

Crystallographic characterization of *trans*-bis(acetato)(1,1-cyclobutanedicarboxylato)ethylenediamineplatinum(IV) trihydrate

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Abstract

The crystal structure of *trans*-bis(acetato)(1,1-cyclobutanedicarboxylato)ethylenediamineplatinum(IV) trihydrate, *trans*-Pt^{IV}(en)(CBDCA)(OCOCH₃)₂·3H₂O, was determined by X-ray crystallographic analysis. The title compound crystallized in the monoclinic space group *P*2₁/*c* with four formula units in a cell of dimensions *a* = 10.320(4), *b* = 18.764(6), *c* = 9.926(4) Å and β = 90.89(3)°. The structure was refined using 2903 observed Mo K α reflections to *R* = 0.036. The coordination about Pt is a slightly distorted octahedron with the Pt atom only 0.03 Å out of the equatorial plane formed by the two bidentate ligands 1,1-cyclobutanedicarboxylate and ethylenediamine. As might be anticipated, both δ and λ forms of the bound ethylenediamine ligand occurred with equal frequency in the crystal. A comparison of bond distances between the C=O double bond and the C–O single bond for each COO group suggested that there is no significant delocalization of any of the four C=O bonds. A strong network of hydrogen bonding involving the three water molecules of solvation was observed, and the two axial acetate ligands appeared to be locked into position by intramolecular hydrogen bonds to the ethylenediamine.

Introduction

The chemistry of platinum complexes has been an active area of research since the discovery of the antitumor properties of *cis*-diamminedichloroplatinum(II) (CDDP) by Rosenberg *et al.* in 1969 [1]. Extensive studies reveal that the platinum containing compounds of the type *cis*-PtA₂X₂ (where A₂ is either two monodentate or one bidentate amine ligand and X₂ is either two monodentate or one bidentate anionic ligand) are more active than their *trans* isomers [2–4]. To understand the nature of platinum–DNA interaction, i.e. the mechanism of drug action [5–8], the structure–activity relationship and the molecular structures of these complexes have been investigated, resulting in several publications focused on new platinum drugs [9–20]. Like platinum(II) complexes, platinum(IV) compounds are one category of promising agents. Some *trans* dicarboxylate platinum(IV) compounds with chlorine as the leaving group have recently been described in the literature [21]. We have synthesized a series of new asymmetric carboxylate platinum(IV) compounds that have the general formulae of Pt^{IV}(en)XA₂ and Pt^{IV}(en)X'A₂, where X = 1,1-cyclobutanedicarboxylato or malonato; X' = chloro, cyclobutanedicarboxylato, cyclopentanedicarboxylato or cyclo-

hexanedicarboxylato; A = acetato or trifluoroacetato [22]. These compounds exhibited antitumor activity comparable to or greater than that of cisplatin. Although their structure has been proposed based on the reaction between the *trans* dihydroxy compound and an anhydride [22], confirmation through diffraction is scarce. We report here the first crystallographic characterization of one of the compounds: *trans*-bis(acetato)(1,1-cyclobutanedicarboxylato)ethylenediamineplatinum(IV) trihydrate.

Experimental

Preparation and characterization

The preparation and characterization of *trans*-diacetato(1,1-cyclobutanedicarboxylato)ethylenediamineplatinum(IV) (IR, nuclear magnetic resonance, elemental analysis and an *in vitro* antitumor test) have been described in detail elsewhere [22]. Single crystals suitable for X-ray crystallographic measurement were grown from aqueous solution at room temperature.

Crystallographic measurement

Crystallographic analysis was performed at the University of Houston X-ray Crystallography Center. A clear, colorless block having approximate dimensions 0.65 × 0.55 × 0.35 mm was cut from a much larger, thick

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plate and mounted in a random orientation on a Nicolet R3m/V automatic diffractometer. The radiation used was Mo $K\alpha$ 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 $2/m$, and from the systematic absences noted, the space group was shown unambiguously to be $P2_1/c$. Intensities were measured using the omega scan technique, with the scan rate depending on the count obtained in rapid pre-scans of each reflection. Two standard reflections were monitored after every 2 h or every 100 data collected, and these showed no significant change. The sample crystal, however, turned bright amber during data collection. The change seems to be permanent, since the color persisted even several weeks after being removed from the X-ray beam. During data reduction, Lorentz and polarization corrections were applied, as well as an empirical absorption correction based on psi scans of ten reflections having chi values between 70 and 90° .

The structure was solved by interpretation of the Patterson map, which revealed the position of the Pt atom. The remaining non-hydrogen atoms were located in subsequent difference Fourier syntheses. The usual sequence of isotropic and anisotropic refinement was followed, after which all non-water hydrogens were entered in ideal calculated positions and constrained to riding motion. A single isotropic temperature factor was varied for all of them. Hydrogens attached to the three water molecules of solvation could not be located, and attempts to refine ideal rigid body models of water led to meaningless hydrogen orientations. Therefore

TABLE 1. Data collection and processing parameters

Molecular formula	$C_{12}H_{20}N_2O_8Pt \cdot 3H_2O$
Formula weight	569.49
Space group	$P2_1/c$ (monoclinic)
Cell constants	
a (Å)	10.320(4)
b (Å)	18.764(6)
c (Å)	9.926(4)
β ($^\circ$)	90.89(3)
V (Å ³)	1922
Formula units per cell, Z	4
Density, ρ (g cm ⁻³)	1.97
Absorption coefficient, μ (cm ⁻¹)	74.3
Radiation (Mo $K\alpha$), λ (Å)	0.71073
Collection range ($^\circ$)	$4 \leq 2\theta \leq 50$
Scan width, $\Delta\theta$ ($^\circ$)	$1.20 + (K\alpha_2 - K\alpha_1)$
Scan speed range ($^\circ$ min ⁻¹)	2.0–15.0
Total data collected	3521
Independent data, $I > 3\sigma(I)$	2903
Total variables	239
$R(F)$	0.036
$R_w(F)$	0.035
Weights, w	$\sigma(F)^{-2}$

the water hydrogens were omitted from the final refinement. After all shift/e.s.d. ratios were less than 0.2, convergence was reached at the agreement factors listed in Table 1. No unusually high correlations were noted among 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 $1.5 e/\text{Å}^3$, located near Pt. All calculations were made using Nicolet's SHELXTL PLUS (1987) series of crystallographic programs.

Results and discussion

After oxidative-addition reaction, square planar (1,1-cyclobutanedicarboxylato)ethylenediamineplatinum(II) reacts with hydrogen peroxide in an aqueous solution to form an octahedral platinum(IV) complex with two hydroxyl groups in *trans* axial positions. This complex further reacts with acetic anhydride in dichloromethane to generate the title compound, *trans*-bis(acetato)(1,1-cyclobutanedicarboxylato)ethylenediamineplatinum(IV) [22]. The molecular structure presented in Fig. 1 clearly shows that the two acetate ligands lie in *trans* positions, since the reaction occurs only between the hydroxyl and the acetic anhydride.

Table 2 gives the final atomic coordinates, while Tables 3 and 4 list the bond distances and angles, respectively. The coordination geometry about Pt was a slightly distorted octahedron; the platinum atom was only 0.03 Å out of the equatorial plane, which was formed by the two bidentate ligands, 1,1-cyclobutanedicarboxylate (CBDCA) and ethylenediamine. The average Pt–N bond length of 2.03 Å (Table 3) was well within the normal range for other ethylenediamine platinum(II) as well as platinum(IV) complexes: 2.03 Å is the value for *trans*-*S,S*-[*N,N'*-bis(2-hydroxyethyl)ethylenediamine(oxalato)platinum(II)] [12] and 2.06 Å, for *cis*-dichlorobis(ethylenediamine)-

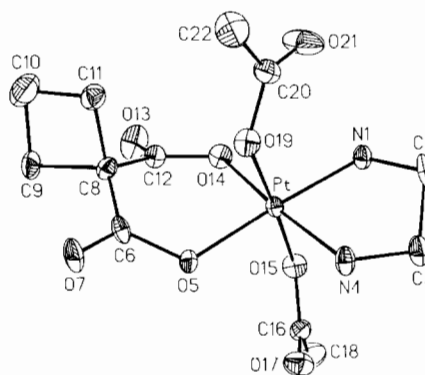


Fig. 1. View of the molecule showing the atom numbering scheme. The thermal ellipsoids are 30% equiprobability envelopes, with hydrogens omitted for clarity.

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

	x	y	z	U_{eq}^a
Pt	5032(1)	1206(1)	1327(1)	22(1)
N1	4754(7)	1025(4)	-662(7)	30(3)
C2	5093(10)	1680(5)	-1445(9)	40(3)
C3	6329(10)	1957(5)	-760(9)	41(4)
N4	5968(7)	2095(4)	659(7)	33(3)
O5	5384(5)	1423(3)	3254(5)	31(2)
C6	4473(9)	1289(5)	4226(8)	33(3)
O7	4477(7)	1680(3)	5198(6)	45(2)
C8	3511(8)	703(5)	4051(9)	30(3)
C9	3090(9)	386(6)	5402(10)	45(4)
C10	1681(11)	498(8)	4999(12)	73(5)
C11	2095(9)	982(5)	3847(10)	40(4)
C12	3772(9)	131(5)	3030(9)	33(3)
O13	3570(7)	-496(3)	3268(8)	60(3)
O14	4131(6)	289(3)	1805(6)	34(2)
O15	6604(6)	563(3)	1157(6)	34(2)
C16	7765(9)	789(6)	1517(10)	36(3)
O17	8009(6)	1369(4)	1904(7)	49(3)
C18	8731(10)	216(6)	1384(14)	68(5)
O19	3494(6)	1842(3)	1597(6)	35(2)
C20	2430(9)	1830(6)	852(10)	42(4)
O21	2241(6)	1458(5)	-74(8)	69(3)
C22	1467(10)	2365(6)	1366(11)	58(4)
O23	9287(8)	1985(5)	4077(8)	76(4)
O24	9621(7)	3402(5)	3675(9)	80(4)
O25	7996(8)	3300(5)	1374(8)	71(4)

^aEquivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

TABLE 3. Bond lengths (\AA)

Pt-N1	2.019(7)	Pt-N4	2.044(7)
Pt-O5	1.984(5)	Pt-O14	2.017(6)
Pt-O15	2.030(6)	Pt-O19	2.008(6)
N1-C2	1.498(11)	C2-C3	1.527(14)
C3-N4	1.486(11)	O5-C6	1.383(10)
C6-O7	1.211(11)	C6-C8	1.490(13)
C8-C9	1.536(13)	C8-C11	1.562(12)
C8-C12	1.504(13)	C9-C10	1.516(15)
C10-C11	1.526(16)	C12-O13	1.217(11)
C12-O14	1.310(11)	O15-C16	1.315(11)
C16-O17	1.180(12)	C16-C18	1.474(15)
O19-C20	1.315(11)	C20-O21	1.168(13)
C20-C22	1.507(15)		

platinum(IV) chloride [13]. The four Pt-O distances found in the complex were not significantly different from one another. The average Pt-O bond length was 2.01 \AA , consistent with those found in other carboxylate complexes [14-20]. Comparison of the bond distances between C=O double bonds and C-O single bonds indicated no significant delocalization of any of the C=O bonds.

Possible conformers of *trans*-dihydroxoplatinum(IV) complexes were derived from computer graphics. The malonate platinum ring in CBDCA may adopt three

TABLE 4. Bond angles ($^\circ$)

N1-Pt-N4	83.2(3)	N1-Pt-O5	176.7(3)
N4-Pt-O5	93.7(3)	N1-Pt-O14	91.6(3)
N4-Pt-O14	174.4(3)	O5-Pt-O14	91.5(2)
N1-Pt-O15	85.4(3)	N4-Pt-O15	94.4(3)
O5-Pt-O15	93.9(2)	O14-Pt-O15	83.4(2)
N1-Pt-O19	97.5(3)	N4-Pt-O19	86.3(3)
O5-Pt-O19	83.2(2)	O14-Pt-O19	96.2(2)
O15-Pt-O19	177.1(3)	Pt-N1-C2	109.8(5)
N1-C2-C3	104.4(7)	C2-C3-N4	105.2(7)
Pt-N4-C3	106.9(5)	Pt-O5-C6	121.4(5)
O5-C6-O7	116.9(8)	O5-C6-C8	120.8(7)
O7-C6-C8	122.2(8)	C6-C8-C9	112.4(8)
C6-C8-C11	112.8(8)	C9-C8-C11	88.0(7)
C6-C8-C12	118.7(8)	C9-C8-C12	111.6(8)
C11-C8-C12	109.2(7)	C8-C9-C10	90.0(8)
C9-C10-C11	90.1(8)	C8-C11-C10	88.6(7)
C8-C12-O13	121.7(8)	C8-C12-O14	121.3(8)
O13-C12-O14	116.8(8)	Pt-O14-C12	123.3(5)
Pt-O15-C16	120.7(6)	O15-C16-O17	125.1(9)
O15-C16-C18	110.8(9)	O17-C16-C18	124.1(9)
Pt-O19-C20	124.7(6)	O19-C20-O21	125.5(9)
O19-C20-C22	110.3(9)	O21-C20-C22	124.2(9)

conformations: boat, chair and planar, which is the intermediate between boat and chair [17]. In a normal boat conformation there would be considerable steric interaction between the cyclobutane ring and one of the axial acetate ligands of the Pt complex. However, this steric crowding was much relieved in the latter two conformers. The conformation of CBDCA in the present crystal structure does not belong to any of these three forms. A careful examination reveals that C6 bends upward to the plane O5-C12-C14 rather than in this plane. Thus, this malonate platinum ring may adopt a twist-boat conformation. Since the cyclobutane ring bends towards only one of the axial acetate ligands, the two axial acetate ligands are no longer equivalent.

The N1-Pt-O5, N4-Pt-O14 and O15-Pt-O19 systems were quasi linear, the angular values being 176.7(3), 174.4(3) and 177.1(3) $^\circ$, respectively. The N1-Pt-N4 angle is 83.2(3) $^\circ$, similar to other platinum compounds containing a five-membered chelate ring with the same donor atoms, e.g. 84.7 $^\circ$ for *trans*-*S,S*-[*N,N'*-bis(2-hydroxyethyl)ethylenediamine(oxalato)platinum(II)] [12], 84 $^\circ$ for *cis*-dichlorobis(ethylenediamine)platinum(IV) chloride [13] and 85 $^\circ$ for bis(acetate)(*trans*-1,2-diaminocyclohexane)platinum(II) [14]. Table 4 shows that the remaining bond angles in the platinum-ethylenediamine chelate ring were very close to tetrahedral. The O5-Pt-O14 angle of 91.5(2) $^\circ$ resembles that found in other six-membered chelate ring with the same donor atoms [16, 18]. As might be anticipated, both δ and λ forms of the bound ethylenediamine ligand occurred with equal frequency in the crystal. The

N1–C2–C3–N4 torsion angle modulus of 59° compares well with the corresponding values observed in other ethylenediamine complexes [12, 13].

Figure 2 gives a view of the molecular packing in the unit cell, while Table 5 summarizes the hydrogen bonding parameters. Hydrogen bonding between neighboring molecules in a crystal is common [12, 16–18]. In the present structure there was a strong network of hydrogen bonding involving the three solvated water molecules since the two axial acetate ligands were locked into position by intramolecular hydrogen bonds to the ethylenediamine. Because of the rigidity of the bound ligands the bonding angles for the intramolecular hydrogen bonding were about 120° while those for intermolecular hydrogen bonding were close to linear (160°).

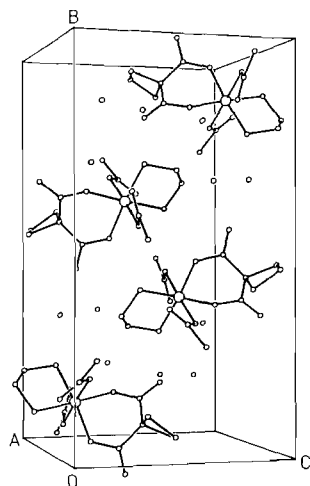


Fig. 2. Packing diagram of the molecules in the unit cell as viewed along the *a* axis.

TABLE 5. Hydrogen bonding parameters

A–H...B	A–H	A...B	H...B	$\langle H$
N(1), H(1A), O(21)	1.05	2.79	2.07	124
N(1), H(1B), O(14')	1.05	2.96	1.95	160
N(4), H(4A), O(17)	1.05	2.78	2.08	122
N(4), H(4B), O(7'')	1.05	2.80	1.79	160
O(23), , O(17)		2.76		
O(23), , O(25)		2.71		
O(24), , O(23)		2.71		
O(24), , O(25)		2.82		
O(25), , O(13)		2.80		

Supplementary material

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

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References

- B. Rosenberg, L. Van Camp, J. E. Trosko and V. H. Mansour, *Nature (London)*, 222 (1969) 385.
- C. F. J. Barnard, *Platinum Met. Rev.*, 33 (1989) 162.
- M. J. Cleare and J. D. Hoeschele, *Bioinorg. Chem.*, 2 (1973) 187.
- P. Umapathy, *Coord. Chem. Rev.*, 95 (1989) 129.
- L. S. Hollis and S. J. Lippard, *J. Am. Chem. Soc.*, 105 (1983) 3494.
- M. Gullotti, G. Pacchioni, A. Pasini and R. Ugo, *Inorg. Chem.*, 21 (1982) 2006.
- Y. Qu and N. Farrell, *J. Am. Chem. Soc.*, 113 (1991) 4851.
- J. F. Vollano, E. E. Blatter and J. C. Dabrowiak, *J. Am. Chem. Soc.*, 106 (1984) 2732.
- T. K. Miyamoto and H. Ichida, *Bull. Chem. Soc. Jpn.*, 64 (1991) 1835.
- M. Yamashita and K. Toriumi, *Inorg. Chim. Acta*, 178 (1990) 143.
- J. Arpalahti, B. Lippert, H. Schöllhorn and U. Thewalt, *Inorg. Chim. Acta*, 153 (1988) 45.
- Q. Y. Xu, A. R. Khokhar and J. L. Bear, *Inorg. Chim. Acta*, 178 (1990) 107.
- C. F. Liu and J. A. Ibers, *Inorg. Chem.*, 9 (1970) 773.
- F. D. Rochon, R. Melanson, J.-P. Macquet, F. Belanger-Gariepy and A. L. Beauchamp, *Inorg. Chim. Acta*, 108 (1985) 17.
- M. A. Bruck, R. Bau, M. Noji, K. Inagaki and Y. Kidani, *Inorg. Chim. Acta*, 92 (1984) 279.
- C. G. Van Kralingen, J. Reedijk and A. L. Spek, *Inorg. Chem.*, 19 (1980) 1481.
- R. Kuroda, I. M. Ismail and P. J. Sadler, *J. Inorg. Biochem.*, 22 (1984) 103.
- S. Neidle, I. M. Ismail and P. J. Sadler, *J. Inorg. Biochem.*, 13 (1980) 205.
- S. D. Cutbush, R. Kuroda, S. Neidle and A. B. Robins, *J. Inorg. Biochem.*, 18 (1983) 213.
- A. Kobayashi, Y. Sasaki and H. Kobayashi, *Bull. Chem. Soc. Jpn.*, 52 (1979) 3682.
- C. M. Giandomenico, M. J. Abrams, B. A. Murrer and J. F. Vollano, in *Sixth Int. Symp. Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy, San Diego, CA, Jan. 23–26, 1991*, p. 58.
- A. R. Khokhar, Y. J. Deng, Y. Kido and Z. H. Siddik, *J. Inorg. Biochem.*, in press.