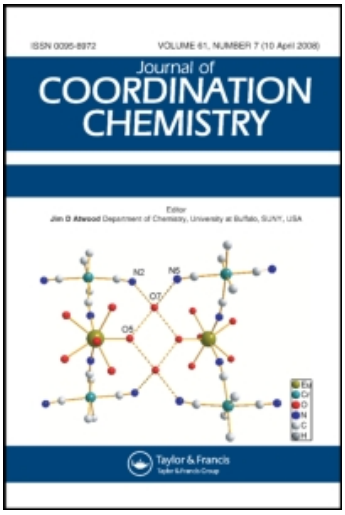

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Synthesis and Characterization of New *CIS*-1,4-Diaminocyclohexane and Piperidine Platinum(II) Complexes Containing Disubstituted Sulfide Groups

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SYNTHESIS AND CHARACTERIZATION OF NEW *CIS*-1,4-DIAMINOCYCLOHEXANE AND PIPERIDINE PLATINUM(II) COMPLEXES CONTAINING DISUBSTITUTED SULFIDE GROUPS

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A series of cationic platinum(II) complexes of the type [Pt(*cis*-1,4-DACH)(R′R″S)Cl]NO_3 and [$Pt(PIP)_2$(R′R″S)Cl]NO_3 (where *cis*-1,4-DACH = *cis*-1,4-diaminocyclohexane; PIP = piperidine; and R′R″S = dimethylsulfide, diethylsulfide, dipropylsulfide, diisopropylsulfide, dibutylsulfide, diphenylsulfide, dibenzylsulfide, methylphenylsulfide, or methyl-*p*-tolylsulfide) have been synthesized and characterized by elemental analysis and infrared, ^1H, and ^{195}Pt nuclear magnetic resonance spectroscopy.

Keywords: Platinum complexes; *cis*-1,4-diaminocyclohexane; piperidine; disubstituted sulfides

INTRODUCTION

The discovery of anticancer activity by cisplatin[1] and its use as a drug in the treatment of several human tumors have given considerable attention to platinum metal complexes. However, over time it became clear that cisplatin has several undesirable side effects, such as nephrotoxicity, ototoxicity, neurotoxicity, nausea, vomiting, and myelosuppression,[2–4] a narrow spectrum of clinical usefulness, and drug resistance in tumor cells. These limitations of

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cisplatin stimulated the synthesis and evaluation of new platinum agents with reduced toxicity, no cross-resistance, and better antitumor activity.[5,6]

Most of the cisplatin analogs tested so far have been neutral platinum(II) and (IV) compounds of the type *cis*-(PtA_2X_2) and *cis*-(PtA_2X_4), respectively, where A is an amine ligand and X is an anionic leaving group.[7–10] The clinical effectiveness of cisplatin has been improved by displacing the labile chloro ligands with other leaving groups of intermediate lability to alter its pharmacokinetics and also by extending the stable amine ligands to a series of cyclic or acyclic amines. Carboplatin (diammine-1,1-cyclobutanedicarboxylatoplatinum(II),[11] one of a number of cisplatin analogs developed in this way, is now used clinically. Other compounds, such as oxaliplatin (*trans-l*-1,2-diaminocyclohexaneoxalatoplatinum(II)) and L-NDDP [liposome-entrapped bis(neodecanoato)(*trans*-1R,2R-cyclohexane)platinum(II)] which have 1,2-diaminocyclohexane (DACH) as a carrier ligand and chloride or carboxylate as a leaving group, are now in clinical trials.[12]

In an interesting development, Hollis *et al.*[13] have reported a series of interesting cationic platinum(II) complexes whose antitumor activity violates some of the rules of classical structure–activity relationships. However, cationic diamineplatinum(II) complexes with substituted sulfoxide have been known for the past two decades[14,15] and reportedly have antitumor activity against certain tumor models.[16,17] We have been developing platinum complexes with diamines such as DACH as a carrier ligand and chloride and/or carboxylate as a leaving group.[18] In light of a report that some thioether groups can reduce cisplatin-induced nephrotoxicity when administered simultaneously with cisplatin,[19] we report here the synthesis and characterization of cationic platinum(II) complexes of the type [Pt(*cis*-1,4-DACH)(R′R″S)Cl]NO_3 and [$Pt(PIP)_2$(R′R″S)Cl]NO_3, where R′R″S is a dialkyl or diaryl sulfide.

EXPERIMENTAL

Chemicals

K_2PtCl_4 was purchased from Johnson Matthey (Seabrook, NH). *cis*-1,4-DACH was purchased from CTC Organics (Atlanta, GA). Piperidine (PIP), dimethylsulfide, diethylsulfide, dipropylsulfide, diisopropylsulfide, dibutyl sulfide, diphenylsulfide, dibenzylsulfide, methylphenylsulfide and methyl-*p*-tolylsulfide were purchased from Aldrich Chemical Co. (Milwaukee, WI).

Silver nitrate was obtained from Fisher Scientific Co. (Houston, TX). All chemicals obtained from commercial sources were used as supplied.

Physical Measurements

Elemental analyses of the complexes were performed by Robertson Laboratory Inc. (Madison NJ). Infrared (IR) spectra in the range of 600–4000 cm^{-1} and far-IR spectra in the range of 150–600 cm^{-1} were recorded in KBr pellets and polyethylene pellets, respectively on a Perkin Elmer 2000 spectrophotometer. ^1H NMR spectra in MeOH-d_4 and ^{195}Pt NMR spectra in methanol were recorded using a Bruker 200/AF spectrometer. ^{195}Pt spectra were recorded with a 10 mm tunable probe at 43.055 MHz, with the shift measured relative to an external standard of 2.2 M Na_2PtCl_6 in D_2O at 0.00 ppm.

Preparation of {Pt[*cis*-1,4-DACH][$(CH_3)_2S$]Cl}NO_3 (Complex 1)

K_2PtCl_4 (6.25 g, 15 mmol) was dissolved in 100 mL of deionized water and filtered. DMSO (2.34 g, 30 mmol) in 10 mL of water was then added. The reaction mixture was kept at room temperature for 2 days. The resulting pale yellow needles of *cis*-[$Pt(DMSO)_2Cl_2$] were filtered, washed with cold water, and dried *in vacuo* (yield, 75%). *cis*-[$Pt(DMSO)_2Cl_2$] (6.16 g, 14.6 mmol) was dissolved in 250 mL of warm water. To this solution, a suspension of Ag_2CBDCA (5.07 g, 14.16 mmol) in 100 mL of water was added. The reaction mixture was stirred continuously for 24 h at room temperature in the dark. The solution was then filtered. The yellow filtrate was evaporated to 50 mL under reduced pressure at 35°C and kept in ice. White crystalline [$Pt(DMSO)_2$(CBDCA)] was isolated, washed with cold water, and dried *in vacuo* (yield, 70%). To a hot solution of [$Pt(DMSO)_2$(CBDCA)] (4.94 g, 10 mmol) in 300 mL of water, a solution of *cis*-1,4-DACH (1.14 g, 10 mmol) in 10 mL of water was added. The reaction mixture was stirred continuously at 90°C for 1.5 h. The solution was filtered while hot, cooled to room temperature, evaporated to a minimum volume under reduced pressure, and kept in ice. An off-white compound precipitated, which was then filtered and recrystallized from water. White crystalline [Pt(*cis*-1,4-DACH)(CBDCA)] was obtained (yield, 50%). [Pt(*cis*-1,4-DACH)(CBDCA)] (1.00 g, 2.13 mmol) was then dissolved in 100 mL of concentrated HCl and stirred continuously for 3 days at room temperature. A yellow solution was obtained, which was then slowly evaporated at room temperature. After 3–4 days, a yellow crystalline compound [Pt(*cis*-1,4-DACH)Cl_2] was

separated. This was filtered, washed with water, and dried *in vacuo* (yield, 80%). To a slurry of [Pt(*cis*-1,4-DACH)Cl_2] (0.760 g, 2 mmol) in 100 mL of methanol, an equivalent amount of $AgNO_3$ (0.338 g, 2 mmol) dissolved in 100 mL of hot methanol was added. One equivalent of dimethylsulfide (0.15 mL, 2 mmol) in 20 mL of methanol was then added. The reaction mixture was stirred overnight in the dark. The AgCl precipitate was filtered off, and the filtrate was evaporated to dryness under reduced pressure. A yellow solid was obtained, which was purified from methanol and ether. Finally, a light yellow compound, {Pt[*cis*-1,4-DACH][$(CH_3)_2$S]Cl}NO_3 was obtained, which was dried *in vacuo* (yield, 70%).

Complexes 3, 5, 7, 9, 11, 13, 15, and 17 (Table I) were prepared in a similar manner.

Preparation of {Pt(PIP)$_2$][$(CH_3)_2$S]Cl}NO_3 (Complex 2)

K_2PtCl_4 (20.76 g, 50 mmol) was dissolved in 250 mL of deionized water and filtered. KI (83.0 g, 0.5 mol) in 100 mL of water was added, and the reaction mixture was stirred for 10 min. PIP (8.5 g, 100 mmol) was added drop-wise while stirring to get a yellow precipitate, [Pt$(PIP)_2I_2$]. The stirring was

TABLE I Elemental analyses of platinum(II) complexes

Complex no.	*Complex name*	*Observed (calculated)*			*% Yield*
		% C	*% H*	*% N*	
1.	[Pt(*cis*-1,4-DACH)(dimethylsulfide)Cl]NO_3	20.48 (20.47)	4.39 (4.26)	8.80 (8.95)	70
2.	[Pt$(PIP)_2$(dimethylsulfide)Cl]NO_3	27.50 (27.44)	5.53 (5.33)	8.24 (8.00)	45
3.	[Pt(*cis*-1,4-DACH)(diethylsulfide)Cl]NO_3	23.95 (24.14)	4.85 (4.82)	8.24 (8.45)	85
4.	[Pt$(PIP)_2$(diethylsulfide)Cl]NO_3	30.28 (30.37)	5.72 (5.78)	7.63 (7.59)	45
5.	[Pt(*cis*-1,4-DACH)(dipropylsulfide)Cl]NO_3	27.17 (27.43)	5.35 (5.33)	7.79 (8.00)	58
6.	[Pt$(PIP)_2$(dipropylsulfide)Cl]NO_3	33.28 (33.06)	6.15 (6.19)	7.54 (7.23)	48
7.	[Pt(*cis*-1,4-DACH)(diisopropylsulfide)Cl]NO_3	27.28 (27.43)	5.30 (5.33)	7.86 (8.00)	45
8.	[Pt$(PIP)_2$(diisopropylsulfide)Cl]NO_3	33.14 (33.06)	5.95 (6.19)	7.16 (7.23)	47
9.	[Pt(*cis*-1,4-DACH)(dibutylsulfide)Cl]NO_3	20.47 (20.48)	4.26 (4.39)	8.95 (8.80)	45
10.	[Pt$(PIP)_2$(dibutylsulfide)Cl]NO_3	30.25 (30.37)	5.70 (5.78)	6.76 (6.89)	48
11.	[Pt(*cis*-1,4-DACH)(diphenylsulfide)Cl]NO_3	36.57 (36.42)	4.32 (4.04)	6.80 (7.08)	85
12.	[Pt$(PIP)_2$(diphenylsulfide)Cl]NO_3	40.43 (40.68)	5.16 (4.93)	6.22 (6.47)	35
13.	[Pt(*cis*-1,4-DACH)(dibenzylsulfide)Cl]NO_3	38.47 (38.64)	4.63 (4.50)	6.47 (6.76)	72
14.	[Pt$(PIP)_2$(dibenzylsulfide)Cl]NO_3	42.69 (42.54)	5.56 (5.31)	5.93 (6.20)	34
15.	[Pt(*cis*-1,4-DACH)(methylphenylsulfide)Cl]NO_3	29.35 (29.38)	4.22 (4.14)	8.14 (7.91)	40
16.	[Pt$(PIP)_2$(methylphenylsulfide)Cl]NO_3	34.92 (34.76)	5.28 (5.11)	7.21 (7.15)	58
17.	[Pt(*cis*-1,4-DACH)(methyl-*p*-tolylsulfide)Cl]NO_3	20.47 (20.48)	4.26 (4.39)	8.95 (8.80)	75

cis-1,4-DACH = *cis*-1,4-diaminocyclohexane; PIP = piperidine.

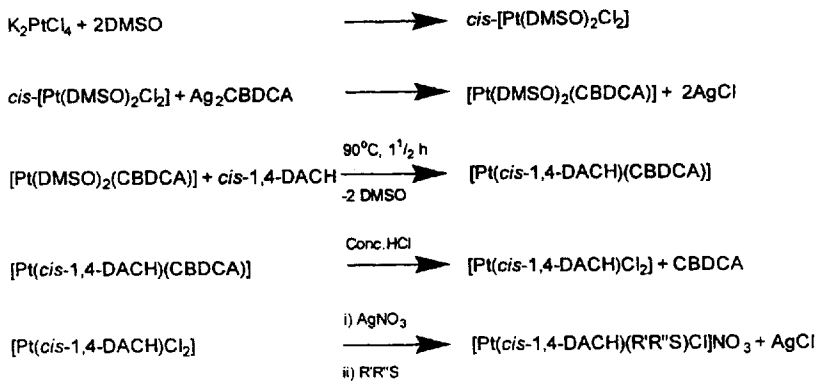
continued for 30 min, and the precipitate was collected by filtration. This compound was dissolved in dimethylformamide and filtered. To the filtrate, excess cold water was added to get a bright yellow precipitate, $[Pt(PIP)_2I_2]$, which was washed with water, ethanol, and acetone and dried *in vacuo* (yield, 95%). $[Pt(PIP)_2I_2]$ (12.38 g, 20 mmol) was suspended in an aqueous solution of silver nitrate (6.72 g, 39.8 mmol) in 250 mL of water. The reaction mixture was stirred for 24 h at room temperature in the dark. The AgI precipitate was filtered off, and a solution of NaCl was added drop-wise to the filtrate with constant stirring until a yellow precipitate of $[Pt(PIP)_2Cl_2]$ formed. The precipitate was filtered and recrystallized from dimethylformamide. The yellow crystals obtained were washed with water and acetone and dried *in vacuo* (yield, 75%). An equivalent amount of $AgNO_3$ (0.338 g, 2 mmol) dissolved in 100 mL of hot methanol was added to a slurry of $[Pt(PIP)_2Cl_2]$ (0.872 g, 2 mmol) in 100 mL of methanol. To this one equivalent of dimethylsulfide (0.15 mL, 2 mmol) in 20 mL of methanol was added. The reaction mixture was then stirred overnight in the dark. The AgCl precipitate was filtered off and the filtrate was evaporated to dryness under reduced pressure. A yellow solid was obtained, which was purified from methanol and ether. Finally a light yellow compound, $\{Pt(PIP)_2[(CH_3)_2S]Cl\}NO_3$, was obtained, which was then dried *in vacuo* (yield, 70%).

Complexes 4, 6, 8, 10, 12, 14, and 16 (Table I) were prepared in a similar manner.

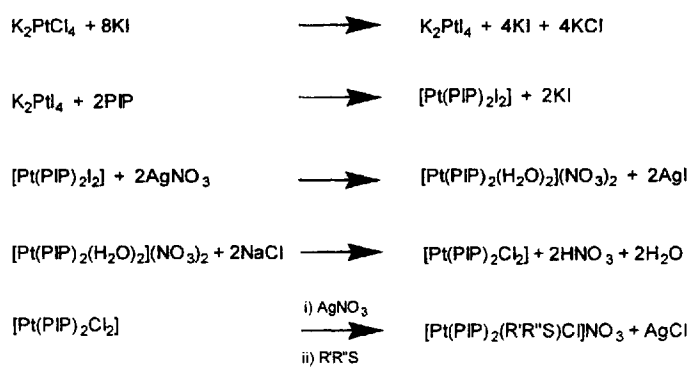
RESULTS AND DISCUSSION

Synthesis of Platinum Complexes

The steps involved in the synthesis of platinum(II)sulfide complexes are shown in Schemes 1 and 2. $[Pt(DMSO)_2Cl_2]$[20] and $[Pt(DMSO)_2(CBDCA)]$[21] were prepared according to previously described procedures (Scheme 1). [Pt(*cis*-1,4-DACH)Cl_2] was also prepared as previously reported.[10] $[Pt(PIP)_2Cl_2]$ was prepared according to Dhara's method (Scheme 2).[22] Both the dichloride [Pt(*cis*-1,4-DACH)Cl_2] and $[Pt(PIP)_2Cl_2]$ were reacted with one equivalent of $AgNO_3$ and subsequently with thioethers to form compounds of the type [Pt(*cis*-1,4-DACH)(R′R″S)Cl]NO_3 and $[Pt(PIP)_2(R'R''S)Cl]NO_3$, respectively, in solution, while the insoluble AgCl was separated by filtration. Syntheses of [Pt(*cis*-1,4-DACH)(R′R″S)Cl]NO_3 and $[Pt(PIP)_2(R'R''S)Cl]NO_3$ followed well established procedures as reported earlier.[13,17,23–25]



SCHEME 1



SCHEME 2

Characterization of Platinum Complexes

The complexes were characterized by elemental analysis and by IR, ^{1}H NMR, and ^{195}Pt NMR spectroscopy. The composition of each complex, as determined by elemental analysis, showed good agreement between the theoretical and actual values. The analytical results are summarized in Table I.

The results of characterization by IR are shown in Table II. The IR spectra of the complexes, in general, showed a broad absorption between 3235 and 3060 cm^{-1} which was assigned to the νN–H stretching vibrations of coordinated *cis*-1,4-DACH and PIP. The intense band observed in the region 1271–1393 cm^{-1} was due to ν(S–C) stretching vibrations in all complexes. The νPt–S stretching vibrations were observed around 350–400 cm^{-1} which are close to the values reported for such compounds.[26] The νPt–Cl stretching vibrations were seen around 300 cm^{-1}.

TABLE II IR and ^{195}Pt NMR data for platinum(II) complexes

Complex no.	*IR*, cm^{-1}		^{195}*Pt NMR** ppm
	$\nu(N-H)$	$\nu(S-C)$	
1	3200	1351	−3063
2	3163	1297	−3169
3	3210	1393	−3082
4	3150	1285	−3152
5	3210	1335	−3069
6	3150	1282	−3183
7	3060	1380	−3045
8	3170	1271	−3154
9	3200	1327	−3056
10	3158	1285	−3182
11	3207	1327	−3002
12	3150	1298	−3181
13	3202	1326	−3088
14	3155	1302	−3183
15	3206	1330	−3170
16	3155	1297	−3182
17	3235	1328	−3023

*^{195}Pt NMR spectra were recorded in methanol with K_2PtCl_4 in D_2O at −1620 ppm as an external reference.

^{1}H NMR spectra given in Table III were most informative with respect to the structures of the complexes. The peaks corresponding to *cis*-1,4-DACH protons were observed between 1.6 and 2.8 ppm in complexes 1, 3, 5, 7, 9, 11, 13, 15, and 17. The peaks corresponding to PIP ring protons resonate between 3.11 to 3.21 and 1.67 to 1.72 ppm in complexes 2, 4, 6, 8, 10, 12, 14, and 16.

In complexes 1 and 2, the $-S-CH_3$ protons of dimethylsulfide shifted downfield by about 0.38 ppm upon complexation and were observed as singlets at 2.45 ppm. In complex 3, the peaks due to $-S-CH_2-$ protons showed two multiplets centered at 2.80 and 3.06 ppm, due to the inequivalence of the protons attached to the sulfur atom. The $-S-CH_2-$ protons shifted downfield by about 0.28 ppm upon complexation. Methyl protons of diethylsulfide produced triplet centered at 1.44 ppm which shifted downfield by about 0.22 ppm upon complexation. In complex 4, the $-S-CH_2-$ protons are observed at 2.78 and 3.05 ppm, whereas the methyl protons are observed 1.46 ppm, respectively.

In complex 5, the $-S-CH_2-CH_2-$ protons gave two unresolved broad peaks at 3.03 and 2.70 ppm, which were shifted downfield by about 0.57 and 1.12 ppm, respectively upon complexation. In complex 6, these peaks appeared as two multiplets centered at 3.04 and 2.63 ppm, which shifted downfield by about 0.58 and 1.05 ppm, respectively, as compared to the free ligand. The methyl protons of dipropylsulfide gave a triplet centered at 1.09 and 1.10 ppm in complexes 5 and 6, respectively.

TABLE III ^{1}H NMR data for platinum(II) complexes*

Ligand/ complex no.	*S–CH_3*	*S–CH_2–*	*–CH_2–*	*–CH_2–*	*–CH_3*	*S–$\overset{|}{\underset{|}{C}}$–H*	*C_6H_5*	*DACH*	*PIP*
Dimethylsulfide	2.07 s	—	—	—	—	—	—	—	—
1	2.45 s	—	—	—	—	—	—	1.75 s	—
2	2.45 s	—	—	—	—	—	—	—	1.67 m 3.19 b
Diethylsulfide	—	2.52 q	—	—	1.22 t	—	—	—	—
3	—	2.80 m 3.06 m	—	—	1.44 t	—	—	1.77 s	—
4	—	2.78 m 3.05 m	—	—	—	—	—	—	1.71 m 3.13 b
Dipropylsulfide	—	2.46 t	1.58 m	—	0.97 t	—	—	—	—
5	—	3.03 b	2.70 b	—	1.09 t	—	—	1.71 s	—
6	—	3.04 m	2.63 m	—	1.10 t	—	—	—	1.69 m 3.11 b
Diisopropylsulfide	—	—	—	—	1.21 d	2.95 m	—	—	—
7	—	—	—	—	1.50 d	3.50 m	—	1.78 s	—
8	—	—	—	—	1.58 d	3.50 m	—	—	1.71 m 3.21 b
Dibutylsulfide	—	2.49 t	1.54 m	1.42 m	0.91 t	—	—	—	—
9	—	3.04 m	2.70 m	1.51 m	0.98 t	—	—	1.76 s	—
10	—	3.04 m	2.58 m	1.48 m	0.96 t	—	—	—	1.70 m 3.14 b
Diphenylsulfide	—	—	—	—	—	—	7.17 m 7.25 m	—	—
11	—	—	—	—	—	—	7.49 m 7.82 m	1.79 s	
12	—	—	—	—	—	—	7.51 m 7.80 m	—	1.72 m 3.13 b
Dibenzylsulfide	—	3.59 s	—	—	—	—	7.26 m	—	—
13	—	4.00 d 4.47 d	—	—	—	—	7.38 m 7.56 m	1.62 s	—
14	—	4.02 d 4.56 d	—	—	—	—	7.39 m 7.73 m	—	1.70 m 3.10 b
Methylphenylsulfide	2.42 s	—	—	—	—	—	7.08 m 7.20 m	—	—
15	2.83 s	—	—	—	—	—	7.48 m 7.98 m	1.78 s	—
16	2.80 s	—	—	—	—	—	7.50 m 8.00 m C_6H_4	—	1.69 m 3.21 b
Methyl-*p*-tolylsulfide	2.25 s	—	—	—	2.38 s	—	7.02 d 7.14 d	—	—
17	2.79 s	—	—	—	2.37 s	—	7.29 d 7.84 d	1.77 s	—

*Chemical shift in ppm. ^{1}H NMR spectra were recorded in deuterated methanol. s = singlet, d = doublet, t = triplet, m = multiplet, b = broad.

In complexes 7 and 8, a multiplet at 3.50 ppm was due to –S–$\overset{|}{\underset{|}{C}}$–H protons of isopropylsulfide which was shifted downfield by about 0.55 ppm as compared to the free ligand. A doublet at 1.50 and 1.58 ppm in complexes 7 and 8, respectively was assigned to the methyl protons, which were shifted

downfield by about 0.29 and 0.37 ppm, respectively as compared to the free ligand.

In complexes 9 and 10, the $S-CH_2$ protons were shifted downfield by about 0.65 ppm upon complexation and were observed at 3.04 ppm. In complex 9, the ethylene protons appeared as two multiplets centered at 2.70 and 1.51 ppm, whereas the methyl protons appeared as a triplet centered at 0.98 ppm. In complex 10, these protons appeared at 2.58, 1.48, and 0.96 ppm, respectively.

In complex 11, the phenyl protons shifted downfield by about 0.57 and 0.32 ppm upon complexation as compared to the free ligand and were observed as two multiplets centered at 7.82 and 7.49 ppm, respectively. In complex 12, these peaks were shifted downfield by about 0.34 and 0.55 ppm upon complexation and were observed as two multiplets centered at 7.51 and 7.80 ppm, respectively.

In complexes 13 and 14, the CH_2- protons of dibenzylsulfide were shifted downfield and were observed as two doublets centered at 4.00 and 4.47 ppm and at 4.02 and 4.56 ppm, respectively, due to the inequivalence of these protons. The benzene ring protons resonated at 7.38 and 7.56 ppm in complex 13, and 7.39 and 7.73 ppm in complex 14, respectively.

In complex 15, a singlet observed at 2.83 ppm was due to the $S-CH_3$ protons of methylphenylsulfide, which was shifted downfield by about 0.41 ppm, upon complexation. In complex 16, however, this peak was shifted downfield by about 0.38 ppm and was observed at 2.80 ppm. In complex 15 the benzene ring protons were also shifted downfield and were observed as two multiplets centered at 7.48 and 7.98 ppm. In complex 16, these protons were observed as two multiplets centered at 7.50 and 8.00 ppm, respectively.

In complex 17, the $S-CH_3$ protons of methyl-*p*-tolylsulfide gave a singlet at 2.79 ppm, which shifted downfield by about 0.41 ppm when compared to the free ligand. The $-CH_3$ protons appear at 2.37 ppm and the benzene ring protons resonated at 7.29 and 7.84 ppm, respectively.

The ^{195}Pt NMR spectra shown in Table II further confirmed the structures of these platinum complexes. The singlet observed in the range of -3002 to -3183 ppm indicate the coordination of amino nitrogens of *cis*-1,4-DACH and PIP, to the two adjacent corners of square-planar platinum(II), while the other two positions were bound to the chloride atom and the sulfur atom of the thioether group. Such chemical shift values are characteristic of the square-planar platinum(II) complexes, where platinum(II) is bound by two nitrogen atoms, one sulfur atom, and one chloride.[27] Figures 1 and 2 show the general structures of the complexes.

In summary, we have synthesized and characterized a series of new cisplatin analogs containing dialkyl- or diaryl-substituted sulfide as a leaving group.

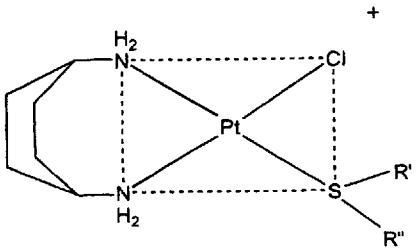


FIGURE 1 R′,R″ = methyl, ethyl, propyl, isopropyl, butyl, phenyl, and benzyl groups in complexes 1, 3, 5, 7, 9, 11, and 13, respectively. R′ = methyl and R″ = phenyl and *p*-tolyl groups in complexes 15 and 17, respectively.

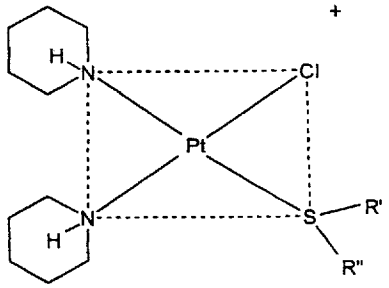


FIGURE 2 R′,R″ = methyl, ethyl, propyl, isopropyl, butyl, phenyl, and benzyl groups in complexes 2, 4, 6, 8, 10, 12, and 14, respectively. R′ = methyl and R″ = phenyl group in complex 16.

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