Synthesis, Structure and Antitumor Activity of a Water-Soluble Platinum Complex, (1*R*,3*R*,4*R*,5*R*)-(−)-Quinato(1*R*,2*R*-cyclohexanediamine)platinum(II)

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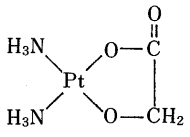
The reaction of dihydroxo(1*R*,2*R*-cyclohexanediamine)platinum(II) with (−)-quinic acid gave a water soluble complex, (−)-quinato(1*R*,2*R*-cyclohexanediamine)platinum(II). The crystal structure of the complex was determined by X-ray analysis. The data indicate a chelation of the α-hydroxycarboxylic acid part of quinic acid to platinum(II). The complex shows moderate antitumor activity against murine leukemia L1210 at high doses ($T/C \times 100 = 179\%$ at a dose of 200 mg/kg).

Keywords (1*R*,2*R*-cyclohexanediamine)platinum(II) complex; (1*R*,3*R*,4*R*,5*R*)-(−)-quinic acid; X-ray analysis; antitumor activity

The discovery of *cis*-dichlorodiamineplatinum(II) (CDDP)[1] marked a major advance in chemotherapy of solid tumors. There is still a great need for new platinum complexes which might demonstrate decreased renal toxicity and cross resistance to CDDP. 1,2-Cyclohexanediamineplatinum(II) complexes have been reported to show a lack of cross resistance to CDDP against murine leukemia L1210.[2] However, it is generally difficult to obtain 1,2-cyclohexanediamineplatinum(II) complex with high solubility and stability in water.

Recently, Totani *et al.*[3] reported a new type of Pt complexes, (glycolato-*O*,*O*')platinum(II) complexes; a typical example is diammine(glycolato-*O*,*O*')platinum(II) (**1**). Miyamoto *et al.*[4] also reported a similar type of complex, mandelato(*trans*-1,2-cyclohexanediamine)platinum(II). To get a 1,2-cyclohexanediamineplatinum(II) complex with high solubility and stability in water, we investigated a reaction of dihydroxo(1*R*,2*R*-cyclohexanediamine)platinum(II) with (1*R*,3*R*,4*R*,5*R*)-(−)-quinic acid.



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This paper reports the preparation, X-ray crystal structure determination and antitumor activity of (1*R*,3*R*,4*R*,5*R*)-(−)-quinato(1*R*,2*R*-cycohexanediamine)-platinum(II) (**2**).[5] The complex was synthesized by the reaction of dihydroxo(1*R*,2*R*-cyclohexanediamine)platinum(II) with an equivalent amount of (1*R*,3*R*,4*R*,5*R*)-(−)-quinic acid in water, and then in ethanol, at 60 °C. The recrystallization from water gave a colorless crystal. The solubility of the complex in water was high as expected (39 mg/ml at room temperature).

In order to elucidate the absolute the configuration of the complex, a single crystal of the complex was subjected to X-ray diffraction analysis. Crystal data are as follows: Orthorhombic (from water), space group $P2_12_12_1$; $a=10.106(2)$, $b=19.604(4)$, $c=9.178(4)$ Å; $U=1818.3(7)$ Å^3; $Z=4$, $D_X=1.956$ g cm^{-3}.

An ORTEP drawing of the complex with two molecules of hydrated water is shown in Fig. 1. This defines the configuration of the complex as (1*R*,3*R*,4*R*,5*R*)-(−)-quinato(1*R*,2*R*-cyclohexanediamine)platinum(II). The presence of two molecules of hydrated water is consistent with the result of elemental analysis. Selected bond lengths and angles are listed in Table I. Figure 1 shows a chelation of (−)-quinic acid to platinum(II) which forms a planar five-membered ring. The complex has square planar geometry with Pt–O distances of 2.04 and 1.98 Å, and Pt–N distances of 2.02 and 2.04 Å.

The antitumor activity of the complex against murine leukemia L1210 *in vivo* was tested. The results are summarized in Table II. The complex showed moderate activity at high doses ($T/C \times 100 = 179\%$ at a dose of 200 mg/kg) but practically no activity at low doses, while

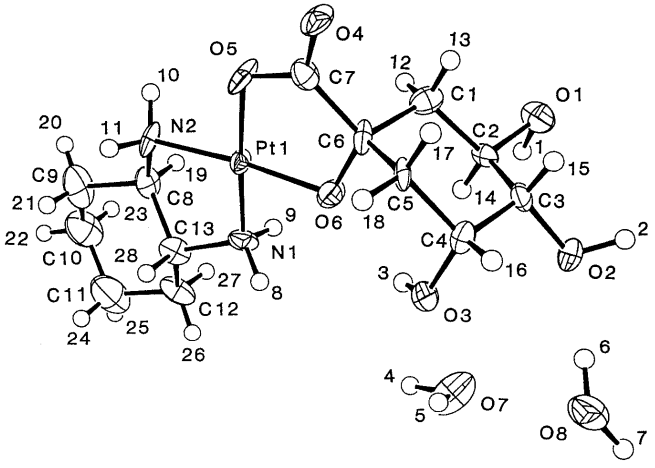

Fig. 1. ORTEP Drawing of Complex **2**

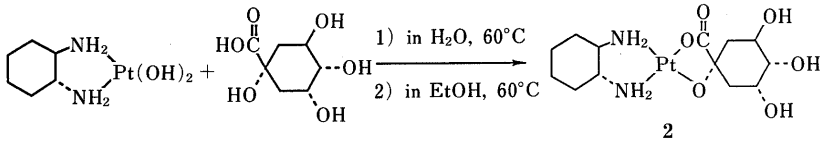

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Chart 1

TABLE I. Selected Bond Lengths (Å) and Angles (°)

Bond lengths (Å)		Bond angles (°)	
Pt(1)–O(5)	2.04	O(5)–Pt(1)–O(6)	82.6
Pt(1)–O(6)	1.98	O(5)–Pt(1)–N(2)	100.0
Pt(1)–N(1)	2.02	O(6)–Pt(1)–N(1)	94.2
Pt(1)–N(2)	2.04	N(1)–Pt(1)–N(2)	83.2
O(6)–C(6)	1.41	Pt(1)–O(5)–C(7)	113
O(5)–C(7)	1.29	Pt(1)–O(6)–C(6)	113
O(4)–C(7)	1.25	O(6)–C(6)–C(7)	112
C(6)–C(7)	1.52	O(5)–C(7)–C(6)	117

TABLE II. Antitumor Activity against Murine Leukemia L1210 in Mice[a)]

	Complex **2**					
Dose (mg/kg)	1	10	25	50	100	200
$T/C^{b)} \times 100$ (%)	102	142	126	140	167	179

	CDDP				
Dose (mg/kg)	1.0	2.5	5.0	7.5	15
$T/C^{b)} \times 100$ (%)	121	173	179	280	189

a) L1210 cells were inoculated i.p. on day 0. Platinum complexes were inoculated i.p. on days 1, 5 and 9. *b*) *T* and *C* are the mean survival times of treated and control mice, respectively.

CDDP showed high activity at very low doses.

The complex **2** is a polyhydroxycarboxylic acid derivative of 1*R*,2*R*-cyclohexanediaminepalatinum(II) complex. As such a polyhydroxycarboxylic acid derivative, bis(D-glucuronato)(1*R*,2*R*-cyclohexanediamine)platinum(II) was reported. The glucuronato complex shows high antitumor activity at low doses,[6)] but is unstable in water.[7)] On the other hand, the complex **2** has been confirmed to be stable in water by the fact that there is no change in proton nuclear magnetic resonance (^{1}H-NMR) spectrum (D_2O) after 24 h. This high stability in water would be due to the chelation of the α-hydroxycarboxylic acid part of quinic acid to platinum(II).

Experimental

^{1}H- and ^{13}C-NMR spectra were recorded on JEOL GX-400 in D_2O with HOD (δ 4.80) and dioxane (δ 67.4) as an internal standard, respectively. Chemical shifts are given in δ values, and coupling constants (*J*) are given in hertz (Hz). The hydrogen atoms on the ORTEP (Fig. 1) were numbered for the convenience of assigning the protons in ^{1}H-NMR. The numbers for the atoms on the ORTEP are used as the numbers for assignment of the protons and carbons in NMR. ^{195}Pt-NMR spectrum was recorded on JEOL GX 400 at 86 MHz with H_2PtCl_6 as an external standard.

Synthesis of the Complex 2 An aqueous solution of dihydroxo(1*R*,2*R*-cyclohexanediamine)platinum(II) was prepared by passing (1*R*,2*R*-cyclohexanediamine)platinum(II) $(NO_3)_2$[8)] solution through a column packed with a strong anion exchange resin (Diaion SA 10A, OH^- type). To a solution of (1*R*,3*R*,4*R*,5*R*)-(−)-quinic acid (3.86 g, 20.1 mmol) in water (60 ml), a solution of dihydroxo(1*R*,2*R*-cyclohexanediamine)-platinum(II) (20.1 mmol) in water (300 ml) was added at 0 °C. The resultant solution was stirred for 3 h at 60 °C and concentrated to dryness. The residual solid was stirred in ethanol (200 ml) for 3 h at 60 °C. The resultant powder was filtered and submitted to column chromatography on MCI GEL (CHP20P) with water. The eluate was evaporated under reduced pressure. The residue was recrystallized from water to afford **2** (3.02 g, 5.64 mmol) as colorless crystals. mp *ca.* 230 °C (dec.) *Anal.* Calcd for $C_{13}H_{28}N_2O_8Pt$: C, 29.16; H, 5.27; N, 5.27; Pt, 36.43. Found: C, 29.14; H, 5.30; N, 5.46; Pt, 36.38. ^{1}H-NMR (D_2O) δ: 1.15 (2H, m, H-24, H-25), 1.30 (2H, br q, *J*=11, H-22, H-28), 1.58 (2H, m, H-23, H-26), 1.65 (1H, dd, *J*=12, 13, H-14), 1.72 (1H, dd, *J*=3, 14, H-18), 2.05 (2H, br d, *J*=12, H-21, H-27), 2.16 (1H, ddd, *J*=3, 5, 13, H-13), 2.33 (2H, m, H-20, H-29), 2.35 (1H, ddd, *J*=3, 5, 14, H-19), 3.49 (1H, dd, *J*=3, 10, H-16), 4.00 (1H, ddd, *J*=5, 10, 12, H-15), 4.12 (1H, dt, *J*=5, 3, H-17). ^{13}C-NMR (D_2O) δ: 24.8 (C-10 or C-11), 24.9 (C-10 or C-11), 32.7 (C-9 or C-12), 32.9 (C-9 or C-12), 39.5 (C-5), 42.8 (C-1), 62.2 (C-8 or C-13), 63.3 (C-8 or C-13), 68.0 (C-2), 72.8 (C-4), 76.7 (C-3), 82.6 (C-6), 194.1 (C-7). ^{195}Pt-NMR (D_2O): −810 ppm from an external standard (H_2PtCl_6).

X-Ray Analysis A total of 1581 observed reflections ($I > 3\sigma(I)$) graphite-monochromated MoK_α radiation. The structure was solved using the Patterson heavey atom method and was refined by the full-matrix least-squares procedure anisotropically for non-H atoms and isotropically for H atoms. The final *R*-factor was 3.4% and ωR was 4.2%.

Antitumor Testing Murine leukemia L1210 cells (10^5 cells) were inoculated intraperitoneally into CDF_1 mice (one group consists of 6 mice) on day 0 and the sample was administered intraperitoneally on days 1, 5 and 9. Antitumor activity was expressed as $T/C \times 100$(%) in which *T* and *C* are the mean survival times of treated mice and those of untreated control mice, respectively.

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