

Preparation and crystal structure of *trans*-*S,S*-[*N,N'*-bis(2-hydroxyethyl)ethylenediamine(oxalato)platinum(II)]: a spontaneous resolution of individual crystals of pure optical isomers upon recrystallization

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Abstract

The crystal structure of the antitumor compound *trans*-*S,S*-[*N,N'*-bis(2-hydroxyethyl)ethylenediamine(oxalato)platinum(II)] has been determined by X-ray diffraction. This pure optical compound is tetragonal and has the following parameters: space group $P4_2, 2_1, 2$, $a = 6.816(5)$, $c = 26.139(15)$ Å, $Z = 4$. The structure was refined on 1042 non-zero Mo $K\alpha$ reflections to $R = 0.035$. The slightly distorted square planar environment of the platinum atom includes two nitrogens of the diamine in *cis* positions and two oxygens from the bidentate oxalate. The Pt–N and Pt–O distances average 2.025 and 2.037 Å, respectively. The binding of the diamine ligand gives a N–Pt–N angle of 84.7° , whereas the smaller O–Pt–O angle of 82.5° probably results from a slight torsional twist of the oxalate. The molecular chirality facilitates the formation of two O–H \cdots O and two N–H \cdots O hydrogen bonds per molecule. This favorable pattern of hydrogen bonding is a possible driving force for resolution of the *trans*-*S,S*- pure optical isomer in a mixture upon crystallization into individual crystals.

Introduction

cis-Diamminedichloroplatinum(II) (cisplatin) is a clinically important antitumor drug currently used in the treatment of various human cancers. However, cisplatin is highly toxic. The major toxicities associated with its use are nephrotoxicity, neurotoxicity and ototoxicity. In an attempt to modify the balance between cisplatin's antitumor activity and its toxicity, systematic studies have been carried out on replacing the NH_3 group in cisplatin with different amine ligands and/or replacing the Cl^- ion with various carboxylate anions [1–5]. We have synthesized a series of platinum(II) compounds with hydroxy-substituted alkylamine as the inert ligand and tested their antitumor activity [6]. Some of these compounds have shown moderate antitumor activity against L1210 leukemia cells both *in vitro* and *in vivo*. We describe here the X-ray crystal structure of one of these

platinum compounds, *trans*-*S,S*-[*N,N'*-bis(2-hydroxyethyl)ethylenediamine(oxalato)platinum(II)]. To our knowledge this is the first example of a platinum(II) coordination compound that undergoes conglomerate crystallization into crystals of pure optical isomers.

Experimental

Preparation

Potassium iodide (6.876 g, 41.4 mmol) was added to a stirred aqueous solution of potassium tetrachloroplatinate (2.149 g, 5.18 mmol). After 30 min, a 5-ml aqueous solution of *N,N'*-bis(2-hydroxyethyl)ethylenediamine (0.767 g, 5.18 mmol) was added. A yellow precipitate was obtained by filtration and purified using acetone. An aqueous suspension of diiodo[*N,N'*-bis(2-hydroxyethyl)ethylenediamine]platinum(II) (0.977 g, 1.6 mmol) was then reacted with silver oxalate (0.487 g, 1.6 mmol) in a

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light-protected environment overnight at room temperature. The silver iodide precipitate was removed by filtration, the filtrate was evaporated to dryness under reduced pressure at 40 °C, and a white solid was obtained. This compound (130 mg) was dissolved in water (5 ml) and was left at room temperature to recrystallize. Colorless crystals were obtained.

Crystallographic measurements and structural resolution

A clear, colorless triangular crystal plate having approximate dimensions of $0.40 \times 0.36 \times 0.05$ mm was broken off of a much larger plate and mounted in random orientation on a Nicolet R3m/V automatic diffractometer. The radiation used was Mo K α monochromatized by a highly ordered graphite crystal. Final cell constants, as well as other information pertinent to data collection and refinement, are listed in Table 1. The Laue symmetry was determined to be $4/mmm$, and from the systematic absences noted, the space group was shown to be either $P4_12_12$ or $P4_32_12$. Intensities were measured using the omega scan technique, with the scan rate depending on the count obtained in rapid prescans of each reflection. Two standard reflections were monitored after every 2 h or every 100 data collected, and these data showed a 10% decay over the course of the experiment. A normalizing factor as a function of X-ray exposure time was applied to the data to account for this decay. During data reduction, Lorentz and polarization corrections were applied, as well as an empirical absorption correction based on psi scans of nine reflections having chi values between 70°

and 90°. An entire octant of data was measured, and the equivalent reflections were averaged after the above corrections were made.

The structure was solved by interpretation of the Patterson map, revealing the position of the platinum atom in the asymmetric unit, which consists of one-half molecule lying about a two-fold axis. Remaining non-hydrogen atoms were located in subsequent difference Fourier syntheses. The usual sequence of isotropic and anisotropic refinement was followed, after which all hydrogens attached to carbon were entered in ideal calculated positions and constrained to riding motion, with a single-variable isotropic temperature factor. The hydrogens attached to oxygen or nitrogen were located in difference maps and allowed to refine independently, although with the same isotropic temperature factor as above.

The platinum(II) compound under study crystallizes in a non-centrosymmetric, enantiomorphic space group, and, therefore, each individual crystal must contain a pure optical isomer. In order to determine the absolute configuration, the Bijvoet test [7] was performed using 21 reflections showing large differences between F_c values for the two separate enantiomers. All of these reflections indicated that the assumed configuration in space group $P4_12_12$ was correct, rather than the opposite configuration in space group $P4_32_12$. Additionally, the R values for the refinement of the inverted configuration in $P4_32_12$ were significantly greater ($R = 0.044/R_w = 0.046$). After all shift/e.s.d. ratios became less than 0.2, convergence was reached at the agreement factors listed in Table 1. No unusually high correlations were noted between any of the variables in the last cycle of full-matrix least-squares refinement, and the final difference density map showed a maximum peak of about $1.2 e/\text{\AA}^3$, located quite close to the platinum atom. All calculations were made using Nicolet's SHELXTL PLUS (1987) series of crystallographic programs.

TABLE 1. Data collection and processing parameters

Molecular formula	C ₈ H ₁₆ N ₂ O ₆ Pt
Formula weight	431.35
Space group	$P4_12_12$ (tetragonal)
Cell constants	$a = 6.816(5)$ Å $c = 26.139(15)$ Å $V = 1214$ Å ³
Formula units per cell	$Z = 4$
Density	$\rho = 2.36$ g cm ⁻³
Absorption coefficient	$\mu = 116.9$ cm ⁻¹
Radiation (Mo K α)	$\lambda = 0.71073$ Å
Collection range	$4^\circ \leq 2\theta \leq 55^\circ$
Scan width	$\Delta\theta = 1.3 + (K\alpha_2 - K\alpha_1)^\circ$
Scan speed range	$1.5 - 15.0^\circ$ min ⁻¹
Total data collected ($h \leq k$)	1256
Independent data, $I > 3\sigma(I)$	1042
Total variables	85
R	0.035
R_w	0.035
Weights	$w = \sigma(F)^{-2}$

Results and discussion

The crystal contains the monomeric molecule shown in Fig. 1, which also defines the labeling of the atoms of the compound. Two adjacent corners of the platinum plane are occupied by the nitrogens of the N,N' -bis(2-hydroxyethyl)ethylenediamine ligand, whereas the remaining *cis* corners are used to bind the bidentate oxalate ion. Coordination about the platinum atom is a slightly distorted square plane. Both ligands attached to the platinum atom show bond strain, since the central C–C bonds are significantly longer than would be expected. As seen in Table 2, the C2–C2' bond length (1.603 Å) in

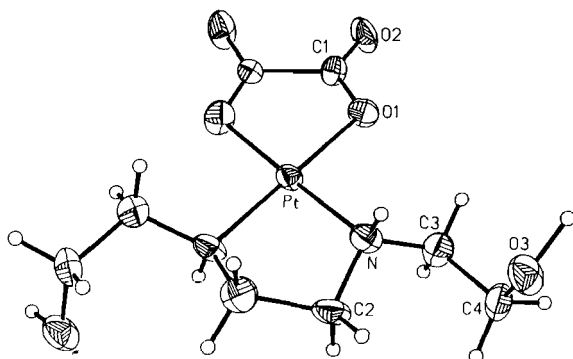


Fig. 1. View of the molecule showing the atom numbering scheme. The thermal ellipsoids are 50% equiprobability envelopes, with hydrogens as spheres of arbitrary diameter.

TABLE 2. Bond lengths (Å)

Bond	Length
Pt-O1	2.037(8)
O1-C1	1.270(14)
O3-H(O)	1.160(138)
N-H(N)	0.790(136)
N-C3	1.472(17)
C2-C2'	1.603(19)
Pt-N	2.025(11)
O2-C1	1.211(15)
O3-C4	1.436(15)
N-C2	1.458(17)
C1-C1'	1.604(23)
C3-C4	1.516(17)

the 'ethylenediamine' fragment is significantly longer than the length of the C-C bond of tetramethylethylenediamine (TMED) in *cis*-[(TMED)Pt(9-MeG)](PF₆)₂·H₂O (1.503 Å) [8], whereas the C1-C1' bond length (1.604 Å) in the oxalate is unusually long for a C(sp²)-C(sp²) bond.

However, the Pt-N distances (2.025 Å) are not very different from those observed in other platinum(II) compounds such as, for example, *trans*-1*R*,2*R*-cyclohexanediamine(oxalato)platinum(II) (2.05 Å) [9], *cis*-dichloro(amine)(dimethyl sulfide)platinum(II) (2.03 Å) [10], bis(acetato)-(trans-1,2-diaminocyclohexane)platinum(II) (2.00 Å) [11], tris(*cis*-dichloro(1,2-diaminocyclohexane)-platinum(II) hydrate (2.01–2.06 Å) [12] and *cis*-(diammino)(1,1-cyclobutanedicarboxylato)platinum(II) (2.01 Å) [13]. The Pt-O distances (2.037 Å) are also consistent with those found with carboxylate compounds in bis(acetato)(trans-1,2-diaminocyclohexane)platinum(II) (2.02 Å) and in *cis*-(diammino)(1,1-cyclobutanedicarboxylato)platinum(II) (2.029 Å), for instance. The bite of the bidentate *N,N'*-bis(2-hydroxyethyl)ethylenediamine ligand imposes a N-Pt-N' angle of 84.7° (Table 3), which is

TABLE 3. Bond angles (°)

Bond angle	Degree
O1-Pt-N	96.5(4)
N-Pt-O1'	177.5(4)
Pt-O1-C1	113.5(8)
Pt-N-H(N)	109.3(95)
H(N)-N-C2	107.9(102)
H(N)-N-C3	101.2(110)
O1-C1-O2	125.5(11)
O2-C1-C1'	119.4(7)
N-C3-C4	113.7(10)
O1-Pt-O1'	82.5(5)
N-Pt-N'	84.7(6)
H(O)-O3-C4	108.6(67)
Pt-N-C2	110.6(8)
Pt-N-C3	114.4(8)
C2-N-C3	112.9(10)
O1-C1-C1'	115.1(7)
N-C2-C2'	107.7(8)
O3-C4-C3	112.1(9)

typical of five-membered rings with similar donor atoms [8, 9].

The oxalate is not perfectly flat, but shows a slight torsional twist. This is apparent from the O1-Pt-O1' angle of 82.5°. There also appears to be some delocalization in the oxalate. The bond lengths of O1-C1 and O2-C1 are 1.270 and 1.211 Å, respectively, and they are not as different in length as would be expected in a localized structure. In the case of bis(acetato)(trans-1,2-diaminocyclohexane)platinum(II), one acetate ion has the O1-C1 bond length of 1.17(4) Å and the O2-C1 bond length of 1.31(4) Å, while in the other acetate ion, the bond distances for O3-C3 and O4-C3 are 1.32(4) and 1.21(3) Å, respectively [11].

There is no chiral atom in the free amine ligand, HOCH₂CH₂NHCH₂CH₂NHCH₂CH₂OH. However, coordination of this ligand with the platinum atom produces two chiral nitrogen atoms in the resulting compound. They could be *cis*-*S,R*-, *trans*-*S,S*-, or *trans*-*R,R*- isomers. As can be seen in Fig. 1, the chirality at both nitrogen atoms is the same and would be classified as *S* using the group ranking order of Pt > C3 > C2 > H. This is also in good agreement with the atomic coordinate in Table 4, which corresponds to the *S* absolute configurations about the two asymmetric nitrogens. The handedness of the 'ethylenediamine' fragment would be designated 'delta', as evidenced by the N-C2-C2'-N torsion angle (47.4°) being positive.

The crystallized solid produced two singlet peaks at -2056.2 and -2075.6 ppm in the ¹⁹⁵Pt NMR spectrum in water and two singlet carbonyl peaks at 165.7 and 163.9 ppm in the ¹³C{¹H} NMR spectrum

TABLE 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$)

Atom	x	y	z	U
Pt	206(1)	206(1)	0	25(1)
O1	-2108(12)	-659(13)	439(4)	37(3)
O2	-4544(15)	-2788(12)	426(4)	46(3)
O3	1587(12)	4635(15)	1417(3)	42(3)
N	1094(16)	2422(16)	461(4)	30(3)
C1	-3039(16)	-2111(17)	255(5)	28(4)
C2	2421(18)	3734(17)	188(5)	36(4)
C3	-513(19)	3468(16)	720(5)	35(4)
C4	165(18)	5198(16)	1039(5)	38(3)

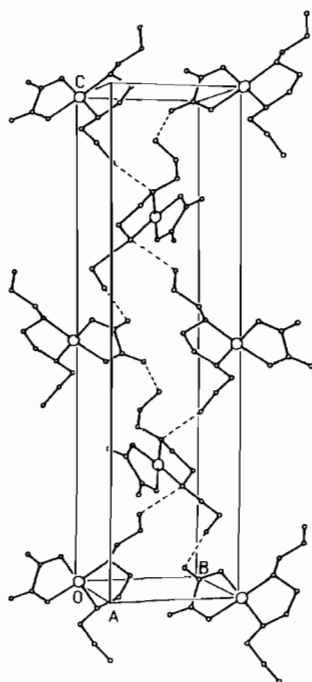


Fig. 2. Molecular packing in the unit cell, with hydrogens omitted for clarity. Intermolecular hydrogen bonds are indicated by dashed lines.

in deuterated water*. These data suggest that the bulk of the material in the crystallized solid is a mixture of *cis-S,R*-, *trans-S,S*- and *trans-R,R*- molecules that undergoes conglomerate crystallization into a mechanical mixture of crystals of pure optical isomers (*cis* isomer is not optically active). The driving force for this separation would be the favorable pattern of hydrogen bonding found in the solid state of the chiral molecules. Such hydrogen-bonded interactions have been shown by Bernal *et al.* [14–17]

*The ^{195}Pt chemical shift is referenced to Na_2PtCl_4 (-1621.0 ppm) and the $^{13}\text{C}\{^1\text{H}\}$ chemical shift is referenced to the dioxane peak at 66.5 ppm.

TABLE 5. Distances (\AA) and angles ($^\circ$) associated with hydrogen bonds

Bond A–H...B	Distance			Angle A–H...B
	A–H	A...B	H...B	
O3–H(O)...O2'	1.16	2.76	1.62	165
N–H(N)...O3''	0.79	2.96	2.23	153

to be responsible for conglomerate crystallization in many cases of related coordination compounds.

Figure 2 shows the molecular packing pattern in a unit cell in which the hydrogen bonding is strong and takes advantage of the molecular chirality. Each molecule forms a set of two O3–H(O)...O2' hydrogen bonds of 2.76 \AA each and another set of two N–H(N)...O3'' hydrogen bonds of 2.96 \AA each (Table 5). Molecules in the stack are held together by these two sets of hydrogen bonds. It is worth noting that though hydrogen bonds are very important in determining the molecular packing, in this case, surprisingly, the water molecule is not involved in strong hydrogen bonding.

Supplementary material

Observed and calculated structure factors as well as anisotropic thermal factors can be obtained from the authors on request.

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