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Chiral palladium(II) and platinum(II) complexes of diaminocyclohexane: X-ray structures of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane dihydrochloride and its corresponding oxalato platinum(II) complex

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Abstract

The nucleophilic substitution reaction of the enantiomerically pure ligand, (1*R*,2*R*)-(−)-1,2-diaminocyclohexane [DACH] (**1**) with *cis*-bis(benzonitrile)palladium(II) dichloride [$(PhCN)_2PdCl_2$] leads to the formation of the complex [(DACH)$PdCl_2$] (**2**) in a high yield. The reaction of the corresponding platinum(II) complex [$(PhCN)_2PtCl_2$] with DACH, under the same reaction conditions, surprisingly, took a different course, in which nucleophilic addition to the benzonitrile ligand occurred forming an enantiomerically pure amidine complex [$(PhC{=}NH{-}NH(C_6H_{10})NH_2)Pt(N{\equiv}CPh)Cl]Cl$ (**3**), where the nitrogen ligand form a seven-membered chelate around the central atom. The aqua and oxalato derivatives of complex **2**, [(DACH)$Pd(H_2O)_2](NO_3)_2$ (**4**) and [(DACH)$Pd(C_2O_4)$] (**5**) have also been prepared and characterized. The platinum analogue complex to **5**, [(DACH)$Pt(C_2O_4)$] (**6**), was prepared starting from the enantiomerically pure isomer (**1**) and the platinum salt K_2PtX_4 (X = Cl, I). According to X-ray structural analysis carried out on the complex, the product does not consist of just the desired isomer, but a mixture of both the *trans*-*l* (*trans*-(−)-1*R*,2*R*) and *trans*-*d* (*trans*-(+)-1*S*,2*S*) isomers. No retention of optical isomerism was observed. The single crystal structural analysis was also carried out on the ligand *N*,*N*′-(1*R*,2*R*)-(−)-diaminocyclohexane dihydrochloride (DACH·2HCl)] (**1a**). The result indicates, however, that only the *R*,*R*-isomer exists in the free ligand.

Keywords: Palladium; Platinum; Chirality; Bidentate nitrogen ligands; Antitumor compounds; Crystal structures

1. Introduction

Since the discovery of the activity of *cis*-[$(H_3N)_2PtCl_2$], clinically called cisplatin, one of the most successful anticancer compounds [1], many new platinum complexes have been synthesized and evaluated for their antitumor activity [2]. This research has been stimulated by the limitations of cisplatin. The *cis* coordination by two amines (at least one NH group on the amine) and two leaving groups with an intermediate binding strength to platinum seems to be a necessary prerequisite for an active Pt-drug. Carboplatin [$(H_3N)_2Pt$(CBDC)], (CBDC, 1,1′-cyclobutyldicarboxylato group), a second generation analogue of cisplatin has reduced toxic side effects for the same efficiency thanks to its much lower reactivity. Unfortunately, carboplatin is only active in the same range of tumors as cisplatin.

The third generation drugs, including compounds which contain different types of chiral amines, has been launched. Oxaliplatin (*trans*-*l*-1,2-diaminocyclohexane platinum(II) oxalate) showed a colorectal antitumor activity, can be administrated orally and had positive preclinical evaluations for use in cisplatin

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resistant tumors. Investigations on this type of chiral complexes showed that the *trans* isomer *trans-l* (*trans*-(−)-1*R*,2*R*) is more efficacious than the corresponding *trans-d* (*trans*-(+)-1*S*,2*S*) and the *cis*-isomer (1*R*,2*S*) [3]. Thus, the activity might be explained by speculating on the stereochemical structures of the complexes.

In an effort to solve the structure of the active species of the oxaliplatin, Bruck et al. were able to carry out X-ray structural investigation on oxaliplatin [4]. The complex was prepared by reacting the enantiomerically pure isomer *trans-l* (*trans*-(−)-1*R*,2*R*-diaminocyclohexane (DACH)) and the platinum salt K_2PtCl_4 in H_2O. Based on the resultant data, they reported that only the absolute configuration of the *trans-l*-DACH ligand exists in the platinum complex.

In the present study, we found that the oxaliplatin which was isolated following the above synthetic procedure or by using K_2PtI_4 as a starting material does not consist only of the desired isomer, but a mixture of both the *trans-l* and *trans-d* isomers. No retention of optical isomerism was observed despite the fact that the enantiomerically pure DACH ligand was utilized. Therefore, it will be desirable to find a new methodology to synthesize the enantiomerically pure (1*R*,2*R*)-oxaliplatin complex.

In previous reports we described the synthesis of square-planar palladium(II) and platinum(II) complexes with bidentate heterodonor ligands [5–7] by displacement of the weakly coordinated benzonitrile ligands with a bidentate chelate. As a continuation of our intrinsic interest in such biologically active complexes [8–10] we applied the same route to synthesize the chiral complexes of platinum(II) and palladium(II) with (1*R*,2*R*-diaminocyclohexane, DACH). The solid state structure of the chiral ligand (1*R*,2*R*-diaminocyclohexane) (DACH **1a**) and the complex [DACH)Pt(C_2O_4)] were determined by X-ray structure analysis.

2. Experimental

2.1. Materials

All manipulations were carried out under argon using standard Schlenk techniques. [$(PhCN)_2PdCl_2$] [11], [$(PhCN)_2PtCl_2$] and oxaliplatin [(DACH)Pt(C_2O_4)] [12] (**6**) were prepared according to literature procedures. (1*R*,2*R*)-(−)-1,2-diaminocyclohexane was purchased from Aldrich. Hydrocarbons solvents were purified by refluxing over $LiAlH_4$ followed by distillation under argon, methylenechloride was dried over CaH_2 and distilled under argon.

2.2. Physical measurements

Elemental analyses were performed at the Pharmacology Department, University of Helsinki (EA 1110 CHNS-O CE instrument). ^{1}H NMR spectra were recorded on a Varian Gemini 200 spectrometer operating at 200 MHz using $CDCl_3$ or DMSO-d_6 as solvents with TMS as an internal standard. Infrared spectra were measured on a BIO-RAD FTS-7 FT-IR spectrometer using KBr pellets. Mass spectra (EI) were acquired with a JEOL JMS-SX102 mass spectrometer.

2.3. Synthesis of compounds

2.3.1. Dichloro[(1*R*,2*R*)-(−)-diaminocyclohexane]palladium(II): [(DACH)$PdCl_2$] (**2**)

To a filtered solution of [$(PhCN)_2PdCl_2$] (3.0 g, 7.82 mmol) in acetone (130 ml) was added a solution of DACH (**1**) (1.0 g, 8.75 mmol) in the same solvent (30 ml). Upon addition a yellow solid started to form. Stirring was continued for 12 h at room temperature then the product was filtered, washed with acetone (25 ml), diethylether (175 ml), and dried under vacuum.

2.3.1.1. **2**. Yield: 1.9 g (84%). Found: C, 25.12; H, 5.19; N, 10.18. *Anal*. Calc. for $C_6H_{14}N_2PdCl_2$: C, 24.72; H, 4.84; N, 9.61. EI MS; *m/e* (rel. int.): 495 (8%, M^+–2Cl), 382 (70%, M^+–$PdCl_2$). IR (KBr, cm^{-1}): 3281 (s), 2934 (s), 1561 (m, sh), 1160 (w).

2.3.2. (Benzonitrile)chloro(*N*-phenylamidine-*N*-cyclohexylamine)-platinum(II) chloride (**3**)

A solution of (1*R*,2*R*)-diaminocyclohexane (0.76 g, 6.65 mmol) in CH_2Cl_2 (30 ml) was added to a solution of [$(PhCN)_2PtCl_2$] (3.0 g, 6.05 mmol) in the same solvent (30 ml). Upon addition, the color changed from yellow to orange. Stirring was continued for 12 h at room temperature then the solution was filtered and concentrated. Upon addition of ether, a yellow precipitate was formed, which was filtered, washed with petroleum ether (50 ml), and dried under vacuum. The yield was 2.5 g (68%). Recrystalization from acetone afforded yellow crystals suitable for X-ray analysis [13].

2.3.2.1. **3**. Yield: 0.83 g (55%). Found: C, 39.47; H, 4.90; N, 9.67. *Anal*. Calc. for $C_{20}H_{27.67}N_4O_{1.33}PtCl_2$: C, 39.74; H, 4.34; N, 9.27. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm); 1.50 (s, 2H, NH), 1.20 (s, 6H, DACH), 0.8 (m, 4H, DACH) EI MS; *m/e* (rel. int.): 694.5 (60%, M^+), 659.4 (40%, M^+–Cl). IR (KBr, cm^{-1}): 3374 (s), 3057 (m), 2931 (m), 2360 (w).

2.3.3. Diaqua[(1R,2R)-(−)-diaminocyclohexane]palladium(II) nitrate: [(DACH)Pd(H_2O)$_2$]-(NO_3)$_2$ (**4**)

To a solution containing compound (**2**) (1.5 g, 5.15 mmol) in distilled water (150 ml) was added silver nitrate (1.9 g, 11.30 mmol). Stirring was continued for 2 days in dark at 25 °C. The resulted yellow solution was filtered and evaporated to dryness. The compound was extracted with CH_2Cl_2 (150 ml) and acetone (100 ml). Both solvents were evaporated to dryness to give a deep yellow powder.

2.3.3.1. ***4***. Yield: 1.37 g (72%). Found: C, 18.59; H, 3.85; N, 15.59. *Anal*. Calc. for $C_6H_{18}N_4O_8Pd$: C, 18.93; H, 4.76; N, 14.72. ^{1}H NMR (200 MHz, CD_3OD): δ (ppm); 5.0 (s, H_2O), 2.58 (m, 2H, CH), 2.34 (m, 4H, NH_2), 2.16 (m, 2H, CH_2), 1.84 (m, 2H, CH_2), 1.43 (m, 4H, CH_2). EI MS; *m/e* (rel. int.): 468.0 (75%, M^+–Cl), 433.0 (40%, M^+–2Cl). IR (KBr, cm^{-1}): 3256 (s), 2937 (m), 2859 (w), 1591 (m), 1488 (s), 1384 (s), 1308 (s), 1263 (s), 1157 (m), 1009 (m).

2.3.4. Oxalato[(1R,2R)-(−)-diaminocyclohexane]palladium(II): [(DACH)Pd(C_2O_4)] (**5**)

This compound was prepared following a previously published procedure [14]. To a deep yellow solution of (**4**) (1.15 g, 3.02 mmol) in distilled water (50 ml) was added potassium oxalate (1.22 g, 6.04 mmol). After stirring at 25 °C for 20 h, the solvent was evaporated under reduced pressure. The yellow solid was extracted with methylenechloride and dried under vacuum.

2.3.4.1. ***5***. The yield was 0.79 g (85%). Found: C, 28.72; H, 4.25; N, 8.34. *Anal*. Calc. for $C_{8.5}H_{15}N_2O_4PdCl$: C, 29.08; H, 4.31; N, 7.98. ^{1}H NMR (200 MHz, D_2O): δ (ppm); 4.5 (s, 2H, NH_2), 2.42 (m, 2H, CH), 2.0 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.15 (m, 4H, CH). EI MS; *m/e* (rel. int.): 252.8 (8%, M^+–$(CO)_2$), 115.7 (70%, M^+–PdC_2O_4). IR (KBr, cm^{-1}): 3257 (m), 3162 (m), 3068 (m), 2934 (m), 2858 (w), 1673 (s, sh), 1605 (s, sh), 1384 (m), 1156 (w), 1063 (w), 774.4 (w).

2.4. X-ray structure determinations for compounds (**1a**) and (**6**)

Crystal data of (**1a**) were collected on a Rigaku AFC7S single-crystal diffractometer at 193(2) K using graphite monochromatized Mo Kα radiation (0.71073 Å). The intensities were corrected for Lorentz and polarization effects [15]. An experimental absorption correction (psi-scan) was performed [16]. The structure was solved by direct methods (SHELX-97) [17]. Final crystal data for (**6**) were collected on a Nonius Kappa CCD diffractometer at 120(2) K with Mo Kα radiation. Lorentz and polarization [18], absorption (multi-scan) [19] and extinction corrections were made. All non-hydrogen atoms were refined anisotropically and hydrogen atoms isotropically on calculated positions. Final calculations were performed with SHELX-97. SHELXTL/PC was used for graphics [20]. The cell parameters and specific data collection parameters are summarized in Table 1.

3. Results and discussion

3.1. Synthesis of complexes

The nucleophilic substitution reaction of the complex [$(PhCN)_2PdCl_2$] with the commercially available (1*R*,2*R*)-(−)-1,2-diaminecyclohexane (DACH) in CH_2Cl_2 at 25 °C afforded the square planar Pd(II) complex [(DACH)$PdCl_2$] (**2**) in a high yield. However, the corresponding platinum(II) complex [(DACH)$PtCl_2$] could not be prepared following the same route, but only through the reaction of the DACH with the platinum salt K_2PtCl_4 [14] or K_2PtI_4. The reaction of the platinum(II) complex [$(PhCN)_2PtCl_2$] with DACH,

Table 1
Crystallographic data and parameters for data collection and refinement of the compounds (**1a**) and (**6**)

Formula	$C_6H_{16}Cl_2N_2$	$C_8H_{14}N_2O_4Pt$
Formula weight	187.11	397.30
T (K)	193(2)	120(2)
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1/m$
a (Å)	9.557(3)	4.6516(1)
b (Å)	11.966(3)	9.9156(3)
c (Å)	8.109(3)	11.2060(4)
α (°)	90	90
β (°)	90	90.361(1)
γ (°)	90	90
V (Å^3)	927.3(5)	516.85(3)
Z	4	2
F(000)	400	372
D_{calcd} (Mg/m^3)	1.340	2.553
Absorption coefficient (mm^{-1})	0.636	13.571
Crystal dimensions (mm)	0.30 × 0.30 × 0.25	0.15 × 0.10 × 0.07
θ range (°)	2.73–25.25	2.74–26.00
Scan mode	$\omega/2\theta$	CCD
Wavelength	Mo Kα	Mo Kα
No. of relections collected	1924	7066
No. of unique data	1644 [$R_{int} = 0.0493$]	1074 [$R_{int} = 0.0390$]
No. of data refined	1644	1074
Reflections observed (criterion)	1550 ($F > 4\sigma(F)$)	1054 ($F > 4\sigma(F)$)
No. of parameters	109	84
Goodness-of-fit on F^2	1.042	1.181
R_1 [a] ($F > 4\sigma(F)$)	0.0510	0.0192
R_2 [b] (all data)	0.1432	0.0520

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$.
[b] $wR_2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

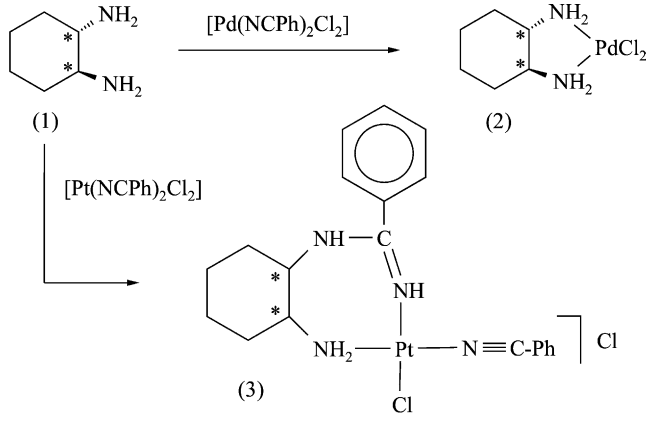
under the same reaction condition applied for the synthesis of (**2**), took a different course, in which nucleophilic addition to the benzonitrile ligand occurred forming an enantiomerically pure amidine complex $[(PhC{=}NH{-}NH(C_6H_{10})NH_2)Pt(N{\equiv}CPh)Cl]Cl$ (**3**), where the nitrogen ligand formed a seven-membered chelate around the central atom (Scheme 1). The reaction is thought to proceed through a nucleophilic addition of the first amine nucleophile at the partially positive carbon atom in the benzonitrile ligand to give the amidine (HN–C(Ph)=NH) followed by a nucleophilic attack by the second amine at the metal center and the displacement of the chloride to form the monocationic amidine complex (**3**). X-ray investigation carried out on complex **3** reveals that in the solid state the molecule is enantiomerically pure (*trans-l*) which indicates that this methodology leads to the formation of just one enantiomer [13].

Abstracting the chlorides in complex **2** with two molar equivalents of $AgNO_3$ in H_2O gave the corresponding diaqua complex $[(DACH)Pd(H_2O)_2](NO_3)_2$ (**4**), which was then treated with potassium oxalate to form the oxalato derivative $[(DACH)Pd(C_2O_4)]$ (**5**). Attempts to grow suitable crystals from (**5**) were unsuccessful, always needle-like crystals were isolated.

To confirm the identity of the compounds prepared in the present study, a variety of techniques including elemental analysis, MS (EI), IR and ^1H NMR spectroscopy have been used. In addition, complex **6** and, for comparison, compound **1a** were a subject to single-crystal X-ray diffraction study.

3.2. Crystal structure of (*1a*) and (*6*)

In order to assign the stereochemistry of both the ligand (*trans*-(−)-1*R*,2*R*) (**1**) and the complex $[(DACH)Pt(C_2O_4)]$ (**6**) an X-ray structural analysis was performed on them. Suitable crystals of the hydrochloride salt of the chiral enantiomerically pure



Scheme 1. Synthesis and structure of the palladium(II) dichloride (**2**) and the platinum(II) amidine (**3**) complexes.

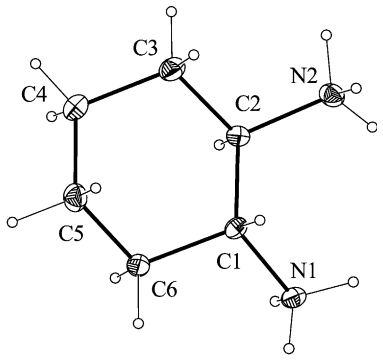


Fig. 1. Crystal structure of dication (DACH·2HCl) (**1a**); displacement ellipsoids are drawn at 30% probability level, hydrogen atoms on an arbitrary scale; chloride ions omitted.

diamine (1*R*,2*R*)-(−)-diaminocyclohexane (DACH·2HCl, **1a**) (Fig. 1) were obtained by treatment of DACH with hydrochloric acid (1.0 M) followed by slow evaporation of the solution to yield colorless crystals. Oxaliplatin complex (**6**) (Fig. 2) was recrystallized from water.

Selected bond lengths and angles are given in Table 2. The molecular structure of complex **6** confirms the monomeric nature of the platinum complex and shows that the oxalato ligand coordinates in a chelating fashion, through an oxygen atom from each of the carboxylic acid groups. The platinum atom is at the center of a square-planar arrangement with two oxygen atoms (O1 and O1a) of the oxalato ligand and two nitrogen atoms (N1 and N1a) of the bidentate nitrogen ligand. The complex crystallizes in the monoclinic space group $P2_1/m$ with $a = 4.6516(1)$ Å, $b = 9.9156(3)$ Å, $c = 11.2060(4)$ Å, $\beta = 90.361(1)^\circ$, and $V = 516.85(3)$ Å^3, $Z = 2$. X-ray structural analysis carried out on the free diamine indicates the presence of the desired chiral 1*R*,2*R*-enantiomer of the diamine ligand.

X-ray data of complex **6** reveal that in the solid state the molecule does not only consist of the desired enantiomer, but also a disordered mixture of both the *trans-l* (*trans*-(−)-1*R*,2*R*) (Fig. 2, A) and *trans-d* (*trans*-(+)-1*S*,2*S*) isomers (Fig. 2, B). No retention of optical isomerism was observed. Platinum complex **6** was made starting from K_2PtCl_4 or K_2PtI_4 and several crystals from both batches were studied by single crystal X-ray methods with Rigaku and Nonius diffractometers with equivalent results.

The final data set which we now publish were also solved and refined in space group $P2_1$. The conventional reliability index ($R1$) was 2.35% for the *R*,*R*-isomer and 2.88% for the *S*,*S*-isomer, when only the platinum atom was refined anisotropically (cf. Table 1). When we tried to refine all non-hydrogen atoms anisotropically, the *R*-values were 2.24% and 2.78%, respectively, but most coordinated atoms and some carbon atoms had their atomic displacement parameters as non-positive definite

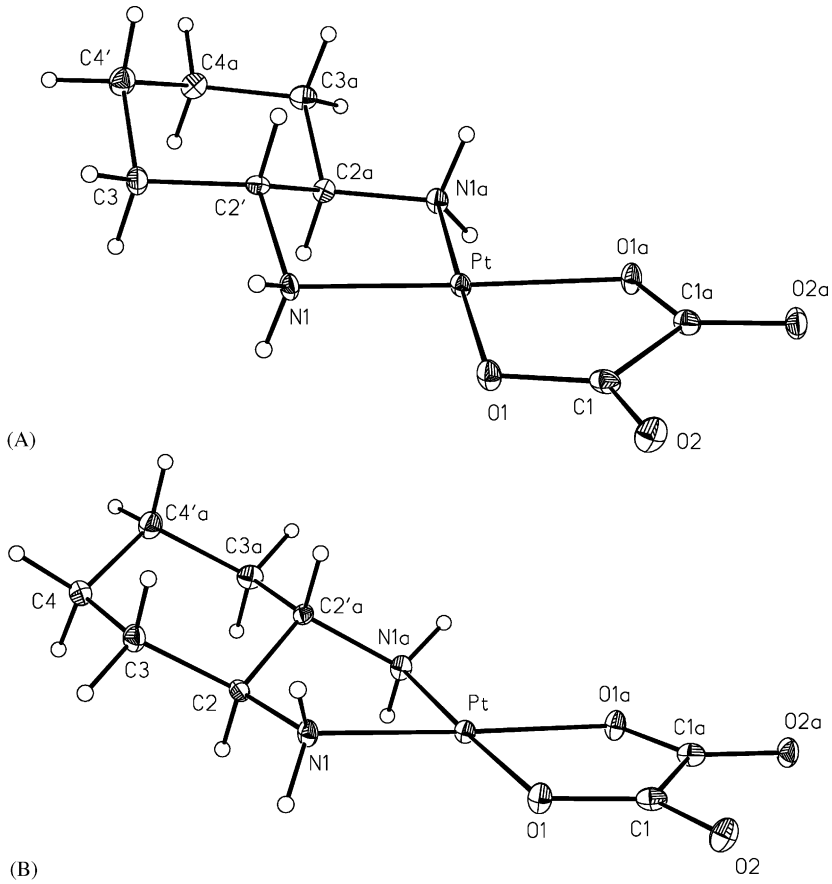


Fig. 2. Crystal structure of the oxaliplatin complex (**6**) showing the labelling scheme; displacement ellipsoids are drawn at 30% probability level. *Trans-l* (*trans*-(−)-1*R*,2*R*) (A) and *trans-d* (*trans*-(+)-1*S*,2*S*) isomers (B).

Table 2
Selected bond length (Å) and angle (°) ranges the compounds **1a** and **6**

1a		**6**	
Bond length			
C1–N1	1.500(4)	Pt–N1 = Pt–N1a	2.033(4)
C1–C2	1.518(4)	Pt–O1 = Pt–O1a	2.026(3)
C1–C6	1.534(4)	C1–O1	1.301(6)
C2–N2	1.497(4)	C1–O2	1.219(6)
C2–C3	1.525(4)	C2′–N1	1.533(10)
C3–C4	1.521(5)	C2a–N1a	1.499(10)
C4–C5	1.512(5)	C1–C1a	1.556(9)
Bond angle			
N1–C1–C2	112.1(3)	N1–Pt–O1	97.00(17)
N1–C1–C6	108.0(3)	N1a–Pt–O1a	97.00(17)
N2–C2–C1	111.6(3)	N1a–Pt–N1	83.5(2)
N2–C2–C3	108.5(3)	O1a–Pt1–O1	82.39(19)
C1–C2–C3	111.2(3)	C2a–N1a–Pt	110.9(4)
C1–C6–C5	110.9(3)	C2′–N1–Pt	105.8(4)
C2–C3–C4	111.8(3)	N1a–C2a–C2′	107.9(7)
C2–C1–C6	111.2(3)	N1–C2′–C3	111.9(7)
		O1–C1–C1a	115.3(3)
		O1–C1–O2	124.0(4)
		O2–C1–C1a	120.7(3)

Label 'a' indicates a symmetry related atom at x, $-y$, $+1/2$, z. In compound **6**, the atomic labels indicate *R*,*R*-isomeric form of DACH.

status. Anisotropical refinement of all non-hydrogen atoms in $P2_1/m$ showed no problems ($R = 1.92\%$), except a disordered structure. There is an extensive H-bond network stabilizing the solid state structure of compound **6**.

It is believed that the transformation of *R*,*R*-DACH took place throughout the synthesis of the corresponding dichloride complex [(DACH)$PtCl_2$]. A breakage of one cyclohexyl–NH_2 bond in the *R*,*R*-DACH during the nucleophilic substitution reaction at K_2PtCl_4 under the applied reaction conditions could be the reason for the formation of the racemates.

4. Supplementary material

Crystallographic data for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC196063 and CCDC196064. Copies of the data can be obtained on application to The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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