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Preparation and Crystal Structure of Bis(acetato)(*trans*-1,2-diaminocyclohexane)platinum(II)

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Abstract

The structure of the complex [Pt(*trans*-1,2-diaminocyclohexane)(acetate)$_2$]·H_2O has been determined by X-ray diffraction. This racemic compound is orthorhombic, space group *Aba*2, a = 20.813(9), b = 7.926(5), c = 17.296(8) Å, Z = 8. The structure was refined on 1214 nonzero Cu Kα reflections to R = 0.028. The square planar environment of Pt includes the amino groups of the diamine in *cis* positions and oxygens from two monodentate acetates. The Pt–N and Pt–O distances average 2.00(3) and 2.02(3) Å, respectively. The bite of the diamine ligand imposes a N–Pt–N angle of 85(1)°, whereas the small O–Pt–O angle of 85(1)° probably results from packing effects. The average plane through the puckered cyclohexyl ring makes an angle of 19° with the PtN_2O_2 plane. The molecules are stacked by pairs along the b axis. The two molecules of each pair are 180° apart about the stacking axis, and form altogether four N–H···O hydrogen bonds.

Introduction

Cisplatin *cis*-$Pt(NH_3)_2Cl_2$ has been found very effective against several animal tumors and quite useful in treating certain human malignancies. However, because of its nephrotoxicity, the search for safer and more effective drugs is continuing. It is widely admitted [1] that the two *cis* nitrogen ligands are still attached to platinum when it reaches its target in cellular DNA, but the chloride ions have been displaced by a hydrolytic process taking place in the biological system. Therefore, to rationalize the activities of these compounds and design new active molecules, attention must be directed to both the leaving groups and the non-leaving nitrogen ligands. The nitrogen ligands being kept constant, it has been shown that complexes with carboxylates as leaving groups are much less toxic than the chloride analogs [2]. The compound studied in this paper contains acetate as leaving group. As to the non-leaving ligands, one series of complexes which shows promises contains the Pt(dach)$^{2+}$ fragment (where dach = 1,2-diaminocyclohexane). Dach is not a bidentate ligand commonly used in coordination chemistry. Its *trans* isomer contains two asymmetric carbons and can exist as a pair of enantiomers (*l* of 1R, 2R, and *d* or 1S, 2S), whereas the *cis* isomer (1R, 2S) is not optically active. At the time the present work was undertaken, the crystal structures of two *cis*-dach complexes, $PtCl_2$(*cis*-dach) and $PtBr_2$(*cis*-dach), had been determined by Lock and Pilon [3]. As for the *trans* isomer, X-ray studies were available for several Co [4] and Rh [5] complexes, and for one mixed-valence Pt(II)/Pt(IV) compound [6]. Very recently, Bau *et al.* [7] reported the crystal structures of [Pt(oxalate)(*l-trans*-dach)] and [Pt(malonate)(*l-trans*-dach)]. The compound described in the present paper is a racemic, obtained from [$PtCl_2$(*dl-trans*-dach)] by substitution of both chloride ions with acetate groups.

Experimental

Preparation

An equimolar mixture of $Na(CH_3CO_2)$ and $AgNO_3$ in water was left overnight in the refrigerator and $Ag(CH_3CO_2)$ was filtered and washed with cold water, ethanol and ether. An aqueous suspension of 0.2 mol of $PtCl_2$(*dl*-dach) prepared as described ear-

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lier [8] was reacted with 0.4 mol of Ag(CH_3CO_2) for 2 h at 60 °C, and then left overnight at room temperature. The AgCl was removed by filtration, the filtrate was rotovaporated to dryness, resuspended in acetone, filtered and washed with acetone and ether. A portion of 250 mg of precipitate was suspended in 30 ml of water at 40–50 °C, filtered, and the filtrate was left in the refrigerator to recrystallize. The crystals are colourless elongated platelets, very thin and brittle, but they were found to be suitable for X-ray work.

Crystal Data

$C_{10}H_{20}N_2O_4Pt \cdot H_2O$, FW = 445.4, orthorhombic, space group *Aba*2, $a = 20.813(9)$, $b = 7.926(5)$, $c = 17.296(8)$ Å, $V = 2853.2$ Å^3, $D_c = 2.073$ g cm^{-3}, $Z = 8$, $T = 296$ K, λ(Cu K$\bar{\alpha}$) = 1.54178 Å (graphite monochromator), μ(Cu Kα) = 18.74 mm^{-1}, crystal dimensions (mm): 0.017 (001 – 00$\bar{1}$) × 0.054 (10$\bar{1}$ – $\bar{1}$01) × 0.426 (010 – 0$\bar{1}$0).

Crystallographic Measurements and Structure Resolution

A set of precession, cone axis and Weissenberg photographs clearly revealed *mmm* Laue symmetry. The systematic absences (hkl, $k + l \neq 2n$; $h0l$, $h \neq 2n$; $0kl$, $k \neq 2n$), which were subsequently confirmed by inspection of the full data set, were consistent with space groups *Aba*2 (No. 41) and *Acam* (nonstandard orientation for *Cmca*, No. 64). The intensity data were collected with a CAD-4 diffractometer as described elsewhere [9]. Three standard reflections showed fluctuations within ±2% during the experiment. A total of 1400 Cu K$\bar{\alpha}$ *hkl* reflections were collected ($2\theta \leqslant 140°$), of which 1214 were retained as significantly above background ($I \geqslant 3\sigma(I)$). These data were corrected for the Lorentz effect, polarization and absorption (Gaussian integration, grid 8 × 8 × 8, transmission range: 0.12–0.55).

Structure Resolution

The eight Pt atoms were located from a Patterson synthesis. In space group *Acam*, they had to lie on a mirror plane (equipoint 8f: $x, y, 0$; $\bar{x}, \bar{y}, 0$; $\frac{1}{2} - x, \frac{1}{2} + y, 0$; $\frac{1}{2} + x, \frac{1}{2} - y, 0$). Since *trans*-1,2-diaminocyclohexane is not expected to possess a mirror plane, this space group was not consistent with the anticipated structure. In space group *Aba*2, if the z coordinate used to fix the origin along c is arbitrarily set to 0, the Pt coordinates are the same as above, but they correspond to a general equipoint. In the ΔF map phased on Pt, the water oxygens and carboxylate groups appeared very clearly, as they were approximately related by the pseudo-mirror present in the phasing model. However, the cyclohexyl portion consisted of two overlapping images. A set of atomic positions corresponding to the ring conformation found in other structures [4, 5] was found. The structure was isotropically refined by full-matrix least-squares procedures. Convergence was reached for $R = \Sigma \| F_o | - | F_c \| / \Sigma | F_o | = 0.085$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2 / \Sigma w |F_o|^2]^{1/2} = 0.098$. The hydrogens in the cyclohexyl rings were placed at the calculated positions. Those of the methyl groups were found in the ΔF map. The corresponding O–C–C–H torsion angles were calculated and ideal hydrogen coordinates were defined (sp^3 hybridization, C–H = 0.95 Å) to give optimum fit with the positions observed in the map. The parameters of the hydrogens were not refined, but their coordinates were recalculated after each cycle of refinement. The hydrogens of the water molecules could not be found. Anisotropic refinement of all nonhydrogen atoms converged to $R = 0.028$ and $R_w = 0.037$. Goodness-of-fit ratio = 1.38. The final ΔF map showed a general background below ±0.26 e/Å^3.

Refinement of the enantiomorphic structure converged to the same parameters within 1.5σ, with the same R and R_w factors. This is not surprising, since the Pt atoms, which are the only anomalous scatterers, define an almost perfectly centrosymmetric pattern. Therefore, the results from the original refinement were retained.

The refined coordinates are listed in Table I. The lists of temperature factors and the tables of structure factors are provided in the supplementary material.*

TABLE I. Fractional Coordinates (×10^3, Pt × 10^5).

Atom	x	y	z
Pt	−4548(2)	27997(4)	0
W(1)	0	500	−300(1)
W(2)	0	500	296(2)
O(1)	−121(1)	267(2)	−78(1)
O(2)	−72(1)	445(3)	−163(1)
O(3)	−113(1)	278(2)	79(2)
O(4)	−78(1)	444(2)	171(1)
N(11)	23(2)	273(3)	−77(2)
N(12)	27(1)	256(2)	79(1)
C(1)	−115(1)	340(5)	−136(2)
C(2)	−175(2)	285(4)	−192(2)
C(3)	−117(1)	342(4)	149(1)
C(4)	−168(1)	287(5)	204(2)
C(11)	92(1)	264(2)	−31(1)
C(12)	81(1)	173(2)	43(1)
C(13)	145(1)	203(2)	84(2)
C(14)	198(1)	91(2)	41(1)
C(15)	205(1)	181(3)	−31(1)
C(16)	142(1)	155(3)	−85(1)

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*The supplementary material includes lists of observed and calculated structure factors, anisotropic temperature factors for nonhydrogen atoms, coordinates of hydrogen atoms, distances and angles in hydrogen bonds, torsion angles, and details of least-squares plane calculations. Copies can be obtained from the authors.

The scattering curves used were from standard sources [10]. The f' and f'' contributions of Pt to anomalous dispersion were included in structure factor calculations [11].

This structure is not ideal to obtain accurate distances and angles in the light-atom portion of the cell. First, a substantial fraction of total electron density is concentrated in the Pt atom, thereby reducing the accuracy in light-atom positions. Secondly, puckering of the cyclohexane ring is the only major effect that destroys a pseudo-mirror plane through Pt, which would otherwise increase space group symmetry to *Acam*. Although the final ΔF map showed no evidence that the space group could be *Acam*, structures of this type tend to show high correlations between pairs of atoms related by pseudosymmetry and to lead to high standard deviations, which are probably underestimated.

Description of the Structure and Discussion

The crystal contains the monomeric molecule shown in Fig. 1. Two adjacent corners of the platinum square plane are occupied by the amino nitrogens of the *trans*-dach ligand, whereas the remaining *cis* corners are used to bind unidentate acetate ions. The Pt–N distances (mean 2.00 Å) (Table II) are not significantly different from those observed in Pt(II) complexes with *trans*-dach [7], *cis*-dach [3] and related ligands [12, 13]. The Pt–O distances (mean 2.02 Å) are also consistent with those found with carboxylate complexes [7, 12–14]. The bite of the bidentate dach ligand imposes a N–Pt–N angle of 85(1)° (Table III), a value typical of five-membered rings with similar donor atoms [3, 7, 13]. However, no similar constraints can explain that the O–Pt–O (85(1)°) is significantly below 90°. The latter distortion is likely due to hydrogen bonding (see below).

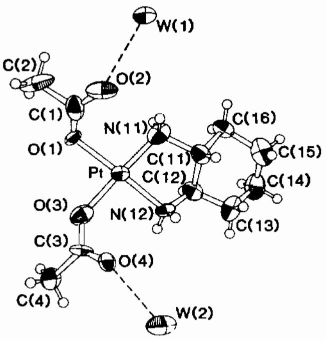

Fig. 1. View of the [Pt(*dl*-dach)(acetate)$_2$] molecule. Ellipsoids corresponds to 50% probability. Hydrogens atoms are represented by spheres of arbitrary size.

Considering the large standard deviations due to pseudo-symmetry (see experimental section), the

TABLE II. Interatomic Distances for Pt(acetate)$_2$(*dl-trans*-dach) Monohydrate.

Bond	Distance (A)
Pt–O(1)	2.07(3)
Pt–O(3)	1.96(3)
Pt–N(11)	1.95(3)
Pt–N(12)	2.04(2)
O(1)–C(1)	1.17(4)
O(2)–C(1)	1.31(4)
C(1)–C(2)	1.64(5)
O(3)–C(3)	1.32(4)
O(4)–C(3)	1.21(3)
C(3)–C(4)	1.49(4)
N(11)–C(11)	1.64(4)
N(12)–C(12)	1.44(3)
C(11)–C(12)	1.49(2)
C(12)–C(13)	1.53(3)
C(13)–C(14)	1.60(3)
C(14)–C(15)	1.44(3)
C(15)–C(16)	1.62(3)
C(16)–C(11)	1.64(3)

TABLE III. Bond Angles for Pt(acetate)$_2$(*dl-trans*-dach) Monohydrate.

Bond	Angle (deg)
O(1)–Pt–O(3)	85(1)
O(1)–Pt–N(11)	96(1)
O(1)–Pt–N(12)	172(1)
O(3)–Pt–N(11)	178(1)
O(3)–Pt–N(12)	94(1)
N(11)–Pt–N(12)	85(1)
Pt–O(1)–C(1)	117(2)
O(1)–C(1)–O(2)	134(3)
O(1)–C(1)–C(2)	107(3)
O(2)–C(1)–C(2)	119(3)
Pt–O(3)–C(3)	133(2)
O(3)–C(3)–O(4)	120(3)
O(3)–C(3)–C(4)	121(3)
O(4)–C(3)–C(4)	118(3)
Pt–N(11)–C(11)	108(2)
N(11)–C(11)–C(12)	108(1)
N(11)–C(11)–C(16)	108(2)
Pt–N(12)–C(12)	109(1)
N(12)–C(12)–C(11)	106(1)
N(12)–C(12)–C(13)	114(2)
C(11)–C(12)–C(13)	101(1)
C(12)–C(13)–C(14)	107(2)
C(13)–C(14)–C(15)	101(2)
C(14)–C(15)–C(16)	111(2)
C(15)–C(16)–C(11)	97(2)
C(16)–C(11)–C(12)	109(1)

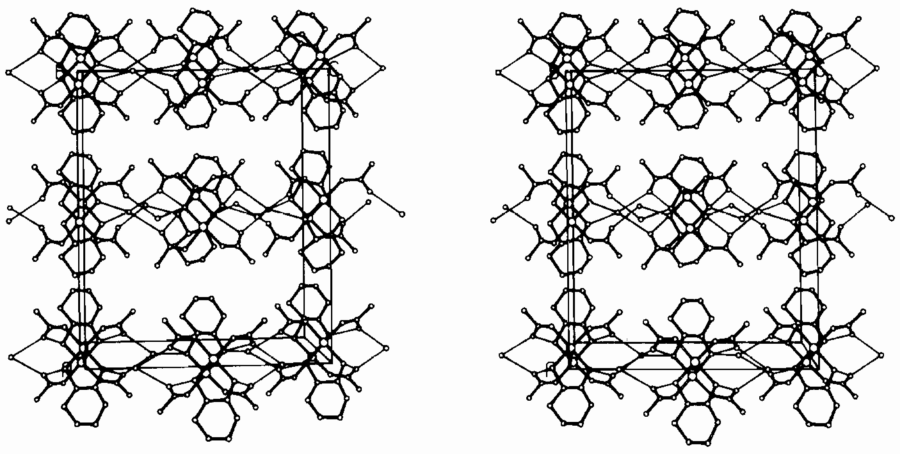

Fig. 2. Stereoview of the unit cell of [Pt(*dl*-dach)(acetate)$_2$]$\cdot$H$_2$O down the *b* axis. The origin is in the upper left corner. The *a* and *c* axis are vertical and horizontal, respectively, in the plane of the figure. Atoms are represented by spheres of arbitrary sizes, the larger ones corresponding to Pt. Hydrogen bonds are shown as thin lines.

distances and angles in the acetate ions and the cyclohexane ring are normal (Tables II and III). The *trans*-dach molecule shows the chair conformation found for the hydrobromide [15] and for the Co [4], Rh [5] and Pt [6, 7] complexes. The atomic coordinates in Table I correspond to the R absolute configurations about the two asymmetric carbons C(11) and C(12) (*l* isomer). The chelate ring is puckered with a λ conformation, as evidenced from the Pt–N(11)–C(11)–C(12) and Pt–N(12)–C(12)–C(11) angles being positive. Since the space group contains glide planes, the unit cell includes equal numbers of λ(1R,2R) and δ(1S,2S) molecules.

The packing pattern shown in Fig. 2 shows that the molecules form layers parallel to the *bc* plane at $x = 0$ and ½. Cohesion between the layers originates from normal van der Waals contacts. Each of these layers consists of columns parallel to the *b* axis, in which the molecules are stacked with their PtN$_2$O$_2$ planes roughly perpendicular to stacking direction and are alternatively rotated 180° about the same direction. Pairs of successive molecules along the stack are held together by a set of four N–H···O (carboxyl) interactions of 2.87–3.05 Å (Table IV). Cohesion between these pairs along the stack, as well as between adjacent stacks, is achieved by water molecules, forming each four H–bonds (2.74–3.12 Å) with either free carboxyl oxygens or N–H bonds not involved in the above mentioned interactions.

The main purposes of the present study was to better define the geometry of the Pt(*trans*-dach)$^{2+}$ fragment in the complex. In this respect, our results and those of Bau *et al.* [7] are in very good agreement. As mentioned earlier by Kidani and coworkers [16], the cyclohexane ring in the Pt complexes of *cis*-dach and *trans*-dach have different orientations. Lock and Pilon [3] have found for *cis*-dach a value of ~67° for the dihedral angle between the PtO$_2$N$_2$ coordination plane and the mean plane through the cyclohexane ring. In the *trans*-dach complexes, this same angle is 19° (present case), 13° (oxalate) [7], 11° (malonate) [7] and 9° (mixed-valence complex) [6]. Since the two types of complexes have very different van der Waals envelopes, differences in other properties, such as antitumor activity, are just as likely as between any other pair of different compounds.

TABLE IV. Distances between Nonhydrogen Atoms Involved in Hydrogen Bonding.

Bond	Distances (Å)
W(1)···O(2)	2.84(3)
W(1)···O(2)[a]	2.84(3)
W(2)···O(4)	2.74(3)
W(2)···O(4)[a]	2.74(3)
N(11)–W(2)[b]	3.12(3)
N(11)–O(2)[a]	2.87(3)
N(12)–W(1)[c]	2.97(3)
N(12)–O(4)[a]	3.05(3)

[a] $-x, 1 - y, z$. [b] $x, -\frac{1}{2} + y, -\frac{1}{2} + z$. [c] $x, -\frac{1}{2} + y, \frac{1}{2} + z$.

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