

Crystal Structure of *cis*-(Malonato)[(4*R*,5*R*)-4,5-bis(Aminomethyl)-2-Isopropyl-1,3-Dioxolane]Platinum(II), A Potent Anticancer Agent*

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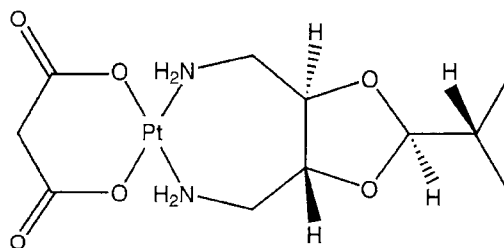
Abstract

The structure of *cis*-(malonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) with a potent anticancer activity has been determined by the X-ray crystallographic method. Crystal data are as follows: Pt(C₁₁H₂₀N₂O₆), M_r=471.38, monoclinic, *P*2₁, *a*=7.112 (1), *b*=33.615 (3), *c*=7.135 (1) Å, β=116.80 (1)°, V=1522.6 (3) Å³, and Z=4. The two independent molecules with very similar structures are approximately related by pseudo two-fold screw axis symmetry, which makes the monoclinic cell look like the orthorhombic cell with one molecule in the asymmetric unit and space group C222₁. The crystal packing mode is similar to that of the analogue with the dimethyl substituents instead of the isopropyl group. The Pt atom is coordinated to two O and two N atoms in a square planar structure. The six-membered chelate ring in the leaving ligand assumes a conformation intermediate between the half chair and the boat forms. The seven-membered ring in the carrier ligand assumes a twist-chair conformation and the oxolane ring assumes an envelope conformation. Crystal packing consists of the extensive hydrogen-bonding networks in the two-dimensional molecular layers and weak van der Waals interactions between these layers.

1. Introduction

cis-Diamminedichloroplatinum(II) (cisplatin) is one of the effective anticancer agents currently available. However, its clinical usefulness is limited by serious toxicity, development of acquired resistance, and poor solubility in water.¹⁾ Numerous derivatives have been synthesized in search for alternative active agents, carboplatin and tetraplatin being the representative examples.^{2,3)} The title compound is one of a new series of compounds synthesized in an effort to find the new potent platinum complexes with a broader spectrum of the anticancer activity, lower toxicity, and higher solubility in water.⁴⁾ They contain the bidentate malonate ligand as a leaving group and

*This article is dedicated to the memory of the late Professor Chung Hoe Koo who pioneered X-ray crystallography in Korea.



the bidentate 4,5-bis(aminomethyl)-1,3-dioxalane ligand as a carrier group, which form the six- and seven-membered chelate rings, respectively, with a platinum atom. The 1,3-dioxalane ring moiety was introduced to render the organoplatinum species higher water solubility, thereby facilitating intravenous administration and being possibly less toxic due to a more facile excretion via the kidney. Various analogues with substituents at the terminal positions of the two ring systems have been found active with

desirable properties.⁴⁾ In particular, the title compound has successfully passed the clinical test and is currently being marketed as an intravenous drug with the name of "Sunfla". The crystal structure of an analogue with the dimethyl substituents instead of the isopropyl group has recently been published.⁵⁾ In this study we report the crystal structure of the title compound.

2. Experimental

Colorless crystals were grown from the aqueous ethanol solution by slow evaporation. Diffraction experiment was performed on a Rigaku AFC 4-circle diffractometer with Zr-filtered, graphite monochromated Mo $K\alpha$ radiation ($\lambda=0.71073$ Å). Crystal data are as follows: Pt(C₁₁H₂₀N₂O₆), $M_r=471.38$, monoclinic, $P2_1$, $a=7.112$ (1), $b=33.615$ (3), $c=7.135$ (1) Å, $\beta=116.80$ (1)°, $V=1522.6$ (3) Å³, $Z=4$, $F(000)=904$, $\rho=2.06$ Mg m⁻³, and $\mu=9.24$ mm⁻¹. The unit cell parameters were refined by a least-squares fit to observed 2θ values for 45 ($7^\circ \leq 2\theta \leq 20^\circ$) centered reflections from a block-shaped crystal with the dimension of 0.52×0.20×0.15 mm. Intensity data were collected with the ω scan method at a scan rate of 2° min⁻¹ with the scan width of $(1.3+0.4 \tan\theta)^\circ$ to a maximum 2θ of 53.0°. Crystals were relatively fragile being easily fragmented and their diffraction profiles were very broad. After correction for Lorentz and polarization effects appropriate for the graphite-monochromated radiation, the intensity data were converted to relative structure factor amplitudes. The standard reflections were monitored every 100 reflections throughout the data collection and showed random variation of $\pm 1.0\%$ with no significant trends. Absorption correction was made by the ψ scan method.⁶⁾ T_{\min} and T_{\max} were 0.086 and 0.259, respectively.

The structure was solved by the heavy atom and difference Fourier methods. Systematic extinctions were consistent with either the space group $P2_1$ or $P2_1/m$. The space group was assumed to be $P2_1$ with two molecules in the asymmetric unit since the molecule is chiral. Heavy atom positions were determined from the inspection of the Patterson map and the remaining non-hydrogen atoms were found

in subsequent difference Fourier maps. The structures were anisotropically refined by full-matrix least-squares methods on F^2 using SHELXL97.⁷⁾ The function minimized was $wR(=[\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2]^{1/2})$. w , the weight of each reflection, was defined as $1/[\sigma^2(F_o^2) + (0.1P)^2]$, where $\sigma^2(F_o^2)$ came from counting statistics and $P=(F_o^2 + 2F_c^2)/3$. The positions of H atoms were calculated and refined with constraints using AFIX 13, 23, or 37 option in SHELXL97 with U_{iso} values 1.2 (or 1.5 for the methyl groups) times those of the bonded atoms. The final R and weighted R factors were 0.044 and 0.113 for all 5349 unique reflections and 0.042 and 0.111 for 5052 reflections with $F > 4\sigma(F)$, respectively. The number of parameters refined was 366 and goodness of fit was 1.12. The absolute structure was assumed from synthesis and the Flack parameter of 0.04 (2) indicates that it is correct.⁸⁾

3. Results and Discussion

Final atomic parameters are listed in Table 1. ORTEP⁹⁾ drawing of one molecule with the atomic numbering scheme is presented in Fig. 1. Bond lengths, bond angles, and selected torsion angles are listed in Table 2.

The two molecules in the asymmetric unit have very similar structures although there are small differences in detail. They are approximately related by pseudo two-fold screw axes symmetry parallel to the a - c direction at $y=0.193$ and to the a + c direction at $y=0.443$. Owing to this pseudo symmetry, the monoclinic cell may look like the orthorhombic cell, transformed by $a'=a+c(7.466$ Å), $b'=a-c(12.134$ Å), and $c'=b$, with one molecule in the asymmetric unit and space group $C222_1$. This crystal packing mode is very similar to that of the analogue with the dimethyl substituents instead of the isopropyl group, namely, *cis*-(malonato)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2,2-dimethyl-1,3-dioxolane]platinum(II).⁵⁾ In the title compound with a larger substituent, the unit cell significantly expanded along the b axis while the a and c axes and the β angle varied only slightly. Unit cell parameters for the analogue are $a=7.092$ (8), $b=30.78$ (3), $c=7.126$ (7) Å, $\beta=116.96$ (12)°, and $V=1386$ (2) Å³. The b axis and the cell volume in the

Table 1. Fractional atomic coordinates and equivalent displacement parameters (\AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq}
Molecule I				
Pt	0.34788(6)	0.12048(2)	0.33960(6)	0.0416(2)
O1	0.0408(12)	0.1269(4)	0.2723(11)	0.045(3)
O2	0.2782(12)	0.1241(5)	0.0345(11)	0.046(2)
O3	-0.2720(13)	0.1467(4)	0.0627(12)	0.057(3)
O4	0.0609(15)	0.1441(4)	-0.2800(14)	0.066(3)
O5	0.737(2)	0.0266(5)	0.8818(19)	0.092(4)
O6	0.786(2)	0.0107(4)	0.603(2)	0.087(4)
N1	0.4061(14)	0.1181(6)	0.6456(13)	0.045(2)
N2	0.6547(16)	0.1138(5)	0.3956(16)	0.053(3)
C1	-0.0825(17)	0.1454(4)	0.1164(17)	0.036(2)
C2	0.010(2)	0.1718(5)	-0.0002(19)	0.049(3)
C3	0.1195(17)	0.1445(5)	-0.0929(16)	0.046(3)
C4	0.451(2)	0.0742(5)	0.7262(17)	0.053(3)
C5	0.678(3)	0.0632(7)	0.749(2)	0.074(4)
C6	0.667(3)	0.0466(6)	0.542(3)	0.072(4)
C7	0.737(2)	0.0738(5)	0.422(2)	0.056(3)
C8	0.813(4)	-0.0014(8)	0.787(3)	0.096(5)
C9	1.050(4)	-0.0040(8)	0.923(3)	0.106(7)
C10	1.102(4)	-0.0159(9)	1.153(4)	0.122(9)
C11	1.148(5)	-0.0326(10)	0.832(5)	0.157(12)
Molecule II				
Pt'	1.00148(6)	0.26608(2)	0.31239(6)	0.0416(2)
O1'	1.0650(12)	0.2620(5)	0.6123(11)	0.050(2)
O2'	1.3105(11)	0.2637(5)	0.3865(11)	0.055(3)
O3'	1.2797(12)	0.2408(4)	0.9394(12)	0.060(3)
O4'	1.6290(13)	0.2394(5)	0.6085(13)	0.082(4)
O5'	0.4411(17)	0.3557(4)	-0.0796(17)	0.078(3)
O6'	0.7253(19)	0.3769(4)	-0.1170(17)	0.082(3)
N1'	0.7006(14)	0.2700(5)	0.2523(13)	0.041(2)
N2'	0.9407(15)	0.2753(4)	0.0035(14)	0.044(3)
C1'	1.2254(16)	0.2409(4)	0.7488(16)	0.038(3)
C2'	1.3474(18)	0.2148(5)	0.6556(18)	0.054(3)
C3'	1.4336(16)	0.2414(5)	0.5399(14)	0.046(3)
C4'	0.593(2)	0.3092(5)	0.194(2)	0.058(3)
C5'	0.587(2)	0.3237(6)	-0.008(2)	0.067(3)
C6'	0.792(3)	0.3399(6)	0.009(3)	0.079(4)
C7'	0.909(3)	0.3133(6)	-0.088(2)	0.069(4)
C8'	0.516(3)	0.3833(8)	-0.178(3)	0.089(5)
C9'	0.369(4)	0.3753(9)	-0.414(3)	0.109(7)
C10'	0.151(3)	0.3942(8)	-0.461(4)	0.121(8)
C11'	0.457(4)	0.4011(8)	-0.530(3)	0.102(7)

$$U_{eq} = 1/3 \sum \sum U_{ij} a_i^* a_j^* a_i a_j \quad (\text{\AA}^2).$$

title compound increased by 2.84 \AA (9.9%) and 137 \AA^3 (9.2%), respectively, compared to those of the analogue.

The Pt atom is coordinated to two O and two N atoms in a square planar structure. The coordination

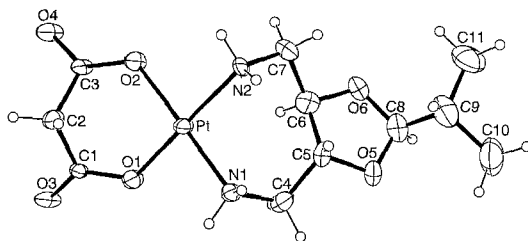


Fig. 1. ORTEP view of molecule I of the title compound with the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

plane, nearly parallel to the *ac* plane, is planar with maximum deviations of 0.01 (1) and 0.03 (1) \AA with the platinum atoms deviating from the least squares planes by 0.01 (1) and 0.06 (1) \AA for the molecules I and II, respectively. Molecular dimensions of two independent molecules in the title compound are comparable with those of the analogue within experimental error. The Pt-O distances are close to 2.0 \AA as observed in several cisplatin analogues containing the same malonate ligand and the various carrier ligands.^{5,10-14} These analogues include the complexes containing two free ammine ligands¹⁰ or the ligand with the five-,^{11,12} six-¹³ or seven-membered^{5,14} ring structure as a carrier group. The Pt-N distances in the title compound and other analogues are also close to 2.0 \AA , indicating that the size of the ring does not exert any significant effect on Pt-N bonding. The O-Pt-O bite angle varies from 88 to 93° and the O-O bite distance varies from 2.78 to 2.93 \AA in the complexes containing the malonate group. The N-Pt-N bite angles are 95.9 (4) and 94.2 (4)° and the N-N bite distances are 3.03 (1) and 2.97 (1) \AA for the molecules I and II, respectively. These are comparable with the normally observed values of 93-100° and 2.9-3.1 \AA for the complexes containing either two free ammine ligands or the ligand with six- or seven-membered chelate ring. However, these are quite small (~84° and ~2.7 \AA) for the complexes with the five-membered ring owing to the constraints imposed by the small-sized chelate ring.

The overall conformations of two independent molecules are quite similar to each other although they have, albeit small, conformational flexibility as

Table 2. Bond distances (Å), bond angles (°) and selected torsion angles (°)

	I	II		I	II
Pt-O1	2.025(8)	1.983(7)	Pt-N1	2.032(8)	1.988(9)
Pt-N2	2.046(10)	2.069(9)	Pt-O2	2.006(7)	2.017(8)
O1-C1	1.230(15)	1.325(16)	O2-C3	1.283(17)	1.290(17)
O3-C1	1.224(13)	1.235(13)	O4-C3	1.206(14)	1.250(13)
O5-C5	1.49(2)	1.423(19)	O5-C8	1.40(3)	1.41(2)
O6-C6	1.42(2)	1.49(2)	O6-C8	1.31(2)	1.36(2)
N1-C4	1.57(2)	1.49(2)	N2-C7	1.45(2)	1.41(2)
C1-C2	1.554(17)	1.575(18)	C2-C3	1.532(19)	1.520(19)
C4-C5	1.59(2)	1.50(2)	C5-C6	1.55(2)	1.51(2)
C6-C7	1.48(2)	1.58(3)	C8-C9	1.52(3)	1.55(3)
C9-C10	1.56(3)	1.57(3)	C9-C11	1.50(3)	1.52(3)
	I	II		I	II
N2-Pt-N1	95.9(4)	94.2(4)	O1-Pt-N1	86.3(3)	86.4(3)
N2-Pt-O2	86.5(4)	88.0(4)	O2-Pt-O1	91.4(3)	91.3(3)
N2-Pt-O1	177.8(4)	175.3(7)	O2-Pt-N1	177.4(6)	177.1(6)
C1-O1-Pt	121.5(8)	122.1(8)	C3-O2-Pt	120.6(8)	119.2(9)
C4-N1-Pt	109.9(9)	119.2(11)	C7-N2-Pt	117.5(11)	123.0(11)
C5-O5-C8	107.9(12)	107.4(13)	C6-O6-C8	111.8(15)	109.3(14)
O3-C1-O1	122.5(11)	123.2(12)	O3-C1-C2	119.1(11)	120.4(11)
O1-C1-C2	118.1(10)	116.4(9)	C1-C2-C3	108.0(12)	109.7(13)
O4-C3-O2	122.2(13)	125.0(13)	O4-C3-C2	119.7(12)	113.9(11)
O2-C3-C2	118.0(10)	121.1(10)	N1-C4-C5	106.5(11)	110.0(12)
O5-C5-C4	103.8(13)	106.8(13)	O5-C5-C6	100.8(15)	106.1(15)
C4-C5-C6	112.0(13)	115.6(13)	O6-C6-C7	113.1(14)	107.2(13)
O6-C6-C5	104.2(13)	102.8(13)	C7-C6-C5	116.3(16)	116.3(17)
C6-C7-N2	115.3(12)	108.2(12)	O5-C8-O6	111.2(18)	109.9(14)
O5-C8-C9	107.0(19)	101.8(18)	O6-C8-C9	106.2(19)	115.1(17)
C8-C9-C10	110.7(18)	106.1(19)	C8-C9-C11	111(2)	104(2)
C10-C9-C10	111(2)	105.4(19)			
	I	II		I	II
Pt-O1-C1-C2	-13.7(17)	-7.1(18)	Pt-O2-C3-C2	10.9(18)	4(2)
O1-C1-C2-C3	65.2(14)	58.6(15)	C1-C2-C3-O2	-63.1(15)	-57.6(17)
Pt-N1-C4-C5	72.5(10)	62.5(14)	Pt-N2-C7-C6	-39.1(17)	-34.6(17)
N1-C4-C5-C6	-87.9(17)	-75.8(19)	C4-C5-C6-C7	105.4(18)	108.5(18)
C5-C6-C7-N2	-47(2)	-55.4(18)	C8-O5-C5-C6	17(2)	21.7(18)
O5-C5-C6-O6	-19.6(19)	-16.6(18)	C8-O6-C6-C5	17(2)	6(2)
C6-O6-C8-O5	-6(3)	7(2)	C5-O5-C8-O6	-8(2)	-19(2)

shown in the selected intracyclic torsion angles listed in Table 3. The six-membered chelate ring formed by the malonate ligand and the platinum atom assumes a conformation intermediate between the half chair and the boat forms. This characteristic conformation is retained in all cisplatin analogues with a malonate ligand. The two planar groups in the malonate moieties form a dihedral angle of 60.0 (6) and 58.6 (6)° and the C2 atoms are displaced by 1.42 (2) and -1.46 (2) Å from the coordination planes for the molecules I and II, respectively. The

seven-membered ring formed by the bidentate carrier ligand and the platinum atom assumes the twist-chair conformation with the oxolane moiety directed to the opposite direction with respect to C2 in the malonate group. The oxolane ring substituted with a *trans* configuration assumes an envelope conformation with O5 at the tip of the flap. The essentially similar conformations of the title compound and the analogue indicate that the two bidentate ligands, seemingly flexible, become relatively rigid upon forming a complex.

Table 3. Hydrogen-bonding geometry (Å, °)

D-H...A	D-H	H...A	D...A	D-H...A
N1-H1A...O3 ⁱ	0.90	2.24	2.98(1)	140.0
N1-H1B...O4 ⁱⁱ	0.90	1.98	2.87(1)	172.8
N2-H2A...O3 ⁱⁱⁱ	0.90	1.98	2.87(1)	174.0
N2-H2B...O4 ⁱ	0.90	2.18	2.95(2)	143.3
N1'-H1'A...O3 ^{iv}	0.90	2.27	2.98(1)	135.1
N1'-H1'B...O4 ^v	0.90	2.09	2.99(1)	173.1
N2'-H2'A...O3 ^{vi}	0.90	1.99	2.89(2)	177.0
N2'-H2'B...O4 ^v	0.90	2.17	2.95(1)	144.2

Symmetry codes: (i) 1+x, y, 1+z; (ii) 1+x, y, z; (iii) x, y, 1+z; (iv) x-1, y, z-1; (v) x, y, z-1; (vi) x-1, y, z.

Crystal packing, shown in Fig. 2, consists of the extensive hydrogen-bonding networks in the two-dimensional molecular layers and weak van der Waals interactions between these layers. Both independent molecules have the same hydrogen-bonding scheme, each with four unique N-H...O hydrogen bonds between the amino and the malonate oxo groups, as listed in Table 3. For each molecule, a hydrogen-bonded dimer is formed between the molecules related by the (*a*+*c*) unit cell translation. These dimers are linked to others through the N-H...O hydrogen bonds along the *a* and *c* axes to

form a hydrogen-bonded molecular layer. Two different modes of van der Waals interactions occur between these layers.

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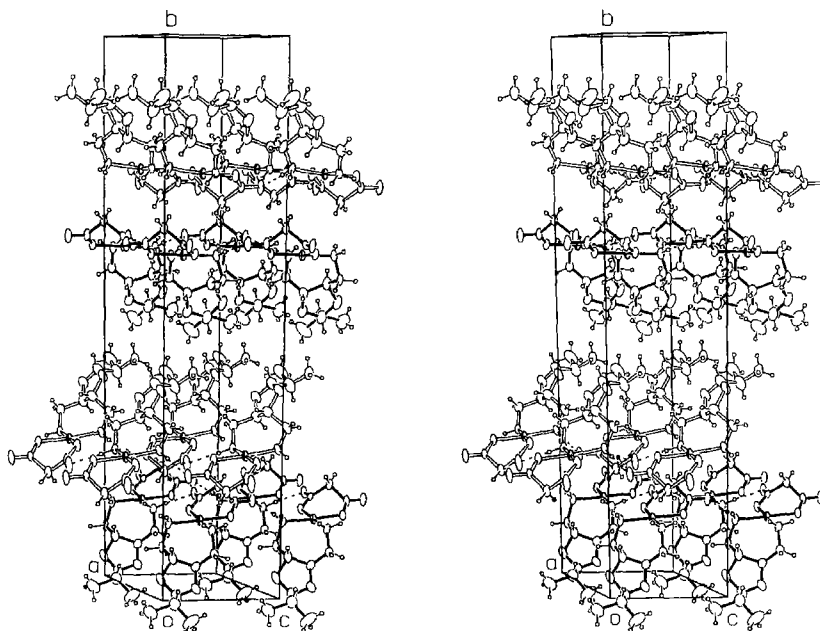


Fig. 2. Stereoscopic packing diagram. Molecule I with filled bonds and II with open bonds. Dashed line denotes the hydrogen bonds.

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