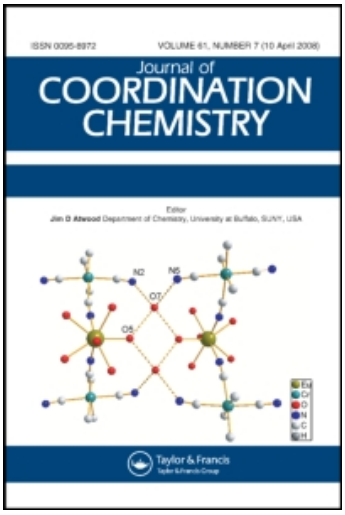

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Synthesis and Characterization of New 1-Methyl-4-(Methylamino)Piperidine and Decahydroquinoline Platinum(II) Complexes Containing Disubstituted Sulfide as a Leaving Group

Uday Mukhopadhyay[a]; Abdul R. Khokhar[a]
[a] Department of Experimental Therapeutics, M. D. Anderson Cancer Center, The University of Texas, Houston, TX, USA

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SYNTHESIS AND CHARACTERIZATION OF NEW 1-METHYL-4-(METHYLAMINO)PIPERIDINE AND DECAHYDROQUINOLINE PLATINUM(II) COMPLEXES CONTAINING DISUBSTITUTED SULFIDE AS A LEAVING GROUP

UDAY MUKHOPADHYAY and ABDUL R. KHOKHAR*

Department of Experimental Therapeutics, Box 353, The University of Texas, M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA

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A series of cationic platinum(II) complexes of the type [Pt(mmap)R′R″S)Cl](NO_3) and [Pt(dhq)$_2$(R′R″S)Cl]-(NO_3) (where mmap = 1-methyl-4-(methylamino)piperidine; dhq = decahydroquinoline; and R′R″S = dimethylsulfide, diethylsulfide, diisopropylsulfide, diphenylsulfide, dibenzylsulfide, methylphenylsulfide or methyl-*p*-tolylsulfide) has been synthesized and characterized by elemental analysis, infrared, ^{1}H and ^{195}Pt nuclear magnetic resonance spectroscopic techniques.

Keywords: 1-Methyl-4-(methylamino)piperidine; Decahydroquinoline; Disubstituted sulfides; Platinum(II) complexes; Antitumor agents

INTRODUCTION

Cisplatin is one of the most effective drugs for the treatment of cancer [1–3]. It is the drug of choice for testicular, ovarian, bladder, and head and neck cancers and is being increasingly used to treat a variety of other malignancies [4–6]. However, cisplatin has several undesirable side effects such as nephrotoxicity, nausea, vomiting, myelosuppression, ototoxicity, and neurotoxicity [7–9] and is active against only a limited number of tumor types. Therefore, researchers around the world have been actively engaged in synthesizing and studying cisplatin and its analogs, hoping to discover better antitumor drugs; those that are less toxic and fairly soluble in water have better antitumor activity. In this light, efforts were directed at developing a second generation of platinum drugs by modifying the chemical structure of cisplatin and thereby altering its pharmacokinetics. The result was carboplatin [diammine-1,1-cyclobutanedicarboxylatoplatinum(II)], which is in clinical use today [10].

*Corresponding author. Tel.: +1-713-792-2387. Fax: +1-713-745-1176.
E-mail: akhokhar@mdanderson.org

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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 [2,11–13]. The clinical effectiveness of cisplatin has been improved by replacing 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 is a cisplatin analog that was developed in this way [10c], now in clinical use. Other compounds, such as oxaliplatin [*trans*-1,2-diaminocyclohexaneoxalatoplatinum(II)] and L-NDDP [liposome-entrapped bis(neodecanoato)(*trans*-1R,2R-diaminecyclohexane)platinum(II)], which have 1,2-diaminocyclohexane (DACH) as a carrier ligand and chloride or carboxylate as a leaving group, are in clinical trial [14].

In an interesting development, Hollis *et al.* [15] 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 [16,17] and reportedly have antitumor activity in certain tumor models [18]. It has been reported 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(mmap)-(R′R″S)Cl]NO_3 and [$Pt(dhq)_2$(R′R″S)Cl]NO_3 (where mmap = 1-methyl-4-(methylamino)piperidine; dhq = decahydroquinoline; and R′R″S is a dialkyl or diaryl sulfide).

EXPERIMENTAL

Chemicals

K_2PtCl_4 was purchased from Johnson Matthey (Seabrook, NH). Dimethylsulfide, diethylsulfide, dipropylsulfide, diisopropylsulfide, dibutylsulfide, diphenylsulfide, dibenzylsulfide, methylphenylsulfide and methyl-*p*-tolylsulfide were purchased from Aldrich Chemical Co. (Milwaukee, WI). Silver nitrate was obtained from Fischer 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 Microlit 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 using KBr pellets and polyethylene pellets, respectively, on a Perkin Elmer 2000 spectrophotometer. ^1H NMR spectra in methanol-d_4 and ^{195}Pt NMR spectra in methanol-d_4 were recorded using a Bruker Advance 300 spectrometer. ^1H spectra were recorded with a 5-mm tunable probe at 300.13 MHz, ^{195}Pt spectra were recorded at 43.055 MHz, and the shifts were measured relative to an external standard of 2.2 M Na_2PtCl_6 in D_2O at 0.00 ppm.

Preparation of {Pt[mmap][$(CH_3)_2$S]Cl}NO_3 (Complex 1)

K_2PtCl_4 (10 g, 24.08 mmol) was dissolved in 100 mL of deionized water and filtered. KI (31 g, 186.7 mmol) in 30 mL of water was added to this solution, and the reaction mixture was stirred for 10 min. Then, mmap (3.09 g, 24.09 mmol) in 20 mL of methanol

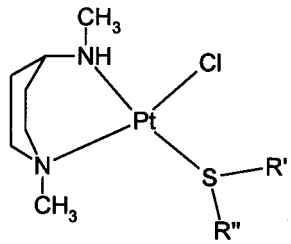

FIGURE 1 R′, R″ = methyl, ethyl, propyl, isopropyl, butyl, phenyl, and benzyl groups in Complexes 1, 3, 5, 7, 9, 11, and 13, respectively. R′ = methyl and R″ = phenyl and *p*-tolyl groups in Complexes 15 and 17, respectively.

was added dropwise to the reaction mixture while stirring. Immediately a brown solid was separated. The stirring was continued for further 2 h and the solid was separated by filtration. The crude brown solid was dissolved in 50 mL of DMF, and filtered. The filtrate was concentrated to 10 mL under reduced pressure and the product was precipitated with excess water. Pure [Pt(mmap)I_2] was filtered and washed with water, ethanol, and acetone, and then dried under vacuum (yield, 95%). Silver nitrate (2.87 g, 16.9 mmol) was dissolved in 100 mL of water, and [Pt(mmap)I_2] (5 g, 8.7 mmol) was added to it. The reaction mixture was stirred for 24 h in the dark. The AgI precipitate was filtered off, and the filtrate was concentrated to 20 mL under reduced pressure. Aqueous solution of NaCl was added until a yellow precipitate of Pt(mmap)Cl_2 was formed. This was filtered, washed with water and acetone, and dried under vacuum (yield, 75%). An equimolar amount of dimethyl sulfide (0.064 g, 1.02 mmol) was added to a slurry of Pt(mmap)Cl_2 (0.4 g, 1.02 mmol) in methanol (30 mL). To this $AgNO_3$ (0.163 g, 0.96 mmol) dissolved in hot methanol (60 mL) was added. The reaction mixture was stirred overnight in the dark. The insoluble AgCl precipitate was filtered off, and the filtrate was evaporated under reduced pressure until the volume of methanol was approximately 5 mL. To this solution, excess ether was added and the flask was then placed in the freezer overnight, and the resultant white crystalline product was collected by filtration and washed with ether. The compound was dried *in vacuo* (yield, 72%). Anal. Calcd. for $C_9H_{22}N_3O_3ClS$ Pt: C, 22.38; H, 4.56; N, 8.70. Found: C, 22.23; H, 4.38; N, 8.65. IR: νN–H, 3000 cm^{-1}; νC–S, 1400 cm^{-1}. ^{1}H NMR: 2.75 (s, 6H). ^{195}Pt NMR: −3380.

Other Complexes (numbers) 3, 5, 7, 9, 11, 13, 15, and 17 in Table I were prepared in a similar manner (Fig. 1).

Preparation of {Pt[dhq]$_2$[(CH$_3$)$_2$S]Cl}NO$_3$ (Complex 2)

K_2PtCl_4 (10 g, 24.08 mmol) was dissolved in 50 mL of deionized water and filtered. KI (31 g, 186.7 mmol) in 30 mL of water was added to this solution, and the reaction mixture was stirred for 10 min. Then, dhq (6.71 g, 48.19 mmol) in 20 mL of methanol was added dropwise to the reaction mixture while stirring. Immediately a brown solid was separated. The stirring was continued for 2 h and the crude solid was then filtered, dissolved in 50 mL of DMF, and filtered. The filtrate was concentrated to 10 mL under reduced pressure and final product was precipitated with excess water. Pure [Pt(dhq)$_2$$I_2$] was filtered and washed with water, ethanol, and acetone, and then dried *in vacuo* (yield, 97%). Silver nitrate (2.28 g, 13.42 mmol) was dissolved in 100 mL of water, and [Pt(dhq)$_2$$I_2$] (5 g, 6.87 mmol) was added to it. The reaction

TABLE I Elemental analysis of the complexes

Complex no.	*Complex name*	*Observed (calculated)*		
		C	*H*	*N*
1	[Pt(mmap)(dimethylsulfide)Cl]NO_3	22.23 (22.38)	4.38 (4.56)	8.65 (8.70)
2	[Pt$(dhq)_2$(dimethylsulfide)Cl]NO_3	37.75 (37.94)	6.30 (6.32)	6.83 (6.64)
3	[Pt(mmap)(diethylsulfide)Cl]NO_3	25.60 (25.86)	4.96 (5.09)	8.28 (8.22)
4	[Pt$(dhq)_2$(diethylsulfide)Cl]NO_3	39.75 (39.97)	6.39 (6.66)	6.62 (6.36)
5	[Pt(mmap)(dipropylsulfide)Cl]NO_3	28.82 (28.97)	5.63 (5.57)	7.51 (7.79)
6	[Pt$(dhq)_2$(dipropylsulfide)Cl]NO_3	41.59 (41.83)	6.69 (6.97)	6.01 (6.10)
7	[Pt(mmap)(diisopropylsulfide)Cl]NO_3	28.81 (28.97)	5.48 (5.57)	7.53 (7.79)
8	[Pt$(dhq)_2$(diisopropylsulfide)Cl]NO_3	41.62 (41.83)	6.83 (6.97)	6.25 (6.10)
9	[Pt(mmap)(dibutylsulfide)Cl]NO_3	31.63 (31.77)	5.73 (6.00)	7.60 (7.41)
10	[Pt$(dhq)_2$(dibutylsulfide)Cl]NO_3	43.28 (43.54)	7.53 (7.26)	5.67 (5.86)
11	[Pt(mmap)(diphenylsulfide)Cl]NO_3	37.71 (37.59)	4.37 (4.28)	6.73 (6.92)
12	[Pt$(dhq)_2$(diphenylsulfide)Cl]NO_3	47.32 (47.59)	5.95 (5.82)	5.69 (5.55)
13	[Pt(mmap)(dibenzylsulfide)Cl]NO_3	39.60 (39.72)	4.49 (4.73)	6.66 (6.62)
14	[Pt$(dhq)_2$(dibenzylsulfide)Cl]NO_3	48.44 (48.95)	5.78 (6.12)	5.70 (5.35)
15	[Pt(mmap)(methylphenylsulfide)Cl]NO_3	30.74 (30.85)	4.48 (4.40)	7.70 (7.71)
16	[Pt$(dhq)_2$(methylphenylsulfide)Cl]NO_3	43.32 (43.19)	6.31 (6.05)	5.92 (6.05)
17	[Pt(mmap)(methyl-*p*-tolylsulfide)Cl]NO_3	32.46 (32.23)	4.39 (4.65)	7.28 (7.52)
18	[Pt$(dhq)_2$(methyl-*p*-tolylsulfide)Cl]NO_3	44.28 (44.04)	6.49 (6.21)	6.96 (6.77)

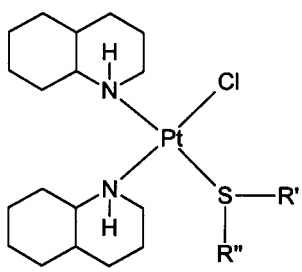

FIGURE 2 R′, R″ = methyl, ethyl, propyl, isopropyl, butyl, phenyl, and benzyl groups in Complexes 2, 4, 6, 8, 10, 12, and 14, respectively. R′ = methyl and R″ = phenyl and *p*-tolyl groups in Complexes 16 and 18, respectively.

mixture was stirred for 24 h in the dark. The AgI precipitate was filtered off, and the filtrate was concentrated to 20 mL under reduced pressure. Aqueous NaCl was added until a yellow precipitate of Pt$(dhq)_2Cl_2$ was formed. This was filtered, washed with water and acetone, and dried under vacuum (yield, 75%). An equimolar amount of dimethyl sulfide (0.046 g, 0.74 mmol) was added to a slurry of Pt$(dhq)_2Cl_2$ (0.4 g, 0.73 mmol) in methanol (30 mL). To this $AgNO_3$ (0.119 g, 0.70 mmol) dissolved in hot methanol (60 mL) was added. The reaction mixture was stirred overnight in the dark. The insoluble AgCl precipitate was filtered off, and the filtrate was evaporated under reduced pressure until the volume of methanol was approximately 5 mL. To this solution, excess ether was added and the flask was then placed in the freezer overnight. The resultant precipitate was washed with ether and dried *in vacuo* (yield, 72%). Anal. Calcd. for $C_{20}H_{40}N_3O_3CIS$ Pt: C, 37.94; H, 6.32; N, 6.64. Found: C, 37.75; H, 6.30; N, 6.83. IR: νN–H, 2929 cm^{-1}; νC–S, 1384 cm^{-1}. ^{1}H NMR: 2.88 (s, 6H). ^{195}Pt NMR: −2992.

Other Complexes (numbers) 4, 6, 8, 10, 12, 14, 16, and 18 in Table I were prepared in a similar manner (Fig. 2).

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. $[Pt(mmap)Cl_2]$ and $[Pt(dhq)_2Cl_2]$ were prepared according to Dhara's method [20], which was adopted because it is rapid and easy and provides a much higher yield than when K_2PtCl_4 is treated directly with the corresponding ligands. Reaction of K_2PtCl_4 with an excess of KI produced K_2PtI_4 in solution. K_2PtI_4 was reacted with 1 equivalent of mmap or 2 equivalents of dhq to precipitate $Pt(mmap)I_2$ or $Pt(dhq)_2I_2$. The rection of these iodide compounds with $AgNO_3$ led to the formation of $[Pt(mmap)(H_2O)_2](NO_3)_2$ and $[Pt(dhq)_2(H_2O)_2](NO_3)_2$ in aqueous solution, and these compounds were further converted into $[Pt(mmap)Cl_2]$ and $[Pt(dhq)_2Cl_2]$ by treating them with excess NaCl solution. Finally, these chloride compounds were reacted with 1 equivalent of $AgNO_3$ and subsequently with thioethers to form the required compounds of the type $[Pt(mmap)(R'R''S)Cl]NO_3$ and $[Pt(mmap)(R'R''S)Cl]NO_3$ in solution, while the insoluble AgCl was separated by filtration. The yellow solid compounds were obtained [21]. The results of characterization by IR and ^{195}Pt NMR are shown in Table II.

$$K_2PtCl_4 + 8KI \longrightarrow K_2PtI_4 + 4KI + 4KCl$$

$$K_2PtI_4 + mmap \longrightarrow [Pt(mmap)I_2] + 2KI$$

$$[Pt(mmap)I_2] + 2AgNO_3 \longrightarrow [Pt(mmap)(H_2O)_2](NO_3)_2 + 2AgI$$

$$[Pt(mmap)(H_2O)_2](NO_3)_2 + 2NaCl \longrightarrow [Pt(mmap)Cl_2] + 2NaNO_3 + 2H_2O$$

$$[Pt(mmap)Cl_2] \xrightarrow[R'R''S]{AgNO_3} [Pt(mmap)(R'R''S)Cl]NO_3 + AgCl$$

SCHEME 1.

$$K_2PtCl_4 + 8KI \longrightarrow K_2PtI_4 + 4KI + 4KCl$$

$$K_2PtI_4 + 2dhq \longrightarrow [Pt(dhq)_2I_2] + 2KI$$

$$[Pt(dhq)_2I_2] + 2AgNO_3 \longrightarrow [Pt(dhq)_2(H_2O)_2](NO_3)_2 + 2AgI$$

$$[Pt(dhq)_2(H_2O)_2](NO_3)_2 + 2NaCl \longrightarrow [Pt(dhq)_2Cl_2] + 2NaNO_3 + 2H_2O$$

$$[Pt(dhq)_2Cl_2] \xrightarrow[R'R''S]{AgNO_3} [Pt(dhq)_2(R'R''S)Cl]NO_3 + AgCl$$

SCHEME 2.

TABLE II IR and ^{195}Pt NMR[a] data spectroscopic data for the platinum(II) complexes

Complex	*IR* (cm^{-1})		*^{195}Pt NMR* (ppm)
	ν(N–H)	*ν(C–S)*	
1	3000	1400	−3380 s
2	2929	1384	−2992 s
3	3129	1372	−3116 s
4	3098	1383	−3051 s
5	3101	1384	−3100 s
6	3100	1384	−3160 s
7	3195	1384	−2969 s
8	2929	1384	−3179 s
9	2957	1384	−3097 s
10	3163	1384	−2968 s
11	3194	1384	−3040 s
12	3135	1383	−2950 s
13	3122	1384	−3107 s
14	2929	1384	−3276 s
15	3169	1383	−3045 s
16	2930	1384	−3180 s
17	2933	1384	−3071 s
18	2927	1384	−3050 s

[a]^{195}Pt NMR spectra in methanol-d_4 were recorded at 43.055 MHz, and the shifts were measured relative to an external standard of 2.2 M Na_2PtCl_6 in D_2O at 0.0 ppm; s = singlet.

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 experimental values (Table I).

The IR spectra of the complexes (Table II) in general showed a broad absorption between 3195 and 2929 cm^{-1}, which was due to the νN–H stretching vibrations of coordinated mmap and dhq. The intense band observed in the region 1372–1400 cm^{-1} was due to the νS–C stretching vibrations in all the complexes [21a,22,23]. The νPt–S stretching vibrations were observed around 350–400 cm^{-1}, and these values were close to those reported previously for such compounds [21,24–26]. The absorption values for νPt–Cl stretching vibrations were approximately 300 cm^{-1} [21,24,27].

The ^{1}H NMR spectra (Table III) were most informative with respect to the structures of the complexes.

In Complexes 1 and 2, the S–CH_3 protons of dimethylsulfide shifted downfield about 0.68 and 0.81 ppm upon complexation and were observed as singlets at 2.75 and 2.88 ppm, respectively. In Complexes 3 and 4, the peaks due to S–CH_2-protons showed a multiplet centered at 3.02 and 3.06 ppm, respectively, due to inequivalence of the protons attached to the sulfur atom. These protons shifted downfield about 0.50–0.54 ppm upon complexation. Also, there was a triplet centered at 1.50 and 1.38 ppm due to the methyl protons of diethylsulfide, which shifted downfield about 0.28–0.16 ppm. In Complex 5, the S–CH_2–CH_2 protons showed two unresolved multiplets at 3.00 and 1.98 ppm, which shifted to the downfield about 0.59 and 0.40 ppm, respectively, upon complexation. In Complex 6, these peaks appeared as two multiplets centered at 3.05 and 1.88 ppm, which shifted downfield about 0.59

TABLE III ^{1}H NMR data for platinum(II) complexes[a]

Ligand/complex no.	*S–CH$_3$*	*S–CH$_2$–*	*–CH$_2$–*	*–CH$_2$–*	*–CH$_3$*	*S–C–H*	*C$_6$H$_5$*
Dimethylsulfide	2.07 s	–	–	–	–	–	–
1	2.75 s	–	–	–	–	–	–
2	2.88 s	–	–	–	–	–	–
Diethylsulfide	–	2.52 q	–	–	1.22 t	–	–
3	–	3.02 m	–	–	1.50 t	–	–
4	–	3.06 m	–	–	1.38 t	–	–
Dipropylsufide	–	2.46 t	1.58 m	–	0.97 t	–	–
5	–	3.05 m	1.98 m	–	1.15 t	–	–
6	–	3.05 m	1.88 m	–	1.12 t	–	–
Diisopropylsulfide	–	–	–	–	1.21 d	2.95 m	–
7	–	–	–	–	1.58 d	3.32 m	–
8	–	–	–	–	1.62 d	3.33 m	–
Dibutylsulfide	–	2.49 t	1.54 m	1.42 m	0.91 t	–	–
9	–	2.72 t	1.82 m	1.60 m	1.04 t	–	–
10	–	2.52 m	1.85 m	1.54 m	0.99 t	–	–
Diphenylsulfide	–	–	–	–	–	–	7.17 m 7.25 m
11	–	–	–	–	–	–	7.32 m 7.59 m
12	–	–	–	–	–	–	7.47 m 7.70 m
Dibenzylsulfide	–	3.59 s	–	–	–	–	7.26 m
13	–	4.11 d	–	–	–	–	7.46 m 7.74 m
14	–	3.96 d 4.18 d	–	–	–	–	7.30 m 7.49 m
Methylphenylsulfide	2.42 s	–	–	–	–	–	7.08 m 7.20 m
15	2.82 s	–	–	–	–	–	7.56 m 8.00 m
16	2.84 s	–	–	–	–	–	7.63 m 7.98 m
Methyl-*p*-tolylsulfide	2.25 s	–	–	–	2.38 s	–	7.02 d 7.14 d
17	2.75 s	–	–	–	2.40 s	–	7.37 d 7.89 d
18	2.79 s	–	–	–	2.44 s		7.44 d 7.63 d

and 0.30 ppm, respectively, as compared with the free ligand. Additionally, the methyl protons of dipropylsulfide produced triplets centered at 1.15 and 1.12 ppm in Complexes 5 and 6, respectively. In Complexes 7 and 8, there were multiplets at 3.32 and 3.33 ppm, respectively, due to S–CH protons of diisopropylsulfide, which shifted downfield about 0.37 and 0.38 ppm, respectively, as compared with the free ligand. A doublet at 1.58 and 1.62 ppm in Complex 7 and 8, respectively, was assigned to the methyl protons, shifted downfield about 0.37 and 0.41 ppm respectively, as compared with the free ligand. Finally, in Complexes 9 and 10, the S–CH_2– protons shifted downfield about 0.23 and 0.03 ppm, respectively, upon complexation were observed at 2.72 and 2.52 ppm, respectively. In Complex 9, the ethylene protons appeared as two multiplets centered at 1.82 and 1.60 ppm, respectively, whereas the methyl protons appeared as a triplet centered at 1.04 ppm. In Complex 10, these protons appeared at 1.85, 1.54, and 0.99 ppm, respectively. The larger downfield shift

of S–CH_2– protons in Complexes 3–10 compared with other protons confirmed the involvement of S–CH_2– in complexation.

In Complex 11, the phenyl protons shifted downfield about 0.15 and 0.34 ppm upon complexation as compared with the free ligand and were observed as two multiplets centered at 7.32 and 7.59 ppm, respectively. In Complex 12, these peaks shifted downfield about 0.30 and 0.53 ppm upon complexation and were observed as two multiplets centered at 7.47 and 7.70 ppm, respectively. In Complexes 13 and 14, the S–CH_2– protons of dibenzylsulfide shifted downfield upon complexation and were observed as two doublets centered at 3.59 and 4.11 ppm and at 4.11 and 4.39 ppm, respectively, due to the inequivalence of these protons. Also, the benzene ring protons resonated at 7.28 and 8.35 ppm in Complex 13 and at 7.45 and 7.66 ppm in Complex 14, respectively. Additionally, in Complex 15, there was a singlet observed at 2.82 ppm due to the S–CH_3 protons of methylphenylsulfide, which shifted downfield by 0.40 ppm upon complexation, whereas in Complex 16, this peak shifted downfield about 0.42 ppm and was observed at 2.84 ppm. The benzene ring protons also shifted downfield and were observed as two doublets centered at 7.56 and 7.00 ppm in Complex 15 and two multiplets centered at 7.63 and 7.98 ppm in Complex 16. Finally, in Complexes 17 and 18, the S–CH_3 protons of methyl *p*-tolylsulfide were observed as singlets at 2.75 and 2.79 ppm, respectively, which shifted downfield about 0.50 and 0.54 ppm when compared with the free ligand. In addition the –CH_3 protons appeared at 2.40 and 2.44 ppm, respectively, and the benzene ring protons resonated at 7.37 and 7.89 ppm and 7.44 and 7.63 ppm, respectively. The larger downfield shift of S–CH_2– protons as compared with phenyl protons in Complexes 13–16 and phenyl and –CH_3 protons in Complexes 17 and 18 supports the coordination of sulfur through platinum.

The ^{195}Pt NMR spectra further confirm the structures of the platinum complexes. The singlet observed in the range of −2950 to −3380 ppm indicates the coordination of amino nitrogens of mmap or dhq to the two adjacent corners of square planar platinum(II), while the other two positions are bound to the chloride atom and the sulfur atom of the thioether group. Such chemical shift values are characteristic of complexes, in which platinum(II) is bound by two nitrogen atoms, one sulfur atom and one chloride atom [22,28].

CONCLUSIONS

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

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