Synthesis and Characterization of Novel Axial Dichloroplatinum(IV) Cisplatin Analogues: Crystal Structure of an Axial Dichloro Complex [Pt(*cis*-1,4-DACH)(*trans*-Cl_2)(CBDCA)]·$^1/_2$MeOH

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Introduction

At present, cisplatin is widely applied in the treatment of various types of cancer.[1] Although effective, the clinical application of cisplatin is limited by severe dose toxicities.[2] Consequently, new platinum drugs with equal or greater antitumor activity but less severe toxicities have been developed through alteration of the pharmacokinetics of cisplatin by replacing the labile chloro ligands with other leaving groups and extending the stable amine ligands to a series of cyclic or acyclic alkylamines. As a result, the second-generation platinum drug carboplatin came into clinical use.[3] Like cisplatin, however, the clinical effectiveness of carboplatin is limited by acquired drug resistance. In pursuing the third-generation platinum complexes for clinical development, the goal was the creation of an agent that overcomes resistance to cisplatin and carboplatin. The focus was on the development of platinum complexes having 1,2-diaminocyclohexane (1,2-DACH)[4] as a ligand because platinum complexes of this ligand retain activity against cisplatin-resistant tumors.[5] As a result, ormaplatin,[6] oxaliplatin,[7] and L-NDDP[8] (liposome-entrapped *cis*-bis(neodecanoato)(*trans*-1(*R*),2(*R*)-diaminocyclohexane)platinum(II), developed in our lab) are currently in clinical trials. Conversion of platinum(II) complexes to platinum(IV) analogues is another approach to moderating the toxicity of platinum(II) complexes.[9] These platinum(IV) complexes, including ormaplatin and JM216 (bis(acetato)amminedichloro(cyclohexanamine)platinum(IV)) are also entered in clinical trials.[10]

In our continuing efforts to develop new platinum-based antitumor agents, we have reported the synthesis, characterization, and antitumor activity of platinum(II) and platinum(IV) complexes with various isomers of 1,2-DACH.[11] We are currently engaged in the development of platinum agents with *cis*-1,4-DACH as a carrier ligand.[12] (1,2-DACH)(*trans*-dichloro)(carboxylato)platinum(IV) complexes are known to possess antitumor activity.[13] These complexes were prepared either by direct chlorination of platinum(II) carboxylate complexes or by oxidation of platinum(II) complexes with 30% H_2O_2 to form axial dihydroxo analogues, which were then converted into axial dichloro complexes with diluted HCl. Many such complexes were prepared, but no structural studies have been reported so far. In this paper we report the synthesis and characterization of new axial dichloroplatinum(IV) complexes of the type [Pt(1,4-DACH)(*trans*-Cl_2)LL] (where 1,4-DACH = *cis*-1,4-diaminocyclohexane, and LL = 1,1-cyclobutanedicarboxylato (CBDCA), oxalato, malonato, methylmalonato, or tartronato ligand. The crystal structure of [Pt(1,4-DACH)(*trans*-Cl_2)(CBDCA)] has been described. The crystal structure, to the best of our knowledge, is the first structure of an axial dichloroplatinum(IV) complex that belongs to the [Pt(DACH)(*trans*-Cl_2)(dicarboxylato)] family.

Experimental Section

Synthetic Procedures. [Pt(1,4-DACH)LL] (where LL = CBDCA, oxalato, malonato, methylmalonato, or tartronato ligand) were synthesized as described previously[12] and oxidized with 30% H_2O_2 to form the corresponding *trans*-dihydroxoplatinum(IV) complexes.

Synthesis of [Pt(1,4-DACH)(*trans*-Cl_2)(CBDCA) (1). Two equivalents of 0.02 M HCl (199.92 mL; 4 mM) was added to [Pt(1,4-DACH)(*trans*-$(OH)_2$)(CBDCA)] (0.97 g; 2 mM) and the mixture stirred. The white precipitate was dissolved immediately in HCl to form a clear, colorless solution. The reaction mixture was continuously stirred for 24 h at room temperature, during which the solution changed from colorless to pale yellow. The pale yellow solution was then filtered and evaporated to dryness at 35 °C under reduced pressure. A pale yellow solid was obtained, which was then dissolved in 100 mL of

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Table 1. Crystallographic Data and Structure Refinement for [Pt(1,4-DACH)(*trans*-Cl_2)(CBDCA)]

empirical formula	$C_{12.50}H_{22}N_2Cl_2O_{4.50}Pt$
fw	538.31
temp, K	223(2)
cryst syst	orthorhombic
space group	*Pbcn* (No. 60)
a, Å	11.320(2)
b, Å	17.361(3)
c, Å	17.589(4)
V, Å^3	3456.7(12)
Z	8
density (calcd)	2.069 g cm^{-3}
abs coeff	8.447 mm^{-1}
final *R* indices [$I > 2\sigma(I)$][a]	$R_1 = 0.0470$, $R_w = 0.1148$
R indices (all data)[a]	$R_1 = 0.1018$, $R_w = 0.1423$

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. $R_w = [\sum w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]^{1/2}$. $w = [\sigma^2(F_o^2) + (aP)^2 + bP]^{-1}$. $P = (F_o^2 + 2F_c^2)/3$.

methanol. The volume of the solution was reduced to 5 mL, and precipitation was induced with acetone. The precipitate was separated by filtration, washed several times with acetone, and then dissolved again in 50 mL of methanol. The volume of the solution was reduced to 10 mL, and the solution was kept at room temperature for slow evaporation. After 2−3 days, pale yellow needles formed as a cluster. The needles were separated from the solution, washed with methanol and acetone, and dried in a vacuum (yield, 40%). Anal. Found: C, 27.42; H, 3.89; N, 5.28; Cl, 13.88. Calcd: C, 27.59; H, 3.86; N, 5.36; Cl, 13.57.

IR (KBr): 3250, 1600, 1350, 350 cm^{-1}.^{195}Pt NMR (in DMF): +659 ppm.

Complexes **2**−**5** were prepared as described above from their corresponding *trans*-dihydroxo complexes except that the compounds were separated from the methanolic solution as crystalline powders during slow evaporation.

[Pt(1,4-DACH)(*trans*-Cl_2)(oxalate)] (2): yield, 60%. Anal. Found: C, 20.68; H, 3.25; N, 5.89; Cl, 14.78. Calcd: C, 20.52; H, 3.01; N, 5.98; Cl, 15.14.

IR (KBr): 3260, 1680, 1350, 350 cm^{-1}. ^{195}Pt NMR (in DMF): +623 ppm.

[Pt(1,4-DACH)(*trans*-Cl_2)(malonate)] (3): yield, 54%. Anal. Found: C, 22.32; H, 3.71; N, 5.52; Cl, 14.84. Calcd: C, 22.42; H, 3.34; N, 5.81; Cl, 14.70.

IR (KBr): 3255, 1670, 1360, 355 cm^{-1}. ^{195}Pt NMR (in DMF): +578 ppm.

[Pt(1,4-DACH)(*trans*-Cl_2)(methylmalonate)] (4): yield, 55%. Anal. Found: C, 24.53; H, 3.79; N, 5.78; Cl, 14.56. Calcd: C, 24.21; H, 3.66; N, 5.65; Cl, 14.29.

IR (KBr) 3260, 1675, 1355, 345 cm^{-1}. ^{195}Pt NMR (in DMF) +647 ppm.

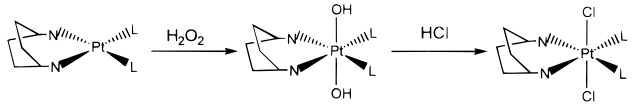
[Pt(1,4-DACH)(*trans*-Cl_2)(tartronate)] (5): yield, 50%. Anal. Found: C, 21.62; H, 3.44; N, 5.51; Cl, 13.87. Calcd: C, 21.69; H, 3.24; N, 5.62; Cl, 14.23.

IR (KBr): 3250, 1650, 1350, 350 cm^{-1}. ^{195}Pt NMR (in methanol): +610 ppm.

IR and ^{195}Pt NMR Spectroscopy. IR spectra were recorded in KBr pellets using a Beckman 250 MX spectrophotometer. ^{195}Pt NMR spectra were recorded at 43.055 MHz using a Bruker 200/AF spectrometer with a 10-mm tunable probe. Chemical shifts were measured relative to an external standard of 2.2 M Na_2PtCl_6 in D_2O at 0.00 ppm.

X-ray Crystallography. The crystal was encapsulated in a thin shell of epoxy cement and mounted on the tip of a glass fiber. Data were collected with a Rigaku AFC5-S automated four-circle diffractometer using the TEXSAN 5.0 software package[14] and were corrected for Lorentz/polarization effects and absorption (Ψ-scans). Data collection and refinement parameters are summarized in Table 1. Scattering factors were taken from the literature.[15] The structure was solved with a personal computer using the SHELXTL-PLUS software package.[16] Refinement of F^2 for all reflections, except those with very negative F^2, was performed with a personal computer using SHELXL-93 software.[17] Weighted *R* factors, R_w, and all goodness-of-fit (*S*) values are based on F^2, while conventional *R* factors, *R*, are based on *F* with *F* set to 0 for negative F^2. *R* factors based on F^2 are statistically about twice as large as those based on *F*, and *R* factors based on all of the data will be even larger. The weighting factor $w = [\sigma^2(F_o^2) + (xP)^2 + yP]^{-1}$ where $p = (F_o^2 + 2F_c^2)/3$ was refined for *x* and *y*.

Scheme 1



Results and Discussion

The aim of this work was to synthesize axial dichloroplatinum(IV) complexes of the type [Pt(1,4-DACH)(*trans*-Cl_2)LL] (where LL = 1,1-cyclobutanedicarboxylato, oxalato, malonato, methylmalonato, or tartronato ligand) from their corresponding axial dihydroxo complexes to evaluate their antitumor activity. These complexes can be prepared by direct oxidation of platinum(II) complexes with chlorine gas,[13a] but direct chlorination of our complexes resulted in tetrachloro complexes. Therefore we prepared these complexes by oxidizing platinum(II) complexes with 30% H_2O_2 to form axial dihydroxoplatinum(IV) complexes; hydroxy ligands were then substituted for by chlorides through the reaction with diluted HCl (0.02 M),[11b,13a] as shown in Scheme 1. The higher concentration of acid leads to the formation of tetrachloroplatinum(IV) complexes because of Pt−O bond breakage in the axial and equatorial positions.[18]

The complexes were characterized by elemental analysis, IR, and ^{195}Pt NMR spectroscopy. The theoretical values of the elemental analyses are in good agreement with the actual findings. The conversion of *trans*-dihydroxoplatinum(IV) complexes to their *trans*-dichloroplatinum(IV) counterparts can easily be seen by significant changes in infrared[20] and ^{195}Pt NMR spectroscopy.[19] The dihydroxoplatinum(IV) compounds showed characteristic PtO−H stretches in the range 3470−3550 cm^{-1} and the Pt−O stretches in the region between 540 and 570 cm^{-1}. After chlorination, both PtO−H and Pt−O stretches disappeared. In all complexes the Pt−Cl stretches in the range 345−355 cm^{-1} were observed. In ^{195}Pt NMR, the peaks corresponding to *trans*-dihydroxoplatinum(IV) (PtN_2O_4 system) ranging from 1580 to 1669 ppm disappeared and the peaks in the range 578−659 ppm assignable to *trans*-dichloroplatinum(IV) ($PtN_2O_2Cl_2$ system) complexes appeared.

Crystal Structure. The structure of [Pt(1,4-DACH)**(*trans*-Cl_2)(**CBDCA)]·$^1/_2$MeOH is the first crystal structure of a platinum(IV) complex of the type [Pt(DACH)(*trans*-Cl_2)-(dicarboxylato)] in which the chlorides occupy the axial

(14) *TEXSAN: Single Crystal Analysis Software*, Version 5.0; Molecular Structure Corporation: The Woodlands, TX, 1989.

(15) The scattering factors are part of the SHELXL-93 package and can be found in the *International Tables, for X-ray Crystallography*; Kluwers Academic Publishers: Dordrecht, The Netherlands, 1992; Vol. C, Tables 4.2.6.8 and 6.1.1.4.

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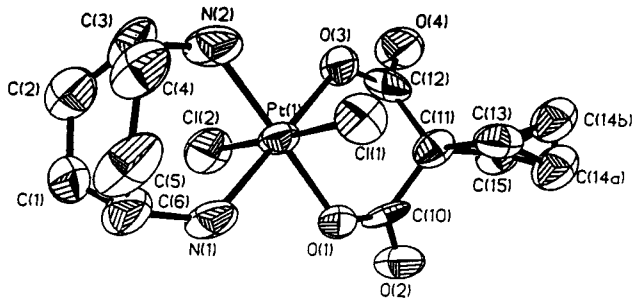

Figure 1. ORTEP representation of the structure of [Pt(*cis*-1,4-DACH)(*trans*-Cl_2)(CBDCA)] showing the two disordered carbon atoms of the cyclobutane ring. Hydrogen atoms are omitted for clarity.

Table 2. Selected Bond Lengths (Å) and Angles (deg) of [Pt(1,4-DACH)(*trans*-Cl_2)(CBDCA)]

Pt−O(1)	1.987(1)	Pt−O(3)	1.995(1)
Pt−N(1)	2.02(2)	Pt−N(2)	2.04(2)
Pt−Cl(1)	2.301(5)	Pt−Cl(2)	2.314(5)
O(1)−Pt−O(3)	96.1(5)	O(1)−Pt−N(1)	82.2(6)
O(3)−Pt−N(1)	178.0(6)	O(1)−Pt−N(2)	178.0(6)
O(3)−Pt−N(2)	82.9(6)	N(1)Pt−N(2)	98.7(7)
O(1)−Pt−Cl(1)	93.6(4)	O(3)−Pt−Cl(1)	91.5(4)
N(1)−Pt−Cl(1)	89.8(5)	N(2)−Pt−Cl(1)	88.2(6)
O(1)−Pt−Cl(2)	86.9(4)	O(3)−Pt−Cl(2)	86.1(4)
Cl(1)−Pt−Cl(2)	177.6(2)		

positions of an octahedral geometry. The structure is complicated by disorder in the cyclobutane ring. Figure 1 shows the view of the molecule along with its atom labels; selected bond lengths and bond angles are given in Table 2. In this complex, platinum(IV) is in a distorted octahedral geometry with two equatorial positions occupied by two nitrogen atoms of 1,4-DACH. Two other equatorial positions are occupied by two oxygen atoms of CBDCA, while the two axial positions are bound to two chloride ions. The 1,4-DACH is in a unique twist-boat configuration, which is necessary for binding to platinum. This configuration contrasts with the chair configuration usually observed in 1,2-DACH complexes.[21] Platinum bonding with amino nitrogens at positions 1 and 4 is considerably strained, resulting in expansion of the N1−Pt−N2 bond angle to 98.7°. The N1−Pt−N2 bond angles in the 1,2-DACH and 1,3-DACH complexes are 83.5° and 94.8°, respectively.[21,22] Expansion of the N−Pt−N bond angle is quite obvious as the position of the amino group changes from 1,2 to 1,4 because the size of the chelating ring increases from five membered to seven membered.[21,22] In compensation, the N1−Pt−O1 bond angle is reduced to 82.9° compared with analogous angles of 93.8−94.4° in 1,2-DACH complexes.[21] The strain in the binding of 1,4-DACH to platinum is also shown in the expansion of the Pt−N−C angle to 126.2° as compared to 105−110° in 1,2-DACH complexes.[21] The Pt−N bond length (2.02 Å) is not significantly different from bond lengths found in the structures of similar complexes.[21] CBDCA forms a six-membered chelating ring with platinum and adopts a boat configuration as in other reported platinum complexes.[12a,18b,23] The average Pt−O bond length of 1.991[6][27] Å is slightly shorter than the Pt−O bond lengths in carboplatin (2.03[2][27] Å)[24] and [Pt(DACH)L] (where DACH = 1(*R*),2(*R*)-diaminocyclohexane and L = CBDCA, oxalate and malonate),[21a,c] whereas the average Pt−Cl bond length (2.308[9][27] Å) is slightly longer than the Pt−Cl bond lengths reported in other Pt(IV) complexes such as *trans*-dichloro(tetraazamacrocycle)platinum(IV) (2.280(5) Å)[25] and *trans*-chloro(1,2-DACH)(*N*-methyliminodiacetato)platinum(IV) chloride (2.289(5) Å).[26]

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Supporting Information Available: Tables S1−S5 listing the complete data collection and structure refinement, bond lengths and bond angles, anisotropic displacement parameters, hydrogen coordinates, and isotropic displacement parameters and Figure S1 illustrating crystal packing in a unit cell of [Pt(*cis*-1,4-DACH)(*trans*-Cl_2)(CBDCA)] (6 pages). Ordering information is given on any current masthead page.

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(27) Esd's average values are calculated via the scatter formula:

$$\sigma = [\sum_{i=1}^{i-N}(d_i - d)^2/(N-1)]^{1/2}$$

They are thus external estimates on the esd on an individual measurement.