl)cyclohexylamine platinum(II) complexes showed marked antitumor activity, while 1,3-diphenyl-1,3-propane diamine platinum(II) complexes were almost inactive because of their low solubility in water.

The structures of the complexes are discussed on the basis of the circular dichroism (CD) and $^{13}C$-nuclear magnetic resonance (NMR) spectral data. The structure of the *cis-l*-2-(aminomethyl)cyclohexylamine complex was much more flexible than that of the *trans-l*-2-(aminomethyl)cyclohexylamine complex, and the cyclohexane ring and the chelate ring of the latter lie in a common plane.

The coplanarity of *trans*-2-(aminomethyl)cyclohexylamine and the flexibility of *cis*-2-(aminomethyl)cyclohexylamine may allow them to approach the target DNA relatively easily.

**Keywords**——platinum(II) complex of 1,3-diamine; CD; $^{13}C$-NMR; antitumor activity; structure-activity relationship

## Introduction

In order to examine the structure activity relationship of platinum(II) complexes having bidentate ligands, we previously determined the antitumor activity of various platinum(II) complexes of 1,2-cyclohexanediamine(=dach) and 2-(aminomethyl)cyclohexylamine(=amcha) isomers against leukemia P388.[2,3)] The latter six-membered complexes exhibited higher activity than the former five-membered complexes in this tumor system.

In addition to the amcha platinum(II) complexes, we newly synthesized the following six-membered platinum(II) complexes: [PtX(1,3-diamine)] (X=$SO_4$, $(NO_3)_2$, oxalato, D-glucuronato, and D-gluconato), where the 1,3-diamine is 2,4-pentanediamine(=ptn), 1,3-butanediamine(=bn), and 1,3-diphenyl-1,3-propanediamine(=dppn). The antitumor activity of these compounds against leukemia L1210 was tested (Chart 1). Furthermore, in order to clarify the relation of the steric structure to the antitumor activity of six-membered platinum complexes, we determined the conformations of the six-membered chelates on the basis of the circular dichroism (CD) and $^{13}C$-nuclear magnetic resonance (NMR) spectral data.

In this paper, we describe the antitumor activity and structures of platinum (II) complexes containing 1,3-diamine.

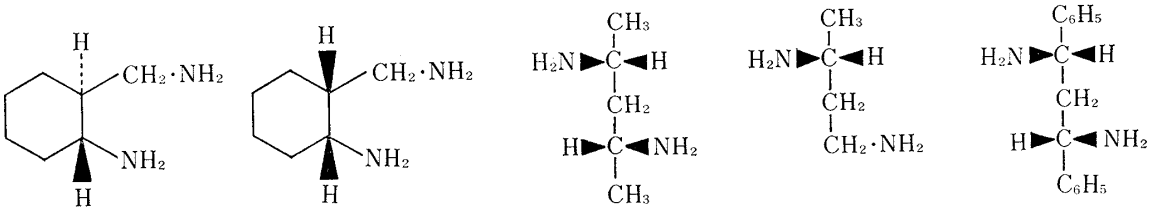


Chart 1

## Experimental

**Ligands**——The ligands amcha,[4] ptn,[5] bn,[6,7] dppn,[8] and their platinum(II) complexes[9–13] were prepared by the cited methods.

Elemental analysis data for the platinum(II) complexes obtained are shown in Table I.

**Evaluation of Antitumor Activity**——Leukemia L1210 ($10^5$ cells) was transplanted intraperitoneally into $CDF_1$ mice on day 0. Treatment was given intraperitoneally three times, on days 1, 5, and 9, according to the National Cancer Institute(=NCI) Protocol. The mean survival times of the treated($T$) and control($C$)

Table I. Elemental Analyses of amcha, ptn, bn, and dppn Platinum (II) Complexes

| Complexes | Analysis (%) | | | | | |
|---|---|---|---|---|---|---|
| | Calcd | | | Found | | |
| | C | H | N | C | H | N |
| [$PtCl_2$(*cis-d*-amcha)] | 21.32 | 4.10 | 7.11 | 21.72 | 4.14 | 7.20 |
| [$PtCl_2$(*cis-l*-amcha)] | 21.32 | 4.10 | 7.11 | 21.20 | 3.98 | 6.96 |
| [$PtCl_2$(*trans-d*-amcha)] | 21.32 | 4.10 | 7.11 | 20.98 | 4.18 | 6.88 |
| [$PtCl_2$(*trans-l*-amcha)] | 21.32 | 4.10 | 7.11 | 21.09 | 3.96 | 6.97 |
| [$PtCl_2$(*d*-ptn)] | 16.31 | 3.84 | 7.61 | 16.28 | 3.84 | 7.56 |
| [$PtCl_2$(*l*-ptn)] | 16.31 | 3.84 | 7.61 | 16.56 | 3.91 | 7.78 |
| [$PtCl_2$(*meso*-ptn)] | 16.31 | 3.84 | 7.61 | 16.23 | 3.89 | 7.65 |
| [$PtCl_2$(*d*-dn)] | 13.56 | 3.42 | 7.91 | 13.90 | 3.53 | 7.86 |
| [$PtCl_2$(*l*-bn)] | 13.56 | 3.42 | 7.91 | 13.55 | 3.56 | 7.79 |
| [$PtCl_2$(*l*-dppn)] | 36.59 | 3.69 | 5.69 | 36.40 | 3.78 | 5.79 |
| [$PtCl_2$(*meso*-dppn)] | 36.59 | 3.69 | 5.69 | 36.62 | 3.85 | 5.67 |
| [$Pt(SO_4)$(*cis-d*-amcha)]·$H_2O$ | 19.22 | 4.16 | 6.41 | 19.35 | 4.00 | 6.08 |
| [$Pt(SO_4)$(*cis-l*-amcha)]·$H_2O$ | 19.22 | 4.16 | 6.41 | 19.26 | 4.22 | 6.61 |
| [$Pt(SO_4)$(*trans-d*-amcha)]·$H_2O$ | 19.22 | 4.16 | 6.41 | 18.40 | 4.07 | 6.03 |
| [$Pt(SO_4)$(*trans-l*-amcha)]·$H_2O$ | 19.22 | 4.16 | 6.41 | 19.15 | 4.14 | 6.10 |
| [$Pt(SO_4)$(*l*-ptn)]·$H_2O$ | 14.60 | 3.93 | 6.81 | 14.90 | 3.97 | 6.76 |
| [$Pt(SO_4)$(*l*-bn)]·$H_2O$ | 12.09 | 3.56 | 7.05 | 12.30 | 3.59 | 6.95 |
| [$Pt(SO_4)$(*l*-dppn)]·$3H_2O$ | 31.52 | 4.24 | 4.90 | 31.44 | 3.60 | 4.82 |
| [$Pt(NO_3)_2$(*cis-d*-amcha)] | 18.79 | 3.61 | 12.53 | 18.76 | 3.40 | 12.44 |
| [$Pt(NO_3)_2$(*cis-l*-amcha)] | 18.79 | 3.61 | 12.53 | 18.91 | 3.57 | 12.38 |
| [$Pt(NO_3)_2$(*trans-d*-amcha)] | 18.79 | 3.61 | 12.53 | 18.99 | 3.73 | 12.34 |
| [$Pt(NO_3)_2$(*trans-l*-amcha)] | 18.79 | 3.61 | 12.53 | 19.23 | 3.83 | 12.50 |
| [$Pt(NO_3)_2$(*d*-ptn)] | 14.25 | 3.36 | 13.30 | 14.06 | 3.40 | 12.87 |
| [$Pt(NO_3)_2$(*l*-ptn)] | 14.25 | 3.36 | 13.30 | 14.13 | 3.38 | 12.93 |
| [$Pt(NO_3)_2$(*meso*-ptn)] | 14.25 | 3.36 | 13.30 | 14.23 | 3.42 | 13.39 |
| [$Pt(NO_3)_2$(*d*-bn)] | 11.80 | 2.98 | 13.76 | 12.19 | 3.06 | 13.62 |
| [$Pt(NO_3)_2$(*l*-bn)] | 11.80 | 2.98 | 13.76 | 11.72 | 3.00 | 13.70 |
| [$Pt(NO_3)_2$(*l*-dppn)]·$1/2H_2O$ | 32.49 | 3.46 | 10.11 | 31.98 | 3.50 | 10.67 |
| [Pt(ox)(*cis-d*-amcha)] | 26.28 | 3.93 | 6.81 | 26.12 | 3.82 | 7.00 |
| [Pt(ox)(*cis-l*-amcha)] | 26.28 | 3.93 | 6.81 | 26.02 | 3.90 | 6.84 |
| [Pt(ox)(*trans-d*-amcha)] | 26.28 | 3.93 | 6.81 | 26.50 | 3.84 | 6.89 |
| [Pt(ox)(*trans-l*-amcha)] | 26.28 | 3.93 | 6.81 | 25.82 | 3.78 | 6.82 |
| [Pt(ox)(*l*-bn)] | 19.41 | 3.26 | 7.55 | 19.42 | 3.33 | 7.62 |

ox=oxalato.

groups (6 mice/group) were calculated, and the antitumor activity was expressed as $T/C(\%)$. Values of $T/C$ exceeding 125 were taken as indicating effectiveness.

**Apparatus**——FT $^{13}$C-NMR spectra were obtained at 25 MHz with broad-band proton decoupling on a JEOL JNM-FX-100 spectrometer, employing the solvent deuterium signal as an internal lock. A total of 14400—25800 FID's (8192 points) were averaged to provide the desired signal-to-noise ratio in the 2.5-kHz frequency spectra. Pulse angles of 45° were employed with no pulse delay. The ambient temperature was room temperature. TMS sealed in a capillary was used as an external reference.

Ultraviolet (UV) spectra were obtained in $H_2O$ with a Shimadzu UV 200 recording spectrometer.

CD spectra were measured in $H_2O$ with a JASCO J-40 spectropolarimeter. All measurements were performed at room temperature.

## Results and Discussion

### $^{13}$C-NMR Spectra

Recently Bagger[14] and Erickson *et al.*[15] have demonstrated that in 1,2-diamine platinum-(II) complexes the coupling constant $^3J_{Pt-N-C-C}$ showed a Karplus-type angle dependence on the dihedral angle between the planes Pt–N–C and N–C–C. In our recent studies,[16,17] the equation $^3J_{Pt-N-C-C}=a\cos^2\phi$ could also be applied to 1,3-diamine platinum(II) complexes, $\phi$ being the dihedral angle between the planes Pt–N–C and N–C–C, and $a$ being a constant. The conformation of [Pt($SO_4$)(*trans-l*-amcha)] was a fixed chair form on the basis of the CD spectral data, while [Pt($SO_4$)(*cis-d*-amcha)] was interconverting between two chair forms,[17] as shown in Fig. 1. When [Pt($SO_4$)(*trans-l*-amcha)] takes the chair form, the dihedral angle of Pt–N–C(1)–C(6) is about 180°, according to the above equation $^3J_{Pt-C(6)}=a$ (Fig. 2). The $^3J_{Pt-C(6)}$ value observed for [Pt($SO_4$)(*trans-l*-amcha)] was 55.5 Hz, *i.e.*, $a$ was 55.5. By using the $a$ value, we will discuss the conformations of other diamine platinum(II) complexes.

Figure 3 shows $^{13}$C-NMR spectra of [Pt($SO_4$)(*l*-ptn)] and [Pt($NO_3$)$_2$(*l*-ptn)]. Table II lists $^{13}$C-NMR chemical shifts and coupling constants between $^{195}$Pt and $^{13}$C nuclei.

As shown in Fig. 4, possible conformations of the chelate ring of [Pt($SO_4$)(*l*-ptn)] and [Pt($NO_3$)$_2$(*l*-ptn)] are $\lambda$-skew, $\delta$-skew, or two chair forms. The $\lambda$-skew form has two equatorially oriented methyl groups, and the dihedral angle of Pt–N–CH–$CH_3$ is about 180°. The $\delta$-skew form has two axially oriented methyl groups, and the dihedral angle is about 60° (Fig. 5). If

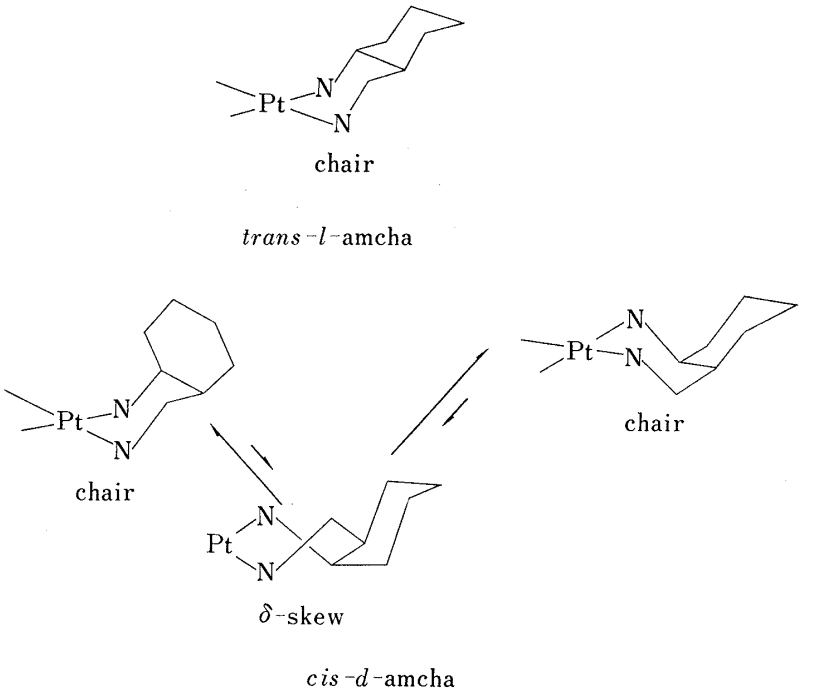


Fig. 1. Proposed Conformations of *trans-l-* and *cis-d*-amcha Platinum (II) Complexes

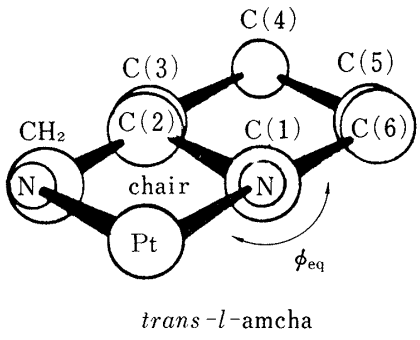


Fig. 2. The Chelate Ring viewed down an N–C Bond

[Pt($SO_4$)(*l*-ptn)] and [Pt($NO_3$)$_2$(*l*-ptn)] take two chair forms with axial-equatorial orientation and the two chair forms interconvert with each other *via* a skew intermediate rapidly on an NMR time scale, averaged coupling due to a rapid interconversion would give $^3J_{Pt-CH_3}=1/2(a\cos^2 180°+a\cos^2 60°)$ ($a$=55.5 Hz), *i.e.*, $^3J_{Pt-CH_3}$=34.7 Hz. Experimental values of $^3J_{Pt-CH_3}$ for [Pt($SO_4$)(*l*-ptn)] and [Pt($NO_3$)$_2$(*l*-ptn)] were 34.8 and 36.6 Hz, respectively. These

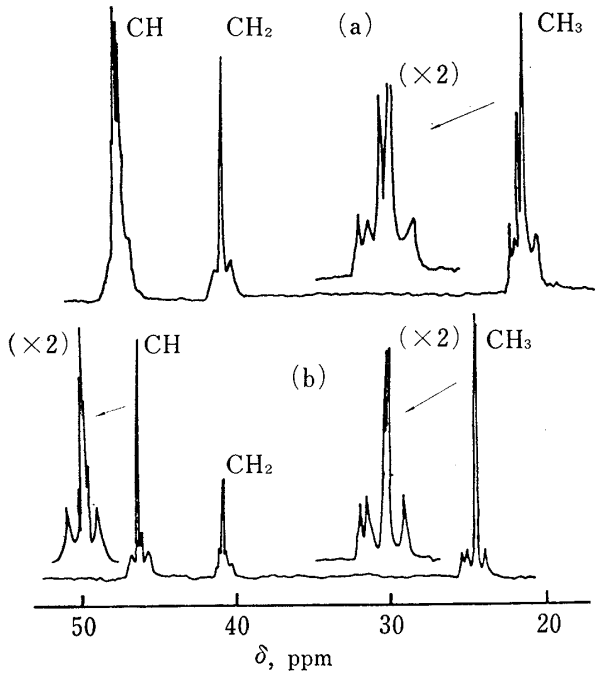


Fig. 3. $^{13}$C-NMR Spectra of (a) [Pt($SO_4$)(*l*-ptn)] and (b) [Pt($NO_3$)$_2$(*l*-ptn)] in $D_2O$

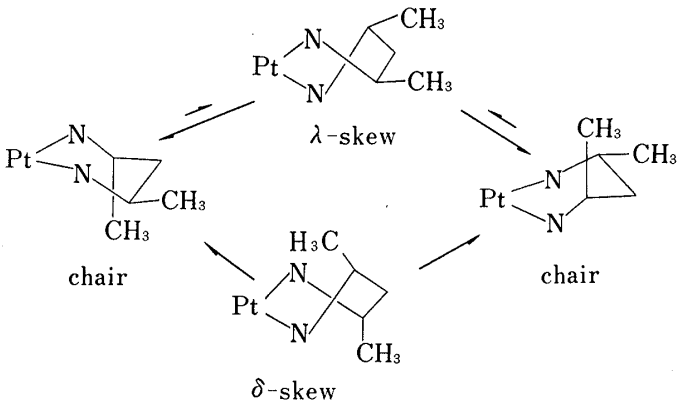


Fig. 4. Possible Conformations of the Chelate Ring of *l*-ptn Platinum (II) Complexes

TABLE II. $^{13}$C-NMR Chemical Shifts[a] and Coupling Constants[b]

| Complexes | CH | $CH_2$ | $CH_3$ |
|---|---|---|---|
| [Pt($NO_3$)$_2$(*l*-ptn)] | 47.24 | 40.76 | 21.69 |
| | (28.1) | 40.59 | 20.73 |
| | 47.15 | (26.3) | (36.6) |
| | 47.00 | | |
| [Pt($SO_4$)(*l*-ptn)] | 47.56 | 40.74 | 22.05 |
| | 47.44 | (25.6) | 21.37 |
| | (28.0) | | 21.10 |
| | 47.34 | | (34.8) |
| | 47.24 | | |
| [Pt($NO_3$)$_2$(*l*-bn)] | 50.46 | 42.79 | 20.98 |
| | (26.9) | (29.9) | (43.3) |
| | | 34.79 | |
| | | (30.5) | |
| [Pt($SO_4$)(*l*-bn)] | 50.75 | 43.37 | 21.73 |
| | 50.65 | 42.98 | 21.59 |
| | 50.46 | 42.83 | 21.42 |
| | 50.31 | 42.99 | (42.1) |
| | 49.95 | 42.52 | 21.32 |
| | | 34.91 | 21.17 |
| | | (30.5) | (42.7) |
| | | 34.84 | |

a) $^{13}$C shifts in ppm from external TMS.
b) The values in parentheses are the coupling constants ($^{195}$Pt-$^{13}$C).

values are in good accord with the expected coupling constant. Therefore, [Pt($SO_4$)(*l*-ptn)] and [Pt($NO_3$)$_2$(*l*-ptn)] are interconverting between two chair forms, and the population of intermediate skew form is small (Fig. 4).

Figure 6 shows $^{13}$C-NMR spectra of [Pt($SO_4$)(*l*-bn)] and [Pt($NO_3$)$_2$(*l*-bn)]. These complexes may take $\lambda$-skew, $\delta$-skew, or two chair forms. One of the chair forms and the $\lambda$-skew form have an equatorially oriented methyl group, and the other chair form and the $\delta$-skew form have an axial orientation of the methyl group. Thus the dihedral angle Pt–N–CH–$CH_3$ of 180° may be expected for either one chair form or a $\lambda$-skew form, and about 60° for the other chair form or a $\delta$-skew form, as shown in Fig. 7. Among these conformations, the $\lambda$- and $\delta$-skew forms are excluded by the CD spectral data, which will be discussed later. Furthermore, if two chair forms interconvert with each other rapidly on an NMR time scale,

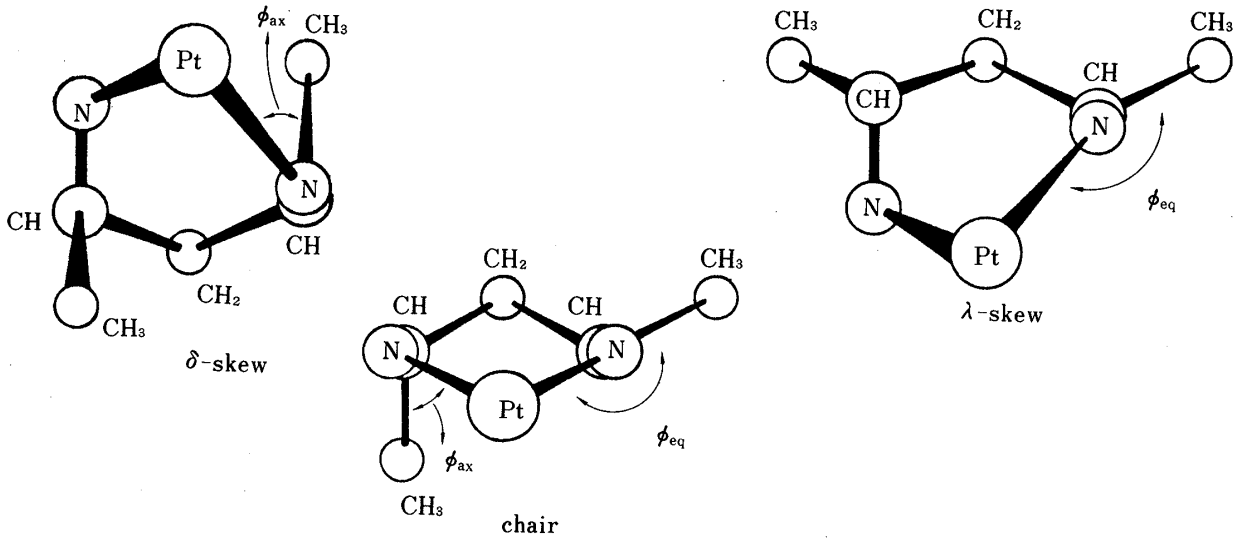


Fig. 5. The Chalate Ring viewed down an N–C Bond

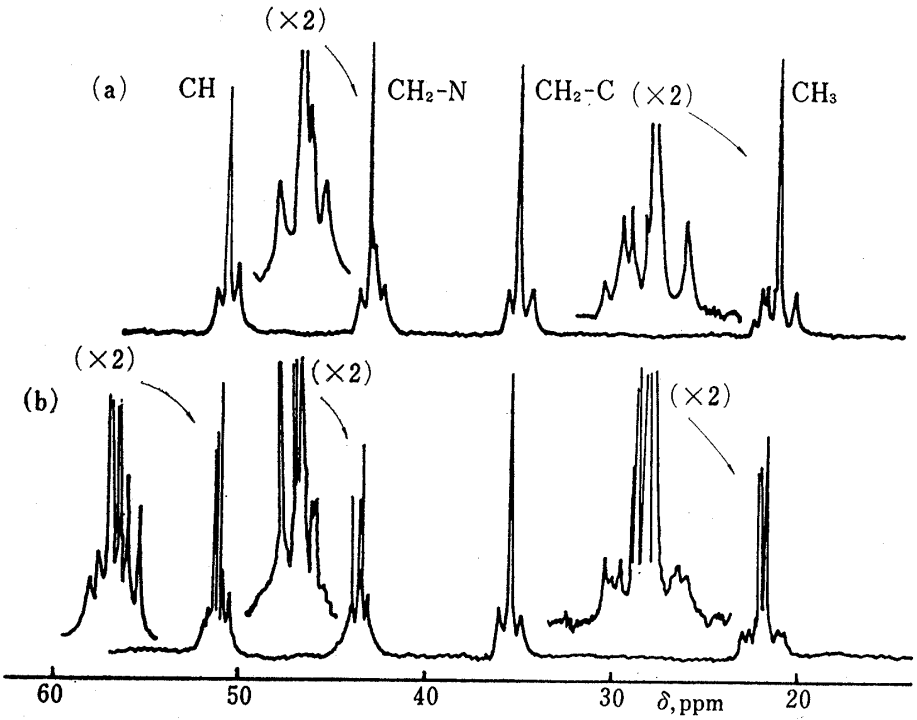


Fig. 6. $^{13}$C–NMR Spectra of (a) [Pt($NO_3$)$_2$(*l*-bn)] and (b) [Pt($SO_4$)(*l*-bn)] in $D_2O$

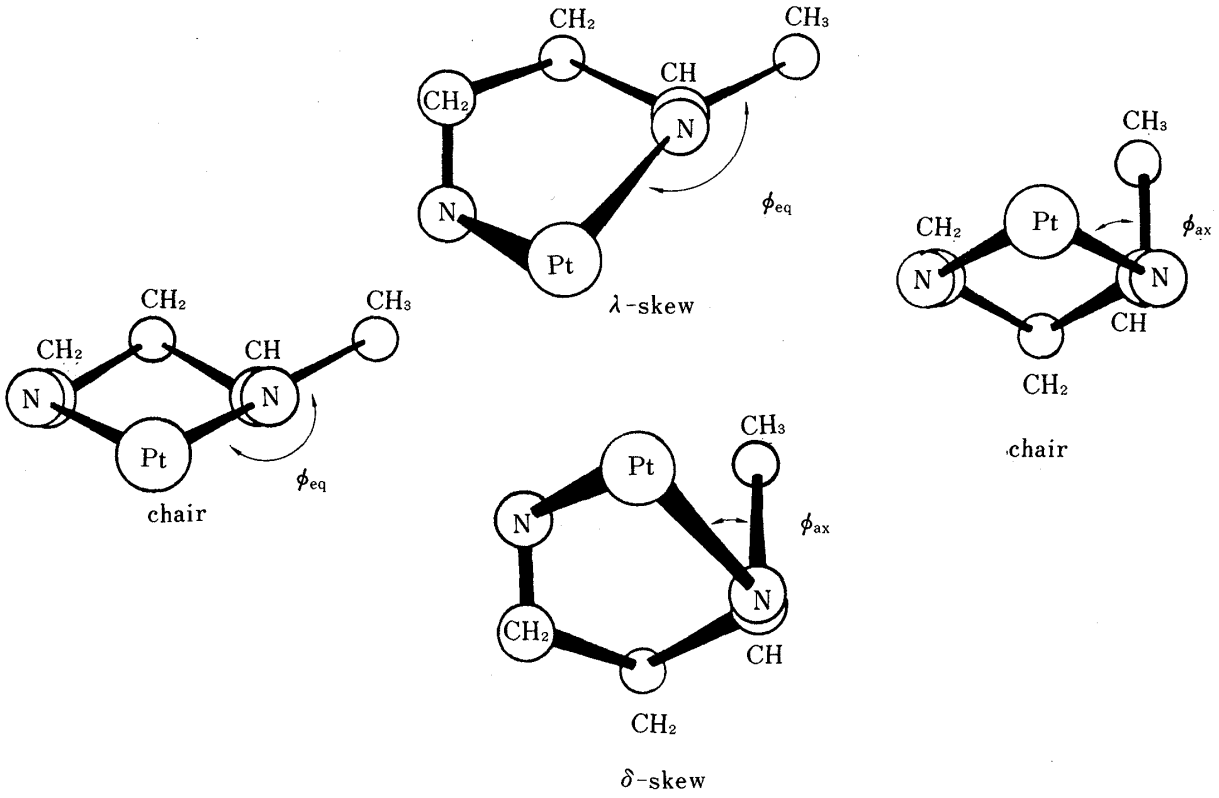


Fig. 7. The Chelate Ring viewed down an N–C Bond

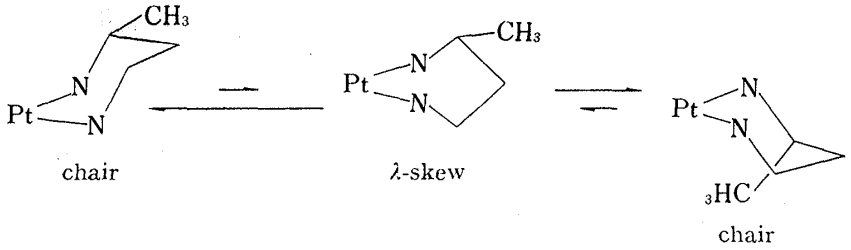


Fig. 8. Proposed Conformations of *l*-bn Platinum (II) Complexes

the averaged coupling constant due to rapid interconversion would be expected, as for the *l*-ptn complexes, *i.e.*, $^3J_{Pt-CH_3}$ is expected to be 34.7 Hz. However, experimental values of $^3J_{Pt-CH_3}$ for [Pt($SO_4$)(*l*-bn)] and [Pt($NO_3$)$_2$(*l*-bn)] were 42.1—42.7 and 43.3 Hz, respectively. Therefore, the population of the chair form with an equatorial-oriented methyl group may be larger than that of the axial methyl chair form, and the abundance ratio of equatorial and axial C–$CH_3$ may be 0.7 : 0.3 (Fig. 8).

**UV and CD Spectra**

Figures 9, 10, and 11 show the UV and CD spectra of the *l*-ptn, *l*-bn, and *d*-dppn platinum-(II) complexes, respectively. The CD spectra of [Pt($SO_4$)(*l*-bn)], [Pt($SO_4$)(*d*-dppn)], and [Pt($NO_3$)$_2$(*d*-dppn)] are very similar to those of the corresponding diammine complexes.[18] Table III shows the UV and CD spectral data of the platinum(II) complexes. The $|\Delta\varepsilon|$ (=the absolute CD strength) values of [Pt($SO_4$)(*l*-bn)] are lower than those of the five-membered platinum(II) complex, [Pt($NH_3$)$_2$(*l*-pn)] $Cl_2$,[19] and the low $|\Delta\varepsilon|$ values can be rationalized by considering only the vicinal effect. The CD spectral patterns and $|\Delta\varepsilon|$ values of [Pt($SO_4$)(*d*-dppn)] and [Pt($NO_3$)$_2$(*d*-dppn)] are similar to those of [Pt($NH_3$)$_2$(*l*-dppn)]$Cl_2$.[18] Therefore, the chelate ring of [Pt($SO_4$)(*l*-bn)] and *d*-dppn platinum complexes may take a chair form.

On the other hand, the $|\Delta\varepsilon|$ values of *l*-ptn platinum(II) complexes and $[Pt(NO_3)_2(l\text{-bn})]$ are also lower than those of the five-membered complexes.[19] However, the CD spectral patterns of the *l*-ptn complexes and $[Pt(NO_3)_2(l\text{-bn})]$ are very different from those of the corresponding diammine complexes,[18] so it is impossible to evaluate the correct CD strength.

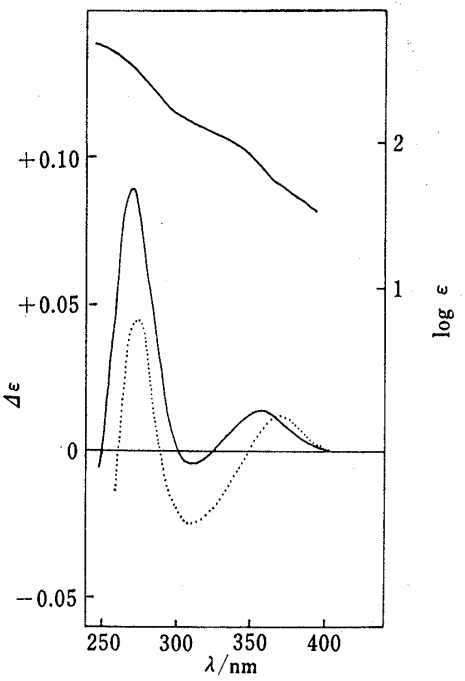


Fig. 9. UV and CD Spectra of $[Pt(SO_4)(l\text{-ptn})]$ —— and $[Pt(NO_3)_2(l\text{-ptn})]$ ····· in $H_2O$

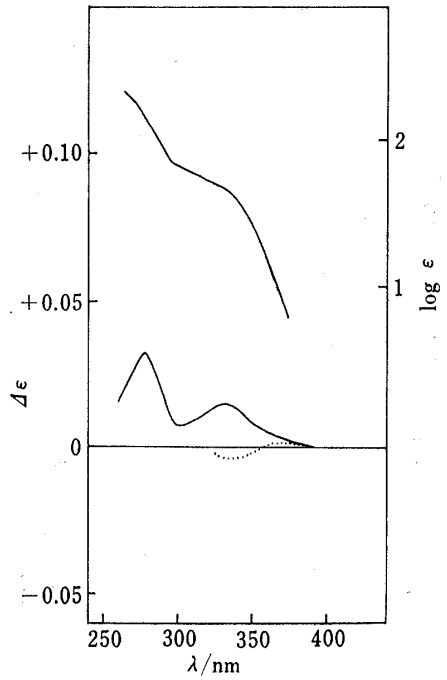


Fig. 10. UV and CD Spectra of $[Pt(SO_4)(l\text{-bn})]$ —— and $[Pt(NO_3)_2(l\text{-bn})]$ ····· in $H_2O$

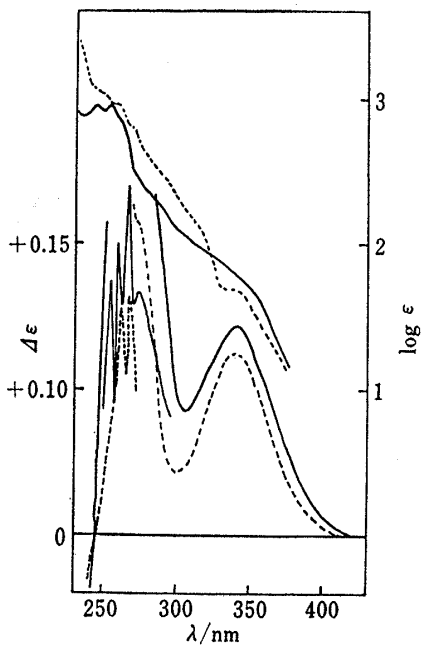


Fig. 11. UV and CD Spectra of $[Pt(SO_4)(d\text{-dppn})]$ —— and $[Pt(NO_3)_2(d\text{-dppn})]$ ---- in $H_2O$

TABLE III. UV and CD Spectral Data

| Complexes | UV λ/nm(log ε) | CD λ/nm (Δε) |
|---|---|---|
| $[Pt(SO_4)(l\text{-ptn})]$ | 330(2.06) | 355(+0.014) |
| | 270 sh. | 310(−0.004) |
| | 240(2.67) | 273(+0.089) |
| $[Pt(NO_3)_2(l\text{-ptn})]$ | | 370(+0.012) |
| | | 310(−0.025) |
| | | 273(+0.045) |
| $[Pt(SO_4)(l\text{-bn})]$ | 320(1.72) | 320(+0.006) |
| | 270 sh. | |
| | 240(2.47) | 275(+0.024) |
| | 215(2.81) | |
| $[Pt(NO_3)_2(l\text{-bn})]$ | | 375(+0.001) |
| | | 335(−0.004) |
| $[Pt(SO_4)(d\text{-dppn})]$ | 330(1.88) | 337(+0.145) |
| | 280(2.38) | 272(+0.332) |
| | 266 sh. | 266(+0.478) |
| | 259(2.88) | 259(+0.395) |
| | 254(2.96) | 254(+0.345) |
| | 247(2.95) | 235(−0.197) |
| $[Pt(NO_3)_2(d\text{-dppn})]$ | 320(1.99) | 337(+0.125) |
| | 280(2.59) | 272(+0.218) |
| | 267 sh. | 266(+0.328) |
| | 263 sh. | 260(+0.328) |
| | 256(2.99) | |
| | 250(3.01) | |

**Antitumor Activity**

Table IV shows the results of antitumor screening tests of platinum(II) complexes of amcha, ptn, bn, and dppn isomers against leukemia L1210. Among the platinum(II) complexes of these 1,3-diamine isomers tested, amcha platinum complexes showed the highest $T/C$ values. The order of the antitumor activity of complexes with different ligands is:

amcha $\gg$ ptn $>$ bn $\gg$ dppn

Among the dichloro platinum complexes of amcha isomers, the *cis-l* analog was the most effective, as shown in Fig. 12 and Table IV. In the case of the dichloro platinum complex of *cis-l*-amcha, 4 out of 6 treated mice survived the 30-day observation period with $T/C$ of 318% at a dose of $3\times6.25$ mg/kg (administered on days 1, 5, and 9). However, as shown in Table V, the therapeutic index of this complex is not large because of its toxicity, and its solubility in water was poor. The dichloro platinum complexes of dppn isomers were quite inactive, possibly because of their low solubility. The solubility of the platinum complexes in water is very important for antitumor activity.

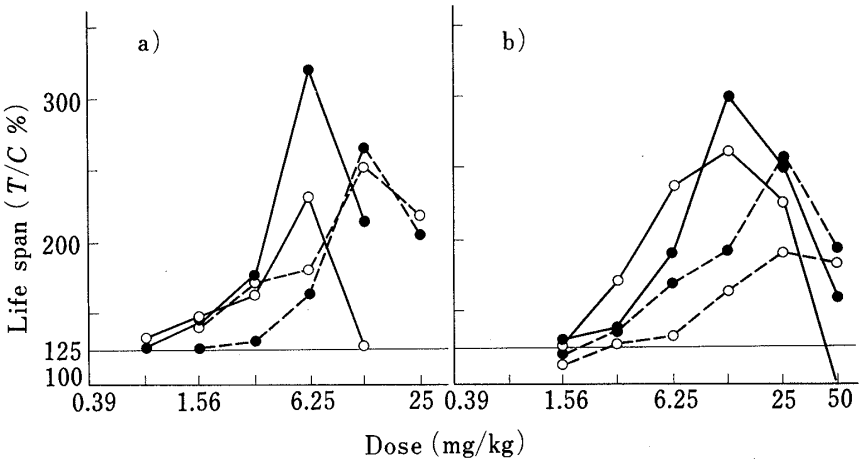


Fig. 12. Dose–Response Curves of the Platinum (II) Complexes of amcha

—●—: *cis-l*, —○—: *cis-d*, ---●---: *trans-l*, ---○---: *trans-d*.
a) [$PtCl_2$(amcha)], b) [Pt(D-gluconato)(amcha)].

In order to obtain more water-soluble complexes by modifying the leaving groups, sulfato and dinitrato platinum complexes were prepared. Sulfato and dinitrato platinum complexes of *meso*-ptn were somewhat effective, showing one long-term survivor among 6 mice, at a dose of 12.5 mg/kg, though the other complexes were not especially effective.

The oxalato platinum complexes of 1,3-diamine have fairly high $T/C$ values, and the platinum complexes of amcha isomers were especially effective, giving 1 to 2 long-term survivors among 6 mice. The oxalato platinum complex of *d*-ptn exhibited a higher $T/C$ value (314% with 3 long-term survivors among 6 mice, treated at a dose of 12.5 mg/kg) than *l*- and *meso*-ptn. Contrary to expectation, the oxalato platinum complexes were not readily soluble in water.

D-Glucuronato and D-gluconato complexes were synthesized in the hope of obtaining reduced toxicity in the kidneys, owing to their high solubility in water. In fact, these complexes were hygroscopic except for the dppn isomers. Among D-glucuronato platinum complexes of 1,3-diamine, amcha isomers were superior to the other 1,3-diamine complexes, as shown in Table IV, but there was little difference in $T/C$ values among amcha isomers. As to the D-gluconato complexes, the platinum complexes of amcha isomers were also the effective. Although there was little difference in T.I. (therapeutic index=optimal dose/minimum effective dose) values among amcha isomers, as shown in Table V, *cis-l*-amcha was superior to *trans-l*-amcha; the former gave a $T/C$ of 300% with 2 long-term survivors among 6 mice at a dose

TABLE IV. Antitumor Screening Test Results of Pt (II) Complexes against Leukemia L1210

| Complexes | Dose (mg/kg) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 100 | 50 | 25 | 12.5 | 6.25 | 3.12 | 1.56 | 0.78 | 0.39 |
| [$PtCl_2$(*cis-d*-amcha)] | | | | 128 | 230 | 162 | 147 | 132 | |
| [$PtCl_2$(*cis-l*-amcha)] | | | | 213 | 318 | 176 | 145 | 127 | |
| [$PtCl_2$(*trans-d*-amcha)] | | | 217 | 252 | 178 | 170 | 139 | | |
| [$PtCl_2$(*trans-l*-amcha)] | | | 204 | 263 | 162 | 130 | 127 | | |
| [$PtCl_2$(*d*-ptn)] | | | | 128 | 162 | 144 | | | |
| [$PtCl_2$(*l*-ptn)] | | | | 153 | 148 | 122 | | | |
| [$PtCl_2$(*meso*-ptn)] | | | 107 | 118 | 168 | | | | |
| [$PtCl_2$(*d*-bn)] | | | 94 | 134 | 137 | | | | |
| [$PtCl_2$(*l*-bn)] | | | 0 | 153 | 136 | | | | |
| [$PtCl_2$(*d*-dppn)] | | | 119 | 119 | 115 | | | | |
| [$PtCl_2$(*l*-dppn)] | | | 113 | 113 | 113 | | | | |
| [$PtCl_2$(*meso*-dppn)] | | | 122 | 121 | 119 | | | | |
| [$Pt(SO_4)$(*cis-d*-amcha)] | | | | | 207 | 177 | 204 | 148 | 137 |
| [$Pt(SO_4)$(*cis-l*-amcha)] | | | | | 207 | 204 | 159 | 146 | 121 |
| [$Pt(SO_4)$(*trans-d*-amcha)] | | | 198 | 190 | 186 | 154 | 126 | | |
| [$Pt(SO_4)$(*trans-l*-amcha)] | | | | 136 | 138 | 148 | 130 | | |
| [$Pt(SO_4)$(*d*-ptn)] | | | | 92 | 148 | 148 | | | |
| [$Pt(SO_4)$(*l*-ptn)] | | | | 107 | 133 | 138 | | | |
| [$Pt(SO_4)$(*meso*-ptn)] | | | | 170 | 176 | 148 | | | |
| [$Pt(SO_4)$(*d*-bn)] | | | 103 | 143 | 143 | | | | |
| [$Pt(SO_4)$(*l*-bn)] | | | 0 | 158 | 136 | | | | |
| [$Pt(SO_4)$(*d*-dppn)] | | 123 | 124 | 116 | | | | | |
| [$Pt(SO_4)$(*l*-dppn)] | | 132 | 136 | 123 | | | | | |
| [$Pt(SO_4)$(*meso*-dppn)] | | 114 | 116 | 97 | | | | | |
| [$Pt(NO_3)_2$(*d*-ptn)] | | 103 | 132 | 140 | | | | | |
| [$Pt(NO_3)_2$(*l*-ptn)] | | | 138 | 153 | 185 | | | | |
| [$Pt(NO_3)_2$(*d*-bn)] | | | | 163 | 126 | 126 | | | |
| [$Pt(NO_3)_2$(*l*-bn)] | | | 100 | 146 | 130 | | | | |
| [$Pt(NO_3)_2$(*d*-dppn)] | | | 128 | 120 | 113 | | | | |
| [$Pt(NO_3)_2$(*l*-dppn)] | | | 127 | 123 | 114 | | | | |
| [$Pt(NO_3)_2$(*meso*-dppn)] | | | 111 | 111 | 102 | | | | |
| [Pt(oxalato)(*cis-d*-amcha)] | | | 191 | 185 | 191 | 134 | | | |
| [Pt(oxalato)(*cis-l*-amcha)] | | >183 | 215 | 228 | 192 | 137 | | | |
| [Pt(oxalato)(*trans-d*-amcha)] | | >94 | 284 | 229 | 185 | 143 | 136 | | |
| [Pt(oxalato)(*trans-l*-amcha)] | | | 213 | 259 | 246 | 152 | >138 | | |
| [Pt(oxalato)(*d*-ptn)] | | 82 | 124 | 314 | 247 | | | | |
| [Pt(oxalato)(*d*-bn)] | | | | 265 | 235 | 152 | | | |
| [Pt(oxalato)(*l*-bn)] | | | 228 | 167 | 130 | | | | |
| [Pt(D-glucuronato)(*cis-d*-amcha)] | | | 281 | 243 | 187 | 136 | 122 | | |
| [Pt(D-glucuronato)(*cis-l*-amcha)] | | | 267 | 195 | 187 | 135 | 124 | | |
| [Pt(D-glucuronato)(*trans-d*-amcha)] | | | 238 | 164 | 145 | 135 | 128 | | |
| [Pt(D-glucuronato)(*trans-l*-amcha)] | | >171 | 213 | 195 | 156 | 139 | 132 | | |
| [Pt(D-glucuronato)(*d*-ptn)] | | | 109 | 130 | 121 | | | | |
| [Pt(D-glucuronato)(*meso*-ptn)] | | | 124 | 136 | 125 | | | | |
| [Pt(D-glucuronato)(*d*-bn)] | 0 | 108 | 119 | | | | | | |
| [Pt(D-glucuronato)(*d*-dppn)] | | 120 | 112 | 110 | | | | | |
| [Pt(D-glucuronato)(*l*-dppn)] | 114 | 116 | 140 | | | | | | |
| [Pt(D-glucuronato)(*meso*-dppn)] | 116 | 106 | 103 | | | | | | |
| [Pt(D-gluconato)(*cis-d*-amcha)] | | 92 | 225 | 262 | 237 | 172 | 129 | | |
| [Pt(D-gluconato)(*cis-l*-amcha)] | | >201 | 250 | 300 | 191 | 141 | 127 | | |
| [Pt(D-gluconato)(*trans-d*-amcha)] | | >184 | 191 | 164 | 135 | 133 | 114 | | |
| [Pt(D-gluconato)(*trans-l*-amcha)] | | | >193 | 256 | 193 | 170 | 138 | 120 | |
| [Pt(D-gluconato)(*d*-bn)] | 76 | 112 | 128 | | | | | | |
| [Pt(D-gluconato)(*l*-dppn)] | | 114 | 110 | 103 | | | | | |

Underlined figures are significantly positive.
$10^5$ cells/mouse, $CDF_1$ mice (6 mice/group), test samples administered on days 1, 5, and 9.

Table V. Comparison of the Antitumor Activity of amcha Pt (II) Complexes against Leukemia L1210

| amcha | Leaving group | Toxic[a] dose (mg/kg) | Optimal dose[b] (mg/kg) | Optimal dose[b] $T/C$% | MED[c] (mg/kg) | MED[c] $T/C$% | TI[d] |
|---|---|---|---|---|---|---|---|
| *cis*-DDP | | ≧12.5 | 3.12 | 230 | 0.78 | 134 | 4 |
| *cis-d* | $Cl_2$ | ≧25 | 6.25 | 230(1) | 0.78 | 132 | 8 |
| *cis-l* | $Cl_2$ | ≧25 | 6.25 | 318(4) | 0.78 | 127 | 8 |
| *trans-d* | $Cl_2$ | ≧50 | 12.5 | 252 | 1.56 | 139 | 8 |
| *trans-l* | $Cl_2$ | ≧50 | 12.5 | 263(2) | 1.56 | 127 | 8 |
| *cis-d* | $SO_4$ | ≧12.5 | 6.25 | 207 | 0.39 | 137 | 16 |
| *cis-l* | $SO_4$ | ≧12.5 | 6.25 | 207 | 0.78 | 146 | 8 |
| *trans-d* | $SO_4$ | ≧50 | 25 | 198 | 1.56 | 126 | 16 |
| *trans-l* | $SO_4$ | ≧25 | 3.12 | 148 | 1.56 | 130 | 2 |
| *cis-d* | ox | ≧50 | 6.25 | 191(1) | 3.12 | 134 | 2 |
| *cis-l* | ox | ≧100 | 12.5 | 228(1) | 3.12 | 137 | 4 |
| *trans-d* | ox | 100 | 25 | 284(2) | 1.56 | 136 | 16 |
| *trans-l* | ox | ≧50 | 12.5 | 259(2) | 1.56 | 138 | 8 |
| *cis-d* | glucu | ≧50 | 25 | 281(1) | 3.12 | 136 | 8 |
| *cis-l* | glucu | ≧50 | 25 | 267 | 3.12 | 135 | 8 |
| *trans-d* | glucu | ≧50 | 25 | 238(1) | 1.56 | 128 | 16 |
| *trans-l* | glucu | ≧100 | 25 | 213(1) | 1.56 | 132 | 16 |
| *cis-d* | gluco | 100 | 12.5 | 262 | 1.56 | 129 | 8 |
| *cis-l* | gluco | ≧100 | 12.5 | 300(2) | 1.56 | 127 | 8 |
| *trans-d* | gluco | ≧100 | 25 | 191 | 3.12 | 133 | 8 |
| *trans-l* | gluco | ≧100 | 25 | 256(2) | 3.12 | 138 | 8 |

Administered to $CDF_1$ mice on days 1, 5, and 9.
*a*) Toxic dose: Dose at which $T/C$ is less than 85%.
*b*) Optimal dose: Dose which produces the maximum $T/C$%.
*c*) MED: The lowest dose at which $T/C$% exceeds 125.
*d*) TI: Therapeutic index (optimal dose/MED).
Numbers in parentheses indicate 30-day survivors out of 6 mice.
ox=oxalate ion, glucu=D-glucuronate ion, gluco=D-gluconate ion.

of 12.5 mg/kg, while the latter showed a $T/C$ of 256% with 2 long-term surviors among 6 mice at a dose of 12.5 mg/kg. Among the platinum complexes tested so far, *cis-l*-amcha complexes seem to be the most potent; in particular, [Pt(D-gluconato)(*cis-l*-amcha)] seemed to show reduced toxicity and high potency, and appears to be a promising candidate for clinical trials in view of its high solubility in water.

The six-membered chelate ring of 1,3-diamine platinum(II) complexes prepared in this work was in a chair form on the basis of CD and $^{13}$C-NMR analyses, and the conformation of the chelate ring seems to have a significant influence on the appearance of antitumor activity, as do the carrier ligands and leaving groups. Recently Tobe *et al.*[20] reported the synthesis of platinum(II) complexes of cycloalkylamine having a $C_3$–$C_8$ side chain and tested their efficacy as antitumor agents. Among them, dichlorobis(cyclohexylamine)platinum(II) and dichlorobis(cyclopentylamine)platinum(II) had remarkably high antitumor therapeutic indices in the ADJ/PC6A tumor system. We indicated in previous papers that dach[21] and 1,2-cyclopentanediamine[22] platinum(II) complexes also showed marked activity against leukemia L1210 and P388, respectively. The steric structures of amcha platinum(II) complexes are similar to those of dach complexes.[17] Therefore, we suggest that the cyclohexane or cyclopentane ring might be necessary for substantial antitumor activity. The cyclohexane ring of *cis-l*-amcha complex is essentially perpendicular to the chelate ring, while both rings of the *trans-l*-amcha complex lie in a common plane. However, the structure of the former is more flexible than that of the latter.

Since the final targets of antitumor platinum(II) complexes are considered to be bases of DNA molecules, the coplanarity of *trans-l*-amcha and the flexibility of *cis-l*-amcha may

allow them easy approach to the bases of DNA molecules. The platinum complexes of bn, ptn, and dppn isomers have bulky groups, which might prevent interactions of the complexes with DNA molecules due to steric hindrance.

## References and Notes

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1) Present address: *Faculty of Pharmacy, Meijo University, Tenpaku-ku, Nagoya 468, Japan.*
2) Y. Kidani, M. Noji, S. Tsukagoshi, and T. Tashiro, *Gann*, **69**, 263 (1978).
3) Y. Kidani, K. Okamoto, M. Noji, and T. Tashiro, *Gann*, **69**, 863 (1978).
4) W.L.F. Armarego and T. Kobayashi, *J. Chem. Soc.*, **1970**, 1597.
5) B. Bosnich and J. MacB. Harrowfield, *J. Am. Chem. Soc.*, **94**, 3426 (1972).
6) E. Strack and H. Schwaneberg, *Ber.*, **67**, 39 (1934).
7) E. Balieu, P.M. Boll, and E. Larsen, *Acta Chem. Scand.*, **23**, 2191 (1969).
8) S. Arakawa, K. Kashiwabara, J. Fujita, and K. Saito, *Bull. Chem. Soc. Jpn.*, **50**, 2108 (1977).
9) T.G. Appleton and J.R. Hall, *Inorg. Chem.*, **9**, 1800 (1970).
10) T.A. Connors, M. Jones, W.C.J. Ross, P.D. Braddock, A.R. Khokhar, and M.L. Tobe, *Chem.-Biol. Interact.*, **5**, 415 (1972).
11) M.J. Cleare and J.D. Hoeschele, *Bioinorg. Chem.*, **2**, 187 (1973).
12) G.R. Gale, E.M. Walker, L.M. Atkins, A.B. Smith, and S.J. Meischen, *Res. Commun. Chem. Pathol. Pharmacol.*, **7**, 529 (1974).
13) H. Ridgway, L.M. Hall, R.J. Speer, D.P. Stewart, G.R. Edwards, and J.M. Hill, *Wadly Med. Bull.*, **6**, 11 (1976).
14) S. Bagger, *Acta Chem. Scand.*, **28**, 467 (1974).
15) L.E. Erickson, J.E. Sarenski, and C.N. Reilley, *Inorg. Chem.*, **14**, 3007 (1975).
16) K. Okamoto, M. Noji, and Y. Kidani, *Bull. Chem. Soc. Jpn.*, **54**, 713 (1981).
17) M. Noji, K. Okamoto, T. Tashiro, and Y. Kidani, *J. Med. Chem.*, in, press.
18) M. Noji, K. Okamoto, and Y. Kidani, *Chem. Lett.*, **1979**, 741.
19) H. Ito, J. Fujita, and K. Saito, *Bull. Chem. Soc. Jpn.*, **40**, 2584 (1967).
20) P.D. Braddock, T.A. Connors, M. Jones, A.R. Khokhar, D.H. Meliack, and M.L. Tobe, *Chem.-Biol. Interact.*, **11**, 145 (1975).
21) Y. Kidani, K. Inagaki, and S. Tsukagoshi, *Gann*, **67**, 921 (1976).
22) Y. Kidani, K. Inagaki, T. Yashiro, T. Tashiro, and S. Tsukagoshi, *Chem. Pharm. Bull.*, **27**, 829 (1979).