Synthesis and X-ray crystal structure of *cis*-1,4-diaminocyclohexanetetrachloroplatinum(IV): a new antitumor agent

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Abstract

cis-1,4-Diaminocyclohexanetetrachloroplatinum(IV), a new antitumor agent, has been synthesized, where *cis*-1,4-diaminocyclohexane (*cis*-1,4-DACH) is a novel carrier ligand. The structure of this complex has been determined by single crystal X-ray diffraction method. The crystal parameters are as follows: space group $P\bar{1}$ (triclinic), $a = 6.880(2)$, $b = 8.177(3)$, $c = 11.784(4)$ Å, $Z = 2$. The platinum has a slightly distorted octahedral coordination with two adjacent corners being occupied by the two amino nitrogens of *cis*-1,4-DACH, and the remaining two equatorial and two axial positions are bound to four chloride ions. The *cis*-1,4-DACH is in a twist-boat conformation, which is necessitated by binding to platinum. It forms a seven-membered chelating ring with platinum, leading to considerable strain in bidentate DACH binding. This strain is evidenced by the large 125.7° C–N–Pt angle. The N–Pt–N angle is expanded to 98.4° owing to geometric constraints of the *cis*-1,4-DACH geometry.

Key words: Crystal structures; Platinum complexes; Bidentate amine ligand complexes; Chelate complexes; Antitumor agents

Introduction

The search for the second generation of platinum anticancer agents was associated with the aim to synthesize compounds that are less toxic but as or more active than cisplatin [1]. Although cisplatin is one of the most effective oncolytic agents against cancers of the testes, ovaries, bladder, and head and neck [2–4], it has severe toxicities such as nephrotoxicity, nausea/vomiting, myelosuppression, ototoxicity and neurologic complications [5–7]. Efforts were generally directed at modifying the drug design by replacing the stable amine and leaving groups, which effectively change the pharmacokinetics of cisplatin. As a result, several second generation cisplatin analogs containing 1,2-diaminocyclohexane (1,2-DACH) as a carrier ligand such as ormaplatin [8], oxaliplatin [9] and liposomal *cis*-bis(neodecanoato) (*trans-l*-1,2-DACH)platinum(II) (L-NDDP) [10] are currently in clinical development. Tetrachloro-*trans-dl*-1,2-DACH-platinum(IV) (ormaplatin) has a broad spectrum of preclinical antitumor activity and remains active against L1210 and P388 cells as well as other tumor cell lines with resistance to cisplatin [11]. Although ormaplatin has shown greater activity than cisplatin in some models [12], it showed less activity than cisplatin against B16 melanoma the MX-1 human breast xenograft [11] and other cell lines [13, 14].

In our continuous efforts to design new anticancer platinum drugs, we have synthesized a series of novel platinum(II) and (IV) complexes using *cis*-1,4-DACH as carrier ligand. These complexes possess outstanding curative antitumor activity against tumor resistant to cisplatin and/or ormaplatin. In this paper, we report the synthesis and crystal structure of a novel antitumor agent, *cis*-1,4-diaminocyclohexanetetrachloroplatinum(IV). The biological activity of this complex will be published elsewhere.

Experimental

cis-1,4-DACH was purchased from CTC Organics, Atlanta, GA. Dimethyl sulfoxide (DMSO) and 1,1-cyclobutanedicarboxylic acid (CBDCA) were obtained from Aldrich Chemical Co., Milwaukee, WI, and po-

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tassium tetrachloroplatinate(II) was purchased from Johnson Matthey, Seabrook, NH.

Synthesis of cis-1,4-diaminocylcohexanetetrachloroplatinum(IV)

$K_2[PtCl_4]$ (6.25 g, 15 mM) was dissolved in 100 ml of water. DMSO (2.43 g, 30 mM) in 10 ml of water was added to it. The reaction mixture was kept at room temperature for 2 days. The pale yellow needles of *cis*-$[Pt(DMSO)_2Cl_2]$ were obtained, filtered, washed with cold water, and dried *in vacuo*. Yield 75%. *cis*-$[Pt(DMSO)_2Cl_2]$ (5.1 g, 12 mM) was dissolved in 250 ml of warm water. To this solution was added a suspension of disilver salt of CBDCA (4.2 g, 11.64 mM). The reaction mixture, protected from light, was kept stirring for 24 h at room temperature. The solution was filtered, and the yellow filtrate was evaporated to 50 ml under reduced pressure at 35 °C and was kept in ice. The white crystalline $[Pt(DMSO)_2(CBDCA)]$ was isolated, washed with cold water, and dried under vacuum. Yield 70%. To a hot solution of $[Pt(DMSO)_2(CBDCA)]$ (2.47 g, 5 mM) in 150 ml of water was added a solution of *cis*-1,4-DACH (0.57 g, 5 mM) in 10 ml of water. The mixture was stirred at 90 °C for 1.5 h. The completion of reaction was monitored by high pressure liquid chromatography. The solution was filtered while hot, cooled, and evaporated to a minimum volume under reduced pressure at 35 °C and kept in ice. An off-white compound was precipitated, and recrystallized from water. The white crystalline [Pt(*cis*-1,4-DACH)(CBDCA)] was obtained with 50% yield. [Pt(*cis*-1,4-DACH)(CBDCA)] (1.17 g, 2.5 mM) was dissolved in 200 ml of water and 30% H_2O_2 (15 ml) was added to it. The reaction mixture was stirred for 15 h at room temperature. A clear colorless solution was obtained and evaporated to dryness under reduced pressure at 35 °C. A white solid [Pt(*cis*-1,4-DACH)(CBDCA)$(OH)_2$] was obtained. [Pt(*cis*-1,4-DACH)(CBDCA)$(OH)_2$] (1.22 g, 2.42 mM) was dissolved in 50 ml of concentrated HCl and stirred for 4 days at room temperature. The solution was kept at room temperature for slow evaporation. Yellow crystals of *cis*-1,4-diaminocyclohexanetetrachloroplatinum(IV) were obtained, which were filtered, and washed with water. Yield 70%. *Anal.* Found: C, 16.07; H, 2.87; N, 6.23. Calc.: C, 15.96; H, 3.10, N, 6.20%.

Crystallographic measurements

A canary yellow flat plate having approximate dimensions of $0.48\times0.35\times0.12$ mm was mounted in a random orientation on a Nicolet R3m/V automatic diffractometer. Since the material was potentially light sensitive, the sample was placed in a stream of dry nitrogen gas at −50 °C to retard any decomposition. The radiation used was Mo Kα 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 $\bar{1}$, and the space group was shown to be either $P1$ or $P\bar{1}$. Intensities were measured using the θ:2θ 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. During data reduction Lorentz and polarization corrections were applied, as well as an empirical absorption correction based on ψ scans of 10 reflections having χ values between 70 and 90°.

Since the unitary structure factors displayed centric statistics, space group $P\bar{1}$ was assumed from the outset. The structure was solved by interpretation of the Patterson map, which revealed the position of the platinum atom. Remaining non-hydrogen atoms were found in subsequent difference Fourier syntheses. The usual sequence of isotropic and anisotropic refinement was followed, after which all hydrogens were entered in ideal calculated positions and constrained to riding motion, with a single variable isotropic temperature factor for all of them. After all shift/e.s.d. ratios were less than 0.1, 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

TABLE 1. Data collection and processing parameters

Space group	$P\bar{1}$ (triclinic)
Cell constants	
a (Å)	6.880(2)
b (Å)	8.177(3)
c (Å)	11.784(4)
α (°)	73.82(2)
β (°)	71.88(2)
γ (°)	67.68(2)
V (Å^3)	573
Molecular formula	$C_6H_{14}N_2Cl_4Pt$
Formula weight	451.11
Formula units per cell, Z	2
Density, ρ (g cm^{-3})	2.61
Absorption coefficient, μ (cm^{-1})	132.7
Temperature, T (°C)	−50
Radiation (Mo Kα), λ (Å)	0.71073
Collection range (°)	$4\leqslant 2\theta\leqslant 50$
Scan width, $\Delta\theta$ (°)	$1.20+(K\alpha_2-K\alpha_1)$
Scan speed range (° min^{-1})	1.5–15.0
Total data collected	2033
Independent data, $I>3\sigma(I)$	1847
Total variables	120
$R=\Sigma\|\|F_o\|-\|F_c\|\|/\Sigma\|F_o\|$	0.032
$R_w=[\Sigma w(\|F_o\|-\|F_c\|)^2/\Sigma w\|F_o\|^2]^{1/2}$	0.035
Weights, w	$\sigma(F)^{-2}$
Extinction coefficient, x	0.00040

final difference density map showed a maximum peak of about 2.00 e/Å^3, located quite close to platinum. All calculations were made using Nicolet's SHELXTL PLUS (1987) series of crystallographic programs.

Results and discussion

The synthesis of *cis*-1,4-diaminocyclohexanetetrachloroplatinum(IV), a new antitumor agent, involves five steps as shown in Scheme 1. *cis*-$[Pt(DMSO)_2Cl_2]$ [15]

$$K_2PtCl_4 + 2DMSO \longrightarrow cis\text{-}[Pt(DMSO)_2Cl_2] + 2KCl \quad (1)$$

$$cis\text{-}[Pt(DMSO)_2Cl_2] + Ag_2CBDCA \longrightarrow [Pt(DMSO)_2(CBDCA)] + 2AgCl \quad (2)$$

$$[Pt(DMSO)_2(CBDCA)] + cis\text{-}1,4\text{-}DACH \xrightarrow[1.5\ h]{90\ ^\circ C} [Pt(cis\text{-}1,4\text{-}DACH)(CBDCA) + 2DMSO \quad (3)$$

$$[Pt(cis\text{-}1,4\text{-}DACH)(CBDCA)] \xrightarrow{H_2O_2} [Pt(cis\text{-}1,4\text{-}DACH)(CBDCA)(OH)_2] \quad (4)$$

$$[Pt(cis\text{-}1,4\text{-}DACH)(CBDCA)(OH)_2] \xrightarrow{conc.\ HCl} [Pt(cis\text{-}1,4\text{-}DACH)Cl_4] + CBDCA + 2H_2O \quad (5)$$

Scheme 1.

and *cis*-$[Pt(DMSO)_2(CBDCA)]$ [16] were prepared as previously described. The crucial step in this method is to synthesize [Pt(*cis*-1,4-DACH)(CBDCA)], in which the reaction mixture is kept at 90 °C for 1.5 h to get [Pt(*cis*-1,4-DACH)(CBDCA)] with 50% yield. If the reaction is kept at 100 °C for 6 h as mentioned in the procedure for the synthesis of [Pt(*trans-l*-1,2-DACH)(CBDCA)] [16], slow decomposition starts, and the whole reaction mixture will turn black yielding only 5%.

Figure 1 shows the view of the molecule along with its atom labeling. Bond lengths and bond angles are given in Tables 2 and 3, respectively. Atomic coordinates are given in Table 4.

The coordination around the platinum atom is a slightly distorted octahedron. The distortion appears to be caused by a longer bite distance of the chelating ligand. The two adjacent corners of the platinum plane are occupied by two nitrogens of the *cis*-1,4-DACH, and the remaining two equatorial and two axial positions are occupied by four chloride ions. *cis*-1,4-DACH forms a seven-membered chelating ring with the platinum atom, and the N–Pt–N angle is expanded to 98.4° owing to geometric constraints of the ligand (Table 3). However, the same bond angle in the complexes of 1,2-DACH, which forms a five-membered chelating ring with the platinum atom, is less than 90°. For example the value of this angle is 82.9° in [Pt(*trans-dl*-1,2-DACH)Cl_4] [17] and 83.5° in [Pt(*trans-l*-1,2-DACH)(CBDCA)] [16]. The bond between *cis*-1,4-DACH and the metal ion is also considerably strained as evidenced by the large C–N–Pt angle of 125.7°, whereas this angle is only 109.3° in [Pt(*trans-dl*-1,2-DACH)Cl_4] [17], 105.5° in [Pt(*trans-l*-DACH)(oxalate)] [18] and 113.2° in Pt(*cis*-1,2-DACH)(L(−)-prolinate-N)$_2$] [19]. Expansion of the N–Pt–N bond angle is compensated for by contraction of the N1–Pt–Cl2 angle

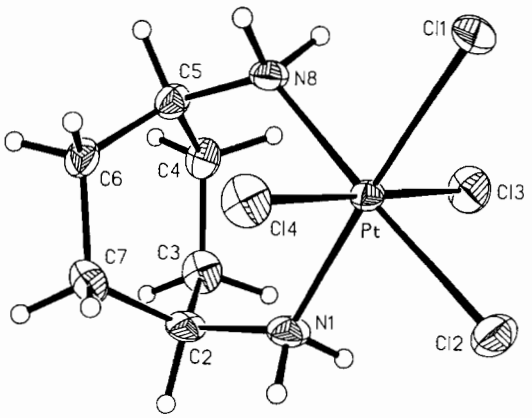

Fig. 1. View of the molecule showing the atom numbering scheme. The thermal ellipsoids are 40% equiprobability envelopes, with hydrogens as spheres of arbitrary diameter.

TABLE 2. Bond lengths (Å)

Pt–Cl(1)	2.310(3)	Pt–Cl(2)	2.316(3)
Pt–Cl(3)	2.310(3)	Pt–Cl(4)	2.311(2)
Pt–N(1)	2.081(9)	Pt–N(8)	2.055(9)
N(1)–C(2)	1.513(10)	C(2)–C(3)	1.496(14)
C(2)–C(7)	1.532(13)	C(3)–C(4)	1.529(19)
C(4)–C(5)	1.510(13)	C(5)–C(6)	1.503(14)
C(5)–N(8)	1.513(10)	C(6)–C(7)	1.520(19)

TABLE 3. Bond angles (°)

Cl(1)–Pt–Cl(2)	92.5(1)	Cl(1)–Pt–Cl(3)	90.2(1)
Cl(2)–Pt–Cl(3)	90.4(1)	Cl(1)–Pt–Cl(4)	89.1(1)
Cl(2)–Pt–Cl(4)	89.3(1)	Cl(3)–Pt–Cl(4)	179.2(1)
Cl(1)–Pt–N(1)	176.4(2)	Cl(2)–Pt–N(1)	84.2(2)
Cl(3)–Pt–N(1)	88.5(2)	Cl(4)–Pt–N(1)	92.2(2)
Cl(1)–Pt–N(8)	84.9(2)	Cl(2)–Pt–N(8)	177.4(3)
Cl(3)–Pt–N(8)	89.6(2)	Cl(4)–Pt–N(8)	90.7(2)
N(1)–Pt–N(8)	98.4(3)	Pt–N(1)–C(2)	125.7(8)
N(1)–C(2)–C(3)	111.6(8)	N(1)–C(2)–C(7)	112.8(7)
C(3)–C(2)–C(7)	112.1(9)	C(2)–C(3)–C(4)	116.5(9)
C(3)–C(4)–C(5)	115.5(9)	C(4)–C(5)–C(6)	112.6(9)
C(4)–C(5)–N(8)	111.5(7)	C(6)–C(5)–N(8)	113.1(7)
C(5)–C(6)–C(7)	117.9(8)	C(2)–C(7)–C(6)	114.2(9)
Pt–N(8)–C(5)	124.5(8)		

TABLE 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$)

	x	y	z	U_{eq}[a]
Pt	5162(1)	5089(1)	2458(1)	21(1)
Cl(1)	6239(4)	2719(3)	1457(2)	35(1)
Cl(2)	8087(4)	3816(3)	3353(3)	41(1)
Cl(3)	3148(4)	3642(3)	4090(2)	41(1)
Cl(4)	7207(4)	6498(3)	817(2)	36(1)
N(1)	4308(12)	7118(10)	3437(8)	32(4)
C(2)	2563(14)	8919(12)	3277(9)	29(4)
C(3)	357(15)	8735(13)	3761(10)	37(4)
C(4)	−448(15)	8089(13)	2948(9)	32(4)
C(5)	949(14)	7965(12)	1682(9)	28(4)
C(6)	1908(15)	9465(12)	1158(9)	29(4)
C(7)	2870(16)	9951(12)	1967(10)	35(4)
N(8)	2616(11)	6119(9)	1626(8)	28(3)

[a]Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

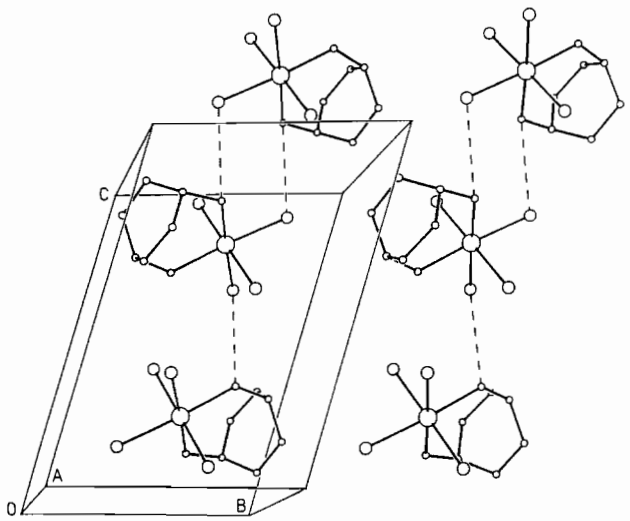

Fig. 2. Packing in the unit cell, as viewed into the *a* axis. Hydrogen bonds are indicated by dashed lines.

TABLE 5. Hydrogen bonding parameters

A–H...B	A–H	A...B	H...B	∢H
N(1), H(1b), Cl(2)	1.05[a]	3.62	2.61	160
N(8), H(8a), Cl(2)	1.05[a]	3.97	2.98	159
N(8), H(8b), Cl(1)	1.05[a]	3.40	2.42	156

[a]Fixed atom position.

to 84.2° in contrast to an analogous bond angle of 90.4° in [Pt(*trans-dl*-1,2-DACH)Cl_4] [17].

The average Pt–N bond length of 2.07 Å is comparable with the Pt–N bond distances observed in [Pt(*trans-dl*-1,2-DACH)Cl_4] (2.06 Å) [17] and other cyclic diamine platinum complexes like [Pt(*trans-l*-1,2-DACH)-(CBDCA)] (2.03 Å) and [Pt(*trans-l*-1,2-DACH)-(CBDCA)(DMSO)] (2.05 Å) [16]. The average Pt–Cl bond distance of 2.312 Å is also consistent with those found in structurally related complexes, such as [Pt(*trans-dl*-1,2-DACH)Cl_4] (2.31 Å) [17], [Pt(*trans-dl*-1,2-DACH)(9-methylguanine)$_2Cl_2$]$(NO_3)_2 \cdot 11H_2O$ (2.31 Å) [20] and [Pt(*trans-l*-DACH)(N-Me-IDA)Cl]Cl (2.289 Å) [21]. There does not appear to be any significant '*trans* effect' by *cis*-1,4-DACH, since all four Pt–Cl bond distances were statistically equal.

cis-1,4-Diaminocyclohexanetetrachloroplatinum(IV) is unique because *cis*-1,4-DACH is in the twist-boat configuration as necessitated for binding to platinum. In contrast, 1,2-DACH is usually in the chair configuration in similar platinum complexes [17, 22].

Figure 2 shows a stereoscopic view of the molecular packing in the unit cell. The molecules in the crystal are held together by a system of weak N–H...Cl hydrogen bonds (Table 5).

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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