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The Crystal Structure and Absolute Configuration of the Antitumor Platinum Complex *trans*(OH)-Pt(OH)$_2$(Malonato)(1*R*,2*R*-Cyclohexanediamine)

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The absolute configuration of the anti-tumor complex *trans*(OH)-Pt(OH)$_2$(malonato)(1*R*,2*R*-cyclohexanediamine) was determined by X-ray anomalous scattering technique. The final unit cell was monoclinic, space group $P2_1$ with $a=9.142$ Å, $b=7.788$ Å, $c=11.946$ Å, $\beta=96.48°$, $Z=2$. The crystal structure was determined by direct method and difference Fourier synthesis, and refined to $R=0.025$ and $R_w=0.033$ based on 2768 independent reflections. The platinum atom has roughly octahedral coordination. The cyclohexane ring has the expected chair configuration, with two amino groups in equatorial positions while the malonato ligand, in contrast, shows a boat conformation for six membered Pt O–C–C–C–O ring.

Keywords X-ray diffraction; anti-tumor platinum complex; antitumor platinum(IV) complex absolute configuration; *trans*(OH)-Pt(OH)$_2$(malonato)(1*R*,2*R*-cyclohexanediamine)

Since the initial discovery of the anticancer properties of *cis*-[PtCl$_2$(NH$_3$)$_2$] many metal complexes have been tested for anticancer activity. *cis*-[PtCl$_2$(NH$_3$)$_2$] analogs are usually prepared by varying the amine ligands, substituting the chloride ligands by different 'leaving groups' or by varying oxidation state to Pt(IV). The analog-screening has resulted in several drugs which are now undergoing clinical trials. [PtCl$_4$(1*R*,2*R*-cyclohexanediamine)] (1*R*,2*R*-cyclohexanediamine = 1*R*,2*R*-dach) is one of them.1) Usually Pt(IV) complexes were synthesized with a strong presumption that the higher oxidation state may increase water solubility, which often prevents the further development of water-insoluble Pt(II) complexes. [Pt(malonato)(1*R*,2*R*-dach)] had been advanced to clinical trials because of its good activity and stability,2) but was abandoned because of its poor water solubility. *trans*(OH)-[Pt(OH)$_2$(malonato)(1*R*,2*R*-dach)], in which leaving groups are replaced by hydroxyl groups, showed increase in solubility but decrease in anticancer activity,1) where the incorporated content of the drug into a cell diminished with an increase in the number of hydroxy groups in platinum(IV) compound.3) Therefore, it is interesting to know the absolute configuration of hydroxyl derivative of (1*R*,2*R*-dach)Pt(IV) compound and to compare it with that of [Pt(malonato)(1*R*,2*R*-dach)].

The crystal structure of *cis, trans, cis*-[PtCl$_2$(OH)$_2$(NH$_3$)$_2$],4−6) [Pt(malonato)(1*R*,2*R*-dach)] and [Pt(oxalato)(1*R*,2*R*-dach)] have been reported in the literature.7) In this paper, the structure of *trans*(OH)-[Pt(OH)$_2$(malonato)(1*R*,2*R*-dach)] is described and the absolute configuration of the compound is determined.

Experimentals

trans-[Pt(OH)$_2$(malonato)(1*R*,2*R*-dach)]4H$_2$O, was prepared by the following procedures. [Pt(malonato)(1*R*,2*R*-dach)] (1.2 g, 2.9 mmol)1) was suspended in 20 ml of H$_2$O and warmed in a water-bath at 70 °C. To the suspension was added 20 ml of H$_2$O$_2$ in several portions and heating for 1 h followed at 70 °C. The solution was concentrated to one half volume and cooled in ice water to deposit colorless crystals. These were collected by filtration and recrystallized from H$_2$O. The crystals were thin, rectangular plates. *Anal.* Calcd for *trans*(OH)-[Pt(OH)$_2$(malonato)(1*R*,2*R*-dach)]4H$_2$O: C, 20.89; H, 5.06; N, 5.41. Found: C, 20.76; H, 4.85; N, 5.50.

For the structure determination of *trans*(OH)-[Pt(OH)$_2$(malonato)(1*R*,2*R*-dach)]4H$_2$O, a crystal with approximate dimensions of 0.29 × 0.18 × 0.08 mm was mounted on a glass capillary. The unit-cell parameters and intensity data were measured on an Enraf-Nonius CAD-4 automated four circle diffractometer with graphite monochromated CuK_α radiation ($\lambda=1.54184$ Å). The final unit cell was monoclinic, space group $P2_1$ with $a=9.142(1)$ Å, $b=7.7876(4)$ Å, $c=11.946(1)$ Å, $\beta=96.48(28)°$, $Z=2$, $D_x=2.03\,\mathrm{g\,cm^{-3}}$, $D_m=2.06\,\mathrm{g\,cm^{-3}}$, and $\mu(\mathrm{Cu}K_\alpha)=6.71\,\mathrm{cm^{-1}}$. Intensity data were collected using ω–2θ scan technique within the range of $2°<\theta<64°$. A total of 3122 reflections were obtained, and of these 2768 having $F_O^2>3\delta(F_O^2)$ were used for structure analysis. Absorption correction was done empirically.

Platinum was located by the direct method using the program MULTAN828) and non-hydrogen atoms of both ligands were located by difference Fourier synthesis. At this stage, four oxygen atoms of crystal waters appeared in pseudo symmetric positions. Sixteen sets of them were examined. The best sets gave $R=0.043$. Successive full-matrix least-squares method yielded the convergence with $R=0.027$ with anisotropic thermal parameters for non-hydrogen atoms. All hydrogen atoms were placed at the calculated positions based on non-hydrogen atoms. The quantity minimized was $\Sigma w(|F_O|-|F_C|)^2$, where $w=4F_O/\delta^2(F_O)$. The final refinement converged with $R=0.025$ and $R_w=0.033$ for the 2768 reflections. Calculations were done on a MicroVAX II computer using the SDP program package.9) Atomic scattering factors taken from reference10) were used on the SDP. Figure 1 was drawn using the ORTEP program11) with the MicroVAX II computer.

Results and Discussion

The final atomic positional and thermal parameters for non-hydrogen atoms of *trans*(OH)-[Pt(OH)$_2$(malonato)(1*R*,2*R*-dach)]4H$_2$O are listed in Table I. Interatomic distances and angles for non-hydrogen atoms are given in Table II. Refinement of the mirror-image of the molecule resulted in significantly higher *R*-value ($R=0.028$, $R_w=0.035$). This indicates that the first set of atomic coordinates had the proper absolute configuration of the 1*R*,2*R*-dach ligand. A stereoscopic drawing of *trans*(OH)-[Pt(OH)$_2$(malonato)(1*R*,2*R*-dach)] is shown in Fig. 1a. The unit cell structure of *trans*(OH)-[Pt(OH)$_2$(malonato)(1*R*,2*R*-dach)] is given in Fig. 1b. In Table II, O7, O8, O9, O10 are oxygen atoms of water molecules in a unit cell.

Figure 1a shows that *trans*(OH)-[Pt(OH)$_2$(malonato)(1*R*,2*R*-dach)] has distorted octahedral geometry around the platnium atom. The bond angle of O3–Pt–N2 was 85.3 degrees and was the narrowest angle around platinum except

Table I. Coordinate and Thermal Parameters for *trans*(OH)-Pt(OH)$_2$-(Malonato)(1*R*,2*R*-dach)

Atom	*x*	*y*	*z*	*B*
Pt	0.68648 (2)	0.00000	0.06213 (1)	1.695 (2)
O1	0.9058 (4)	−0.012 (1)	0.0552 (4)	3.08 (9)
O2	0.6425 (5)	−0.0283 (6)	−0.1055 (4)	2.2 (1)
O3	0.6779 (5)	0.2535 (7)	0.0451 (4)	2.53 (9)
O4	0.6809 (5)	−0.2563 (7)	0.0802 (4)	2.41 (9)
O5	1.0993 (4)	0.015 (1)	−0.0334 (5)	4.1 (1)
O6	0.6867 (6)	0.036 (1)	−0.2761 (4)	4.1 (1)
N1	0.7143 (5)	0.0312 (6)	0.2312 (4)	2.0 (1)
N2	0.4681 (4)	0.0166 (8)	0.0781 (3)	1.71 (6)
C1	0.5717 (8)	0.0890 (9)	0.2688 (5)	2.4 (1)
C2	0.4477 (6)	−0.011 (1)	0.2006 (4)	2.14 (9)
C3	0.2981 (7)	0.051 (1)	0.2292 (6)	3.0 (1)
C4	0.2868 (8)	0.028 (2)	0.3532 (6)	4.5 (2)
C5	0.415 (1)	0.126 (2)	0.4250 (7)	4.5 (2)
C6	0.565 (1)	0.069 (1)	0.3945 (6)	3.7 (2)
C7	0.9659 (6)	0.028 (1)	−0.0323 (5)	2.8 (1)
C8	0.8757 (8)	0.114 (1)	−0.1312 (6)	2.9 (1)
C9	0.7263 (6)	0.0374 (8)	−0.1755 (5)	2.3 (1)
O7	0.0932 (6)	0.507 (2)	0.4215 (4)	4.4 (1)
O8	0.6365 (6)	0.582 (1)	0.2750 (5)	3.9 (1)
O9	0.867 (6)	0.327 (1)	0.2910 (9)	6.8 (1)
O10	0.8679 (8)	0.763 (1)	0.4016 (6)	4.5 (1)

Table II. Distance and Angles for *trans*(OH)-Pt(OH)$_2$(Malonato)(1*R*,2*R*-dach)

Atom	Atom	Distance	Atom	Atom	Distance
Pt	O1	2.018 (4)	N1	C1	1.496 (9)
Pt	O2	2.010 (4)	N2	C2	1.510 (7)
Pt	O3	1.985 (6)	C1	C2	1.530 (9)
Pt	O4	2.009 (5)	C1	C6	1.52 (1)
Pt	N1	2.022 (5)	C2	C3	1.526 (9)
Pt	N2	2.031 (4)	C3	C4	1.51 (1)
O1	C7	1.273 (8)	C4	C5	1.57 (1)
O2	C9	1.301 (7)	C5	C6	1.53 (1)
O5	C7	1.225 (7)	C7	C8	1.52 (1)
O6	C9	1.215 (7)	C8	C9	1.530 (9)

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
O1	Pt	O2	92.4 (2)	Pt	N2	C2	108.2 (3)
O1	Pt	O3	93.9 (3)	N1	C1	C2	107.8 (5)
O1	Pt	O4	89.8 (3)	N1	C1	C6	113.5 (6)
O1	Pt	N1	91.9 (1)	C2	C1	C6	111.4 (6)
O1	Pt	N2	176.8 (2)	N2	C2	C1	106.3 (5)
O2	Pt	O3	90.3 (2)	N2	C2	C3	112.6 (5)
O2	Pt	O4	89.7 (2)	C1	C2	C3	110.4 (6)
O2	Pt	N1	175.7 (2)	C2	C3	C4	110.2 (6)
O2	Pt	N2	90.7 (2)	C3	C4	C5	110.5 (8)
O3	Pt	O4	176.2 (2)	C4	C5	C6	111.2 (8)
O3	Pt	N1	89.0 (2)	C1	C6	C5	109.9 (6)
O3	Pt	N2	85.3 (2)	O1	C7	O5	120.7 (6)
O4	Pt	N1	90.8 (2)	O1	C7	C8	120.0 (5)
O4	Pt	N2	90.9 (5)	O5	C7	C8	118.9 (6)
N1	Pt	N2	85.0 (2)	C7	C8	C9	118.8 (6)
Pt	O1	C7	123.1 (4)	O2	C9	O6	120.1 (6)
Pt	O2	C9	122.1 (4)	O2	C9	C8	119.9 (5)
Pt	N1	C1	108.7 (3)	O6	C9	C8	120.0 (6)

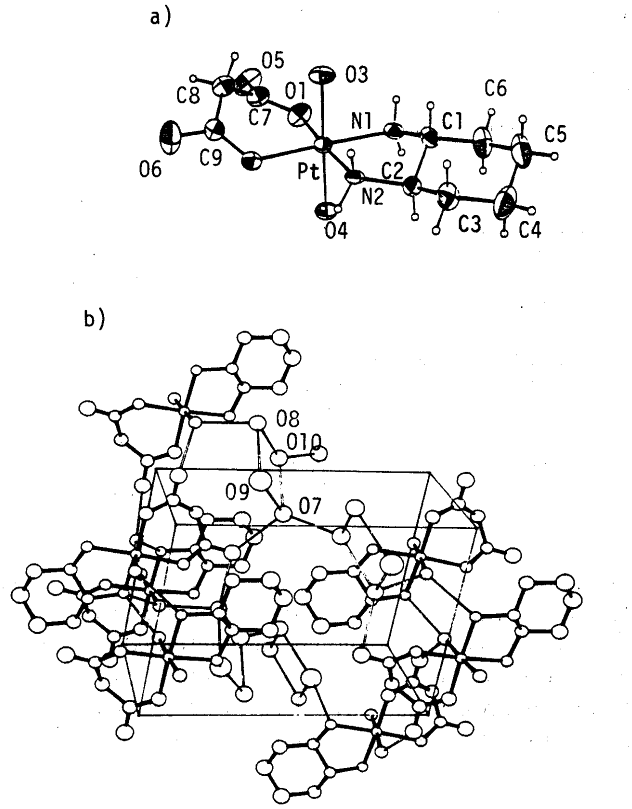

Fig. 1. Stereoscopic Drawings of Crystal Structure (a) of *trans*(OH)-[Pt(OH)$_2$(Malonato)(1*R*,2*R*-dach)] and Hydrogen Bondings (b) in a Unit Cell

for the bond angle of N1–Pt–N2 which is restricted by the fixed cyclohexane ring. In *cis*, *trans*, *cis*-[PtCl$_2$(OH)$_2$-(NH$_3$)$_2$], the bond angles around platinum were slightly deviated from 90 degrees, but most were in the range between 88 and 94 degrees.[5,6] The configuration of cyclohexanediamine and malonato in *trans*(OH)-[Pt(OH)$_2$-(malonato)(1*R*,2*R*-dach)] described here completely agrees with that obtained in [Pt(malonato)(1*R*,2*R*-dach)].[7] The cyclohexane rings have the expected chair conformation, with two amino groups in equatorial positions. The malonato ligand, in contrast, shows a boat conformation for the six membered Pt O–C–C–C–O ring. The bond lengths between platinum(IV) and nitrogen or oxygen atoms of this complex were in the range between 2.02 and 1.99 Å, and are almost same values obtained in *cis*, *trans*, *cis*-[PtCl$_2$(OH)$_2$(NH$_3$)$_2$].

trans(OH)-[Pt(OH)$_2$(malonato)(1*R*,2*R*-dach)] has much lower anticancer activity than [Pt(malonato)(1*R*,2*R*-dach)].[1] In a previous paper,[12] it was shown that the platinum uptaken into L-1210 is directly correlated to the cytotoxicity for L-1210. The uptake platinum content of [Pt(malonato)(1*R*,2*R*-dach)] into L-1210 cells was about 12 times that of *trans*(OH)-[Pt(OH)$_2$(malonato)(1*R*,2*R*-dach)].[3] The configuration of *trans*(OH)-[Pt(OH)$_2$(malonato)(1*R*,2*R*-dach)] is the same as that of [Pt(malonato)-(1*R*,2*R*-dach)] except for hydroxy group (O3 and O4 in Fig. 1a) which bound directly to platinum atom. It is therefore suggested that the hydroxy groups of *trans*(OH)-[Pt(OH)$_2$(malonato)(1*R*,2*R*-dach)] may reduce the cell wall permeability of the drug.[3,12]

There were eight water molecules in a unit cell: the cell's hydrogen-bond network is shown in Fig. 1b. There were many hydrogen bondings between ligands of the complexes and water molecules. The hydrogen bonds are divided into three types, the bonds among ligands between two complexes related with a two-fold screw axis along *b* axis,

TABLE III. Hydrogen Bonds in a Unit Cell

Atom	Atom	Distance (Å)
Type I ligand–ligand		
O5	O3	2.891
N2	O3	2.782
O5	O4	2.790
Type II ligand–water molecule		
N1	O9	2.753
O6(2)	O7	2.806
O6	O8	2.970
O4	O8	2.714
Type III water–water molecule		
O7	O10(2)	2.834
O8	O9	2.89
O8	O10	2.83
O7	O10(1)	2.86
O7	O9(1)	2.82

ligand–water molecules, and water–water molecules (Table III). Four water molecules form a rhombic core; two of the oxygen atoms on a diagonal have tetrahedral geometries and the other two have trigonal geometries. These cores form a hydrogen network of two-fold screw axis along *b* axis with O6 and bind complex molecules and water molecules. The two hydroxo ligands of a platinum complex form hydrogen bonds with amino group (N2) and carboxyl group of the adjacent platinum molecules along *b* axis.

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