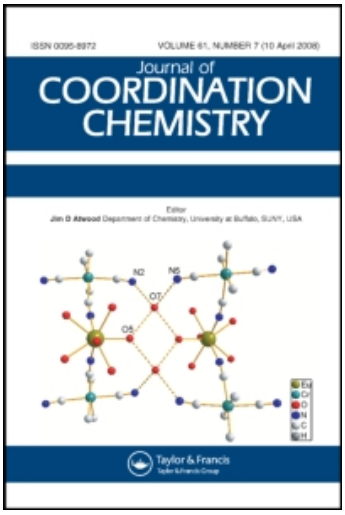

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

SYNTHESIS AND CHARACTERIZATION OF NEW ANTITUMOR *TRANS-R,R-*, *TRANS-S,S-* AND *CIS*-1,2-DIAMINOCYCLOHEXANE PLATINUM (IV) COMPLEXES

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To cite this Article Al-baker, Salaam , Siddik, Zahid H. and Khokhar, Abdul R.(1994) 'SYNTHESIS AND CHARACTERIZATION OF NEW ANTITUMOR *TRANS-R,R-*, *TRANS-S,S-* AND *CIS*-1,2-DIAMINOCYCLOHEXANE PLATINUM (IV) COMPLEXES', Journal of Coordination Chemistry, 31: 2, 109 — 116
To link to this Article: DOI: 10.1080/00958979408024206
URL: http://dx.doi.org/10.1080/00958979408024206

J. Coord. Chem., 1994, Vol 31, pp. 109–116
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SYNTHESIS AND CHARACTERIZATION OF NEW ANTITUMOR *TRANS-R,R-*, *TRANS-S,S-* AND *CIS-*1,2-DIAMINOCYCLOHEXANE PLATINUM (IV) COMPLEXES

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A series of isomeric 1, 2-diaminocyclohexane platinum (IV) complexes of the type DACH-Pt^{IV}-*trans*$(X)_2$*cis*(Y) (where DACH = *trans-R,R-*, *trans-S,S-* or *cis*-1,2-diaminocyclohexane, X = chloro, bromo, acetato, or trifluoroacetato, and Y = dichloro, dibromo, 1,1-cyclobutanedicarboxylato, tartronato, ketomalonato, or methylmalonato) has been synthesized. The isomeric DACH-Pt^{IV}-*trans*$(X)_2$*cis*(Y) complexes were prepared by first oxidizing the corresponding DACH-dihaloplatinum(II) or DACH-dicarboxylato-platinum(II) [DACH-Pt^{II}Y] with hydrogen peroxide to DACH-Pt^{IV}-*trans*$(OH)_2$Y, and then replacing the axial hydroxo groups with chloro, bromo, or monocarboxylato ligands. These complexes were characterized by elemental analysis, and infrared and nuclear magnetic resonance ($^{195}Pt\{^1H\}$) spectroscopic techniques.

KEYWORDS: Platinum, 1,2-diaminocyclohexane, isomer, carboxylate, synthesis

INTRODUCTION

Interest in platinum coordination chemistry has been greatly stimulated by the finding that *cis*-diamminedichloroplatinum(II) (CDDP, cisplatin) is a potent anticancer agent.[1] However, cisplatin has several undesirable side effects,[2–4] it has a narrow spectrum of activity, and resistance develops in originally sensitive tumors[5]. Efforts have been made to synthesize new platinum complexes in an attempt to overcome these impediments.[6] Analogs of cisplatin containing the 1,2-diaminocyclohexane (DACH) carrier ligand coordinated to the central platinum atom are of great interest because of their potential ability to overcome cisplatin resistance in tumor cells.[7–11] In addition to antitumor active four-coordinate platinum(II) complexes, many platinum(IV) complexes have been found to be effective as anticancer agents[12–15]. The antitumor properties of platinum(IV) complexes containing DACH ligands have been investigated by us and several other researchers.[7,16–22] Since platinum(IV) complexes generally undergo substitution reactions slowly, it has been suggested that their ability to kill tumor cells requires reduction to active platinum(II) complexes.[23–26]

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We report here the synthesis and characterization of a series of highly water-soluble platinum(IV) complexes containing *trans-R,R*-DACH, *trans-S,S*-DACH or *cis*-DACH as an inert ligand and chloro, bromo, or carboxylato as leaving groups. The antitumor activity of these complexes has in part, been reported elsewhere.[16–21]

EXPERIMENTAL

Reagents and instrumental techniques

All of the chemicals used were reagent grade. *Trans-R,R-*, and *trans-S,S*-DACH were purchased from Toray Industries (Tokyo, Japan), *cis*-DACH was obtained from Turner Lab (Woodland, TX). Potassium tetrachloroplatinate was purchased from Johnson Matthey (Seabrook, NH). 1,1-Cyclobutanedicarboxylic (CBDCA), tartronic, ketomalonic and methylmalonic acids were purchased from Aldrich Chemical Co. (Milwaukee, WI).

Microanalyses of platinum complexes were performed by Robertson Laboratory Inc. (Madison, NJ). Nuclear magnetic resonance (NMR) spectra were recorded at 43.055 MHz on an IBM BR200/AF spectrometer by using a 10-mm tunable probe. The ^{195}Pt spectra (43.055 MHz) were typically run at 166,000-Hz spectral width, with 100,000 scans, 4k data points, and 0.12 s between 10 μs pulses (90°tilt). ^{195}Pt chemical shifts were collected in water or methanol solution (30 mmol) at room temperature and were measured relative to an external standard of 2.2 mol $Na_2[PtCl_6]$ in D_2O at 0.0 ppm. Infrared (IR) spectra (4000–250 cm^{-1}) were recorded as KBr pellet using a Beckman 250 MX spectrophotometer.

Example I: Preparation of trans-R,R-DACH-tetrachloroplatinum(IV), complex (1)

Complex (1) was synthesized by using the following multistep procedure. $K_2[PtCl_4]$ (8.30 g, 20 mmol) was dissolved in deionized water (400 cm^3) and filtered. Potassium iodide (27 g, 0.16 mol in 30 cm^3 of water) was added and allowed to stir for 5 min. To this solution *trans-R,R*-DACH (2.28 g, 20 mmol) was added with continuous stirring, and the reaction mixture was left stirring for 30 min. A yellow solid was obtained, which was separated by filtration, washed with a small amount of dimethylformamide (DMF) and then repeatedly with water, ethanol, and acetone. The final product, *trans-R,R*-DACH-PtI_2 was dried under vacuum (Yield = 95%). *Trans-R,R*-DACH-PtI_2 (5.628 g, 10 mmol) was added as a solid to an aqueous solution of silver sulfate (2.96 g, 9.5 mmol). The reaction mixture was left stirring (protected from light) overnight at room temperature. Silver iodide was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. A yellow residue was obtained, which was recrystallized from water. The final product, *trans-R,R*-DACH-sulfatoplatinum(II)·H_2O was dried in vacuo (Yield: 98%). When hydrochloric acid (5 cm^{-3}, conc.) was added to a solution of *trans-R,R*-DACH-sulfatoplatinum(II)·H_2O (3.384 g, 8 mmol) in 50 cm^3 of water, a light yellow precipitate of *trans-R,R*-DACH-dichloroplatinum(II) was obtained, which was separated by filtration and washed with water and acetone and dried in vacuo. To a suspension of *trans-R,R*-DACH-dichloroplatinum(II) (2.85 g, 7.5 mmol) in 100 cm^3 of water, 5 cm^3 of 30% aqueous hydrogen peroxide was added dropwise. The mixture was left stirring for 3 h at 70°C, during which the color of

the suspension changed from yellow to a light yellow. *trans-R,R*-DACH-*cis*-dichloro-*trans*-dihydroxoplatinum(IV) complex was obtained and 2 cm^3 of concentrated hydrochloric acid was added to it. The mixture was left stirring for an additional 2 h at 70°C, during which the color of the suspension changed from yellow to orange. Acetone (100 cm^3) was added to the orange suspension, and the mixture was left stirring for 30 min, during which the orange precipitate dissolved and a clear yellow solution formed. The solution was filtered, and the filtrate was evaporated to dryness under reduced pressure. The final yellow complex was recrystallized from acetone to give light yellow crystals (Yield: 95%).

Complexes 2 and 3 (Table 1) were prepared in a similar manner by using either *trans-S,S-* or *cis*-DACH isomer, respectively. Complexes 4-9 were prepared in a similar manner by using HBr plus either *trans-R,R*-DACH, *trans-S,S*-DACH, or *cis*-DACH isomer.

Example II: Preparation of trans-diacetato-trans-R,R-DACH-cis-dichloro platinum(IV), complex (10)

To a stirred suspension of *trans-R,R*-DACH-dichloroplatinum(II) (1.52 g, 4 mmol) in 100 cm^3 of water at 70°C, 5 cm^3 of 30% aqueous hydrogen peroxide was added dropwise. The mixture was left stirring for 3 h at 70°C, during which the color of the suspension changed from yellow to a light yellow. *trans-R,R*-DACH-*cis*-dichloro-*trans*-dihydroxoplatinum(IV) was separated by filtration and washed repeatedly with water, ethanol, and ether. *trans-R,R*-DACH-*cis*-dichloro-*trans*-dihydroxoplatinum(IV) (1.242 g, 3 mmol) was suspended in 100 cm^3 $CHCl_3$, and 10 cm^3 of acetic anhydride was added. The mixture was left stirring for 5 days at room temperature. Methanol (100 cm^3) was added to the mixture to give a clear light yellow solution, which continued to be stirred for 1 h and then filtered. The filtrate was evaporated under reduced pressure at room temperature. The final product was redissolved in 30 cm^3 of acetone and filtered, and the filtrate was treated with 200 cm^3 of ether to give a white precipitate, which was collected on filter paper (Yield: 60%).

By using the above mentioned procedure, complexes 11 and 12 were synthesized

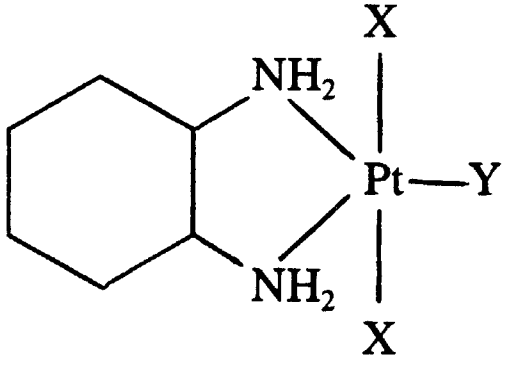

Figure 1 Proposed chemical structure of platinum complexes, where DACH = 1,2-diaminocyclohexane, X = chloro, bromo, acetato, or trifluoroacetato, Y = dichloro, dibromo, 1,1-cyclobutanedicarboxylato, tartronato, ketomalonato, or methylmalonato.

Table 1 Elemental analysis of isomeric DACH-platinum(IV) complexes[a]

Complex No.	Complex Name	Observed (Calculated) %C	%H	%N
1	*Trans-R,R*-DACH-tetrachloroplatinum(IV)	16.07(15.96)	2.93(3.10)	5.99(6.21)
2	*Trans-S,S*-DACH-tetrachloroplatinum(IV)	16.16(15.96)	2.97(3.10)	5.91(6.21)
3	*Cis*-DACH-tetrachloroplatinum(IV)	16.24(15.96)	2.95(3.10)	5.99(6.21)
4	*Trans-R,R*-DACH-tetrabromoplatinum(IV)	11.62(11.45)	2.34(2.23)	4.34(4.45)
5	*Trans-S,S*-DACH-tetrabromoplatinum(IV)	11.71(11.45)	2.29(2.23)	4.28(4.45)
6	*Cis*-DACH-tetrabromoplatinum(IV)·1/2acetone	12.40(12.71)	2.26(2.72)	4.38(4.23)
7	*Trans-R,R*-DACH-*trans*-dibromo-*cis*-dichloroplatinum(IV)·$3H_2O$	12.11(12.12)	2.10(3.36)	3.36(4.71)
8	*Trans-S,S*-DACH-*trans*-dibromo-*cis*-dichloroplatinum(IV)·H_2O	12.73(12.90)	2.10(2.86)	4.86(5.01)
9	*Cis*-DACH-*trans*-dibromo-*cis*-dichloroplatinum(IV)	13.35(13.33)	2.33(2.59)	4.86(5.18)
10	*Trans*-diacetato-*trans-R,R*-DACH-*cis*-dichloroplatinum(IV)·1/2acetone	26.14(26.18)	4.36(4.36)	5.20(5.31)
11	*Trans*-diacetato-*trans-R,R*-DACH-*cis dichloroplatinum(IV)*	23.81(24.09)	4.21(4.01)	5.43(5.62)
12	*Trans*-diacetato-*cis*-DACH-*cis*-dichloroplatinum(IV)·1/2 acetone	25.75(26.12)	4.31(4.36)	5.22(5.31)
13	*Trans-R,R*-DACH-*cis*-dichloro-*trans*-bis-(trifluoroacetato) platinum(IV)	19.79(19.80)	2.25(2.31)	4.68(4.62)
14	*Trans-S,S*-DACH-*cis*-dichloro-*trans*-bis-(trifluoroacetato) platinum(IV)	19.71(19.80)	2.24(2.31)	4.56(4.62)
15	*Cis*-DACH-*cis*-dichloro-*trans*-bis-(trifluoroacetato) platinum(IV)	19.54(19.80)	2.24(2.31)	4.49(4.62)
16	*Trans-R,R*-DACH-*cis*-dibromo-*trans*-di-acetatoplatinum(IV)·1/2acetate	21.37(21.42)	3.85(3.49)	4.67(4.55)
17	*Trans-S,S*-DACH-*cis*-dibromo-*trans*-di-acetatoplatinum(IV)·1/2acetate	21.69(21.42)	3.79(3.49)	4.56(4.55)
18	*Trans*-diacetato-*cis*-DACH-*cis*-dibromoplatinum(IV)	20.60(20.44)	3.46(3.40)	4.76(4.77)
19	*Trans-R,R*-DACH-*cis*-dibromo-*trans*-bis-(trifluoroacetato) platinum(IV)·$1/2H_2O$	16.96(17.04)	2.31(2.13)	4.62(3.98)
20	*Trans-S,S*-DACH-*cis*-dibromo-*trans*-bis-(trifluoroacetato) platinum(IV)·$4H_2O$	15.28(15.64)	2.39(2.34)	4.36(3.65)
21	*Cis*-DACH-*cis*-dibromo-*trans*-bis-(trifluoroacetato)platinum(IV)·H_2O	16.44(16.84)	2.33(2.24)	4.50(3.93)
22	*Trans-R,R*-DACH-*trans*-dichloro-(1,1 cyclo-butanedicarboxylato)platinum(IV)·$2H_2O$	25.83(25.80)	4.42(4.30)	4.72(5.01)
23	*Trans-S,S*-DACH-*trans*-dichloro-(1,1-cyclo-butanedicarboxylato)platinum(IV)·H_2O	26.11(26.66)	4.66(4.07)	4.69(5.18)
24	*Cis*-DACH-*trans*-dichloro (1,1-cyclo-butanedicarboxylato)platinum(IV)·$3H_2O$	24.83(25.00)	4.29(4.51)	4.69(4.86)
25	*Trans-R,R*-DACH-*trans*-dichlorotartronato-platinum(IV)·H_2O	20.73(20.93)	3.36(3.48)	5.08(5.42)
26	*Trans-S,S*-DACH-*trans*-dichlorotartronato-platinum(IV)	21.68(21.68)	3.65(3.21)	5.26(5.62)
27	*Cis*-DACH-*trans*-dichlorotartronatoplatinum(IV)	22.78(21.68)	3.61(3.21)	5.18(5.62)
28	*Trans-R,R*-DACH-*trans*-dichloro-(ketomalonato)platinum(IV)	21.06(21.00)	3.50(3.11)	5.34(5.44)
29	*Trans-S,S*-DACH-*trans*-dichloroketomalonato platinum(IV)	20.90(21.00)	3.14(3.11)	5.06(5.44)
30	*Cis*-DACH-*trans*-dichloroketomalonatoplatinum(IV)	20.89(21.00)	3.40(3.11)	5.48(5.44)
31	*Trans-R,R*-DACH-*trans*-dichloro-(methylmalonato)platinum(IV)·$3H_2O$	20.77(21.81)	3.82(4.36)	5.02(5.09)
32	*Trans-S,S*-DACH-*trans*-dichloro-(methylmalonato)platinum(IV)	23.42(24.19)	3.72(3.63)	5.05(5.64)
33	*Cis*-DACH-*trans*-dichloro(methylmalonato) platinum(IV)·H_2O	23.28(23.34)	3.83(3.89)	4.90(5.44)

[a]DACH = 1,2-diaminocyclohexane

by using either *trans-S,S-*, or *cis*-DACH isomer, respectively. Compelxes 13-15 were prepared by a similar method using trifluoroacetic anhydride. Complexes 16-21 were synthesized by using *trans-R,R-*, *trans-S,S-*, or *cis*-DACH-*cis*-dibromo-*trans*-dihydroxoplatinum(IV), and acetic anhydride, or trifluoroacetic anhydride.

Example III: Preparation of trans-R,R-DACH-trans-dichloro(1,1-cyclobutanedicarboxylato)platinum(IV), complex (22)

Trans-R,R-DACH-sulfatoplatinum(II)·H_2O (see example I) (1.692 g, 4 mmol) was dissolved in 30 cm^3 of water, and a solution of the sodium salt of CBDCA (0.752 g, 4 mmol) in 10 cm^3 of water was added. The clear solution was left stirring at room temperature for 24 h. The off-white precipitate was collected on filter paper and washed with cold water, methanol, and ether. The product, *trans-R,R*-DACH-CBDCA-platinum(II) was recrystallized from water (Yield: 90%). To a stirred suspension of (1.578 g, 3.5 mmol) of *trans-R,R*-DACH-CBDCA-platinum(II) in 100 cm^3 of water, 5 cm^3 of 30% aqueous hydrogen peroxide was added dropwise. After 24 h, the clear colorless solution was filtered, the volume of the filtrate was reduced under vacuum to 25 cm^3, and acetone (250 cm^3) was added. An off-white precipitate was obtained which was collected on filter paper. The crude product was recrystallized from water/acetone to give a white solid, *trans-R,R*-DACH-*trans*-dihydroxo(CBDCA)platinum(IV) (Yield: 95%). Hydrochloric acid (300 cm^3 of .02 N) was added to a suspension of *trans-R,R*-DACH-*trans*-dihydroxo(CBDCA) platinum(IV) (1.48 g, 3.07 mmol) in 20 cm^3 of water. The colorless solution was left stirring for 24 h and filtered. The filtrate was evaporated completely to dryness under reduced pressure. The final light yellow product was redissolved in 30 cm^3 of methanol and filtered, and ether (150 cm^3) was added to the filtrate. A light yellow crystalline solid was obtained, which was separated by filtration and dried in vacuo (Yield: 80%).

All other complexes 23-33 of the type DACH-*trans*-dichloro(dicarboxylato)-platinum(IV) listed in Table 1 were prepared in a similar manner by using sodium salt of tartronic, ketomalonic, or methylmalonic acid.

RESULTS AND DISCUSSION

Subjecting DACH-dihaloplatinum(II) complexes to a strong oxidizing agent such as hydrogen peroxide converts the complex into DACH-*trans*-dihydroxo-*cis*-dihaloplatinum(IV) complex, reaction (iv), scheme I. Further reaction of DACH-*trans*-dihydroxo-*cis*-dihaloplatinum(IV) with two equivalents of hydrochloric or hydrobromic acid yielded DACH-tetrahalo-platinum(IV) complexes as shown in reaction (v), scheme I. Following the treatment of the DACH-*trans*-dihydroxo-*cis*-dihaloplatinum(IV) with an excess of acetic anhydride or trifluoroacetic anhydride in chloroform solution [reaction (vi), scheme I], the DACH-*trans*-diacetato-*cis*-dihaloplatinum(IV) or DACH-*trans*-bis(trifluoroacetato)*cis*-dihaloplatinum(IV) complexes were obtained. Reaction of the DACH-dicarboxylatoplatinum(II) complexes with hydrogen peroxide converted the complexes into DACH-*trans*-dihydroxo(dicarboxylato)platinum(IV) [reaction (iv), scheme I]. Further treatment of DACH-*trans*-dihydroxo(dicarboxylato) platinum(IV) with hydrochloric acid

i) $K_2Pt^{II}Cl_4 + 8KI + DACH \rightarrow DACH\text{-}Pt^{II}I_2 + 6KI + 4KCl$

ii) $DACH\text{-}Pt^{II}I_2 + Ag_2SO_4 \rightarrow DACH\text{-}Pt^{II}SO_4 \cdot H_2O + 2AgI$

iii) $DACH\text{-}Pt^{II}SO_4 \cdot H_2O + 2NaY \rightarrow DACH\text{-}Pt^{II}Y + Na_2SO_4$

iv) $DACH\text{-}Pt^{II}Y + H_2O_2 \rightarrow DACH\text{-}Pt^{IV}(OH)_2Y$

v) $DACH\text{-}Pt^{IV}(OH)_2Y + 2HX \rightarrow DACH\text{-}Pt^{IV}X_2Y$

vi) $DACH\text{-}Pt^{IV}(OH)_2Y + Anhydride \rightarrow DACH\text{-}Pt^{IV}(Acetato)_2Y$

Scheme I

[reaction (v), scheme I], gave DACH-*trans*-dichloro(dicarboxylato)platinum(IV), complexes no. 22 to 33.

All platinum(IV) complexes were characterized by elemental analysis (Table 1). The complexes were further characterized by IR and NMR spectroscopic techniques. The IR spectra were recorded for each of the platinum(IV) complexes, and the characteristic vibrational frequencies are listed in Table 2. In general, for all platinum(IV) complexes, the N-H stretching frequencies occured between 3227 and 3070 cm^{-1}. The carbonyl vibration frequency of the bound trifluoroacetate ligand in complexes 13–15, and 19–21 appeared in the region of 1690 cm^{-1}, about a 90-cm^{-1} shift compared with that of other platinum(IV) complexes with acetate ligands (complexes 10–12 and 16–18). This shift to higher frequencies suggests that the carbonyl attached to the trifluoroacetate group was electron deficient, owing to the presence of fluorine. All these values are consistent with data reported for other carboxylate ligands bound to platinum.[27,28] For all DACH-*trans*-dichloro-(dicarboxylato)platinum(IV) complexes, the IR spectra displayed typical patterns expected for carboxylate ligands coordinated to the platinum atom in unidentate fashion. The carbonyl vibration bands appeared from 1675 to 1630 cm^{-1}, consistent with published data.[27,28] Carbonyl oxygen single-bond vibrations [ν_s (COO)] appeared in the range 1406 to 1345 cm^{-1} (complexes 10–33). In the case of DACH-*trans*-dicarboxylato (complexes 10–21), a strong peak was seen in the range 1290 to 1152 cm^{-1}. For DACH-platinum(IV) complexes (1–3, 7–12, and 22–33) a strong band in the range of 325 to 360 cm^{-1} was obtained and assigned to the Pt-Cl stretching mode. The IR differences between the *trans-R,R-*, *trans-S,S-* and the *cis* form of the complexes are apparent in the locations of the Pt-Cl stretching modes (10 cm^{-1} for the *cis* complexes). This difference is due to the presence of the cyclohexane ring on one side of the nitrogen-metal-nitrogen plane which creates nonequivalent axial Cl groups.

The $^{195}Pt\{^1H\}$ NMR spectroscopic data for the complexes in an aqueous, acetone, or methanol solution are given in Table 2. When hydrochloric acid was added to the DACH-*trans*-dihydroxo-*cis*-dichloroplatinum(IV) complexes, the ^{195}Pt chemical shifts changed from + 1000 ppm to about − 450 ppm (1–3). These values are consistent with those of the related Pt^{IV} having two nitrogen and four chlorine atoms as donor ligands.[24] For tetrabromo complexes (4–6), the ^{195}Pt chemical shift changed to about − 1530 ppm. Substitution of *trans*-dihydroxo groups for *trans*-bromo ligands (complexes 7–9), caused the chemical shifts to change to about −980 ppm. The ^{195}Pt chemical shift for DACH-*trans*-dicarboxylato-*cis*-dichloroplatinum(IV) complexes are about +1030 for complexes 10–12 and about

Table 2 Infrared and nuclear magnetic resonance spectroscopic data of isomeric DACH-platinum(IV) complexes

Complex	IR[a], cm^{-1}				^{195}Pt[b]
No.	ν(N-H)	ν_{as}(C = O)	ν_s(C - O)	ν(M - Cl)	δ,ppm
1	3180,3100	—	—	330m[c]	−445[d]
2	3180,3100	—	—	330m[c]	−445[d]
3	3180,3100	—	—	340m[c]	−460[d]
4	3180,3079	—	—	—	−1525[e]
5	3180,3080	—	—	—	−1525[e]
6	3159,3094	—	—	—	−1540[e]
7	3200br[c]	—	—	335w[c]	−976[e]
8	3215br[c]	—	—	335w[c]	−976[e]
9	3227br[c]	—	—	345w[c]	−990[e]
10	3160,3080	1600	1358,1285	325w[c]	+1040[f]
11	3160,3080	1600	1358,1285	325w[c]	+1040[f]
12	3160,3080	1609	1356,1280	330w[c]	+1025[f]
13	3170,3080	1690	1372,1157		−330[f]
14	3170,3080	1690	1372,1157		−330[f]
15	3170,3080	1700	1370,1152		−340[f]
16	3170–3108	1600	1359,1285		+616[f]
17	3168–3117	1600	1359,1290		+616[f]
18	3174–3107	1610	1357,1286		+600[f]
19	3180,3100	1680	1406,1190		−762[f]
20	3180,3103	1680	1406,1190		−762[f]
21	3180,3100	1690	1406,1190		−745[f]
22	3200br[c]	1630	1345	340m[c]	+564[d]
23	3200br[c]	1630	1345	340m[c]	+564[d]
24	3200br[c]	1640	1345	350m[c]	+550[d]
25	3190,3074	1675	1350	350m[c]	+510[e]
26	3200,3100	1675	1350	350m[c]	+510[e]
27	3200,3100	1685	1349	360m[c]	+495[e]
28	3190,3074	1675	1350	335m[c]	+540[d]
29	3200,3100	1675	1350	335m[c]	+540[d]
30	3200,3100	1685	1350	345m[c]	+525[d]
31	3170,3070	1660	1360	335m[c]	+510[e]
32	3200,3100	1660	1360	335m[c]	+510[e]
33	3200,3100	1670	1360	345m[c]	+495[e]

[a]Infrared spectra were recorded as KBr pellets, and band positions are given in cm^{-1}.
[b]^{195}Pt chemical shifts are relative to Na_2PtCl_6 at 0.0 ppm. For each set of isomers (e.g. isomers 1–3, isomers 4–6, etc.), the concentration of each isomer and the solvent used was the same as for each other isomer in the set, since ^{195}Pt chemical shifts are concentration and solvent dependent.
[c]Abbrev.: m = medium, br = broad, w = weak.
[d]Measured in H_2O.
[e]Measured in methanol.
[f]Measured in acetone.

+ 610 for complexes 16–18, close to those of the related platinum(IV) complexes (iproplatin) having two nitrogen, two oxygen, and two chlorine atoms as donor ligands.[24] When two equivalents of HCl were added to *trans*-dihydroxo(dicarboxylato)platinum(IV), the ^{195}Pt chemical shifts changed from + 1700 ppm to between + 564 and + 495 ppm. For all platinum(IV) complexes the chemical shifts of the *trans-R,R*- and *trans-S,S*-DACH complexes were identical, but 15 ppm lower for the cis form. This occurs because the disposition of the cyclohexane rings in the enantiomeric pair (*trans-R,R* or *trans-S,S*) is different than that of the *cis*-DACH ring. The $^{195}Pt\{^1H\}$ NMR resonances for DACH-*trans*-

dichloro(dicarboxylato)platinum(IV) lie at lower frequency (high field) compared with those of DACH-*trans*-dihydroxo(dicarboxylato)platinum(IV) complexes.

In summary, we have synthesized and characterized a series of new isomeric DACH-platinum(IV) complexes as potential antitumor agents.

Acknowledgements

This work was supported by grant CA-41581 from National Cancer Institute to ARK.

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