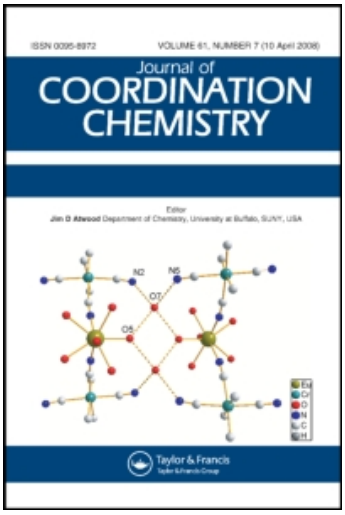

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

SYNTHESIS AND CHARACTERIZATION OF NEW ETHYLENEDIAMINE AND 1,1-BIS(AMINOMETHYL)CYCLOHEXANEPLATINUM(II) COMPLEXES CONTAINING DISUBSTITUTED SULFIDE AS A LEAVING GROUP

Abdul R. Khokhar[a]; Shamsuddin[a]; Salaam Al-baker[a]; Chirayu Shah[a]
[a] Department of Clinical Investigation, The University of Texas, M.D. Anderson Cancer Center, Houston, Texas, USA

To cite this Article Khokhar, Abdul R. , Shamsuddin, Al-baker, Salaam and Shah, Chirayu(1995) 'SYNTHESIS AND CHARACTERIZATION OF NEW ETHYLENEDIAMINE AND 1,1-BIS(AMINOMETHYL)CYCLOHEXANEPLATINUM(II) COMPLEXES CONTAINING DISUBSTITUTED SULFIDE AS A LEAVING GROUP', Journal of Coordination Chemistry, 36: 1, 7 — 12
To link to this Article: DOI: 10.1080/00958979508022214
URL: http://dx.doi.org/10.1080/00958979508022214

J. Coord. Chem., 1995, Vol 36, pp. 7–12
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS AND CHARACTERIZATION OF NEW ETHYLENEDIAMINE AND 1,1-BIS(AMINOMETHYL)CYCLOHEXANE-PLATINUM(II) COMPLEXES CONTAINING DISUBSTITUTED SULFIDE AS A LEAVING GROUP

ABDUL R. KHOKHAR,* SHAMSUDDIN, SALAAM AL-BAKER, and CHIRAYU SHAH

Department of Clinical Investigation, The University of Texas, M.D. Anderson Cancer Center, Houston, Texas 77030, USA

(Received November 12, 1994; in final form March 6, 1995)

A series of cationic platinum(II) complexes of the type $[Pt(en)(R'R''S)Cl]NO_3$ and $[Pt(BAMCH)(R'R''S)Cl]NO_3$ (where en = ethylenediamine; BAMCH = 1,1-bis(aminomethyl)cyclohexane; and R'R''S = dimethylsulfide, diethysulfide, dipropylsulfide, diisopropylsulfide, diphenylsulfide, dibenzylsulfide, thioanisole, and methyl-*p*-tolylsulfide) has been synthesized and characterized by elemental analysis, infrared, and ^{195}Pt nuclear magnetic resonance spectroscopic techniques.

KEYWORDS: ethylenediamine, 1,1-bis(aminomethyl)cyclohexane, disubstituted sulfides, platinum complexes, antitumor agents

INTRODUCTION

Cisplatin is the most active antitumor agent against testicular, ovarian, bladder, and head and neck cancers.[1–3] However, cisplatin causes severe side effects such as nephrotoxicity, ototoxicity, myelosuppression, neurotoxicity, nausea, and vomiting; has a limited spectrum of clinical usefulness, and induces resistance in tumor cells. This has stimulated the synthesis and evaluation of new platinum agents with reduced toxicity, no cross resistance, and better antitumor activity.[4–7] Most of the analogs tested so far have been neutral platinum(II) compounds of the type *cis*-(PtA_2X_2), where A is an amine ligand and X is an anionic leaving group.[1,4,8,9] The clinical effectiveness of cisplatin was improved by displacing the labile chloro ligands with other leaving groups having intermediate lability so as to alter its pharmacokinetics. Such second-generation platinum drugs, as carboplatin[10] then came into clinical use. A number of platinum drugs, including tetraplatin, oxaliplatin, and liposome-entrapped bis(neodecanoato) (*trans*-1R,2R-diaminocyclohexane)platinum(II) (L-NDDP), which have 1,2-diamino-cyclohexane (DACH) as a carrier ligand and chloride or carboxylate as leaving groups, are now in clinical trials.[11]

*Author for correspondence.

Diamineplatinum(II) complexes with substituted sulfoxide as a leaving group have been extensively studied over the past two decades.[12,13] Such complexes reportedly have antitumor activity against certain tumor models[14] and violate some of the rules of classical structure-activity relationships.[15] Consequently we have been developing platinum complexes with diamines such as DACH as a carrier ligand and chloride and/or carboxylate as leaving groups.[16] Furthermore, it has recently been reported that some thioether groups can reduce cisplatin-induced nephrotoxicity when administered simultaneously with cisplatin.[17] This very property of thioethers has moved us to synthesize platinum(II) complexes of the type $[Pt(en)(R'R'')Cl]NO_3$ and $[Pt(BAMCH)(R'R''S)Cl]NO_3$, where R'R''S is a dialkyl or diaryl sulfide leaving group. In this paper, we report the synthesis and characterization of a series of such compounds.

EXPERIMENTAL

Chemicals

K_2PtCl_4 was purchased from Johnson Matthey, Seabrook, NH. BAMCH was obtained from Morton Thiokol, Inc., Danvers, MA. Ethylenediamine, dimethylsulfide, diethylsulfide, dipropylsulfide, diisopropylsulfide, diphenylsulfide, thioanisole, and methyl-*p*-tolylsulfide were purchased from Aldrich Chemical Co., Milwaukee, WI. Silver nitrate was obtained from Fisher Scientific Co., Houston, TX.

Physical Measurements

Elemental analysis of 15 platinum complexes was performed by Robertson Laboratory, Inc., Madison, NJ. Infrared (IR) spectra were recorded in KBr pellets in the range of 250–4000 cm^{-1} on a Beckman 250MX spectrophotometer. ^{195}Pt nuclear magnetic resonance (NMR) spectra were recorded on an IBM BR200/AF spectrometer in methanol. Na_2PtCl_6 in D_2O at 0.00 ppm was used as an external reference.

Preparation of {Pt[en][$(CH_3)_2S$]Cl}NO_3 (complex 1)

K_2PtCl_4 (10.38 g, 25 mmol) was dissolved in 250 ml of deionized water and filtered. Then KI (41.5 g, 0.25 mol) in 100 ml of water was added. The reaction mixture was stirred for 10 min, ethylenediamine (2.00 ml, 25 mmol) was added, and stirring was continued for a further 30 min. The yellow precipitate, $(en)PtI_2$, was separated by filtration; washed with a small amount of dimethyl formamide; washed with water, ethanol, and acetone, and then dried under vacuum. Silver nitrate (7.36 g, 43.0 mmol) was dissolved in 250 ml of water, and $(en)PtI_2$ (11.19 g, 22.0 mmol) was then added. The reaction mixture was stirred for 24 h in the absence of light. The AgI precipitate was filtered off, and 1:1 HCl was added dropwise to the filtrate with constant stirring until a yellow precipitate of $(en)PtCl_2$ formed. The precipitate was then filtered, washed with water and acetone, and dried under vacuum. To a slurry of $(en)PtCl_2$ (0.65 g, 2 mmol) in 50 ml of methanol, an

equivalent amount of $AgNO_3$ (0.34 g, 2 mmol) dissolved in 100 ml of hot methanol was added. To this, one equivalent of dimethylsulfide (0.15 ml, 2 mmol) in 20 ml of methanol was added. The reaction mixture was stirred overnight in the dark. Then the AgCl precipitate was filtered off, and the filtrate was evaporated to dryness under reduced pressure. A pale yellow solid was obtained, which was purified from methanol and ether. Finally, a white compound, $\{Pt[en][(CH_3)_2S]Cl\}NO_3$ was obtained, and dried under vacuum (yield, 50%).

Complexes 2–7 (Table 1) were prepared in a similar manner to complex 1.

Preparation of $\{Pt[BAMCH][(CH_3)_2S]Cl\}NO_3$ (complex 8)

Ten milliliters of 5 N NaOH (50 mmol) was added dropwise to a solution of BAMCH·2HCl (5.37 g, 25 mmol) in 25 ml of water. This solution was mixed with an aqueous solution (300 ml) of K_2PtCl_4 (10.38 g, 25 mmol). The reaction mixutre was then stirred continuously for 3 h. A light yellow precipitate of $(BAMCH)PtCl_2$ was separated by filtration every 60 min, this was then washed with DMF, water ethanol and ether and dried under vacuum (yield, 90%). To a slurry of

Table 1 Elemental Analyses of platinum(II)-sulfide complexes

Complex no.	Complex name*	Observed (calculated)			%Yield
		%C	%H	%N	
1.	en-chloro(dimethylsulfide)-platinum(II) nitrate	11.86 (11.58)	2.98 (3.38)	9.87 (10.13)	50
2.	en-chloro(diethylsulfide)-platinum(II) nitrate	16.89 (16.27)	3.64 (4.07)	9.22 (9.49)	81
3.	en-chloro(diisopropylsulfide)-platinum(II) nitrate	20.27 (20.40)	4.34 (4.68)	9.12 (8.93)	30
4.	en-chloro(diphenylsulfide)-platinum(II) nitrate	30.30 (31.20)	3.35 (3.34)	8.07 (7.80)	80
5.	en-chloro(dibenzylsulfide)-platinum(II) nitrate	33.96 (33.89)	3.55 (3.88)	7.23 (7.41)	48
6.	en-chloro(methylphenylsulfide)-platinum(II) nitrate	23.21 (22.66)	3.11 (3.55)	8.67 (8.81)	35
7.	en-chloro(methyl-*p*-tolylsulfide)-platinum(II) nitrate	24.72 (24.46)	3.80 (3.67)	8.44 (8.56)	36
8.	BAMCH-chloro(dimethylsulfide)-platinum(II) nitrate	24.75 (24.17)	4.65 (4.83)	8.46 (8.46)	85
9.	BAMCH-chloro(diethylsulfide)-platinum(II) nitrate	27.77 (27.45)	5.11 (5.33)	8.05 (8.00)	70
10.	BAMCH-chloro(dipropylsulfide)-platinum(II) nitrate	30.63 (30.40)	5.68 (5.79)	7.66 (7.60)	72
11.	BAMCH-chloro(diisopropylsulfide)-platinum(II) nitrate	30.55 (30.40)	5.60 (5.79)	7.61 (7.60)	63
12.	BAMCH-chloro(diphenylsulfide)-platinum(II) nitrate	38.05 (38.68)	4.42 (4.51)	6.92 (6.76)	75
13.	BAMCH-chloro(dibenzylsulfide)-platinum(II) nitrate	40.47 (40.70)	4.94 (4.93)	6.56 (6.47)	60
14.	BAMCH-chloro(methylphenylsulfide)-platinum(II) nitrate	32.21 (32.33)	4.66 (4.65)	7.54 (7.52)	65
15.	BAMCH-chloro(methyl-*p*-tolylsulfide) platinum(II) nitrate	33.66 (33.47)	4.91 (5.05)	7.41 (7.32)	71

* en = ethylenediamine; BAMCH = 1,1-bis(aminomethyl)cyclohexane.

(BAMCH)$PtCl_2$ (0.82 g, 2.0 mmol) in 50 ml of methanol, an equivalent amount of $AgNO_3$ (0.34 g, 2.0 mmol) dissolved in 100 ml of hot methanol was added. To this, one equivalent of dimethysulfide (0.15 ml, 2.0 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 pale yellow solid was obtained and then purified with methanol and ether. The light yellow final product, {Pt[BAMCH][$(CH_3)_2$S]Cl}NO_3, was dried under vacuum (yield, 85%).

Complexes 9–15 (Table 1) were prepared in a similar manner to complex 8.

RESULTS AND DISCUSSION

The steps involved in the synthesis of platinum complexes are shown in Schemes I and II. Reaction of K_2PtCl_4 with an excess of KI produced K_2PtI_4 in solution. K_2PtI_4 was reacted with one equivalent of ethylenediamine to precipitate (en)PtI_2. The reaction of (en)PtI_2 with $AgNO_3$ led to the formation of (en)Pt$(NO_3)_2$ in solution, which was further converted into (en)$PtCl_2$ by treatment with 1:1 HCl. On the other hand, (BAMCH)$PtCl_2$ was prepared by direct interaction of BAMCH with K_2PtCl_4 (Scheme II). BAMCH was prepared *in situ* by neutralizing BAMCH·2HCl with 1 N NaOH. (en)$PtCl_2$ and (BAMCH)$PtCl_2$ were reacted with $AgNO_3$ and subsequently with substituted disulfides to form compounds of the type [Pt(en)(R′R″S)Cl]NO_3 and [Pt(BAMCH)(R′R″S)Cl]NO_3 respectively, in solution, while the insoluble AgCl was separated by filtration.

Our characterization of the platinum complexes included elemental and spectroscopic analysis. The results are given in Tables 1 and 2. The composition of each complex was determined by elemental analysis, and the theoretical and actual values were in good agreement. In the IR spectra, complexes showed a broad absorption between 3169 and 3190 cm^{-1}, due to the coordinated NH_2 groups of

Table 2 IR and ^{195}Pt NMR data for platinum(II)sulfide complexes

Complex no.	IR, cm^{-1}		^{195}Pt, ppm in MeOH
	ν(N-H)	ν(S-C)	
1	3174	1374	−3195
2	3180	1374	−3211
3	3185	1355	−3164
4	3179	1371	−3154
5	3174	1367	−3200
6	3170	1359	−3161
7	3169	1375	−3159
8	3175	1346	−3135
9	3190	1369	−3137
10	3175	1361	−3123
11	3190	1371	−3096
12	3185	1375	−3065
13	3190	1343	−3125
14	3180	1357	−3080
15	3188	1377	−3078

$$K_2PtCl_4 + 8KI \longrightarrow K_2PtI_4 + 4KI + 4KCl \quad (1)$$

$$K_2PtI_4 + en \longrightarrow (en)PtI_2 + 2KI \quad (2)$$

$$(en)PtI_2 + 2AgNO_3 \longrightarrow [(en)Pt(H_2O)_2](NO_3)_2 + 2AgI \quad (3)$$

$$[(en)Pt(H_2O)_2](NO_3)_2 + 2HCl \longrightarrow (en)PtCl_2 + 2HNO_3 + 2H_2O \quad (4)$$

$$(en)PtCl_2 \xrightarrow[ii)\ R'R''S]{i)\ AgNO_3} [Pt(en)(R'R''S)Cl]NO_3 + AgCl \quad (5)$$

Scheme I

$$BAMCH \cdot 2HCl + 2NaOH \longrightarrow BAMCH + 2NaCl + 2H_2O \quad (1)$$

$$K_2PtCl_4 + BAMCH \longrightarrow (BAMCH)PtCl_2 + 2KCl \quad (2)$$

$$(BAMCH)PtCl_2 \xrightarrow[ii)\ R'R''S]{i)\ AgNO_3} [Pt(BAMCH)\ (R'R''S)Cl]NO_3 + AgCl \quad (3)$$

Scheme II

ethylenediamine and BAMCH. The intense band seen in the region 1343–1377 cm^{-1} was due to ν(S-C) stretching vibrations. Pt-S stretching vibrations were observed around 350–400 cm^{-1}, whereas Pt-Cl stretching vibrations were seen around 300 cm^{-1}. The ^{195}Pt NMR spectra further confirmed the structures of the platinum complexes. The singlet observed in the range of −3154 to −3211 ppm and −3065 to −3137 ppm indicated the coordination of amino nitrogens of ethylenediamine and BAMCH, respectively, to the two adjacent corners of square planar platinum(II), while the other two positions were bound to the chloride atom and sulfur atom of the thioether group. Such chemical shift values are characteristic of platinum complexes, where platinum(II) is bound by two nitrogen atoms, one sulfur atom and one chloride atom.[18] 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.

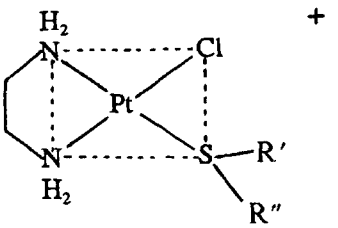

Figure 1 Ethylenediamine complexes with R′,R″ = methyl, ethyl, isopropyl, phenyl, and benzyl groups in complexes 1–5, respectively and R′ = methyl and R″ = phenyl and p-tolyl groups in complexes 6 and 7, respectively.

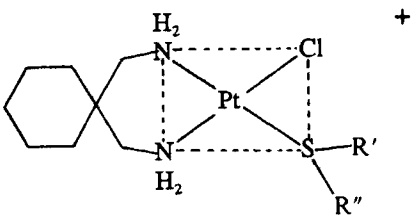

Figure 2 Platinum complexes of 1,1-bis(aminomethyl)cyclohexane with R′,R″ = methyl, ethyl, propyl, isopropyl, phenyl, and benzyl groups in complexes 8–13, respectively, and R′ = methyl and R′ = phenyl and p-tolyl groups in complexes 14 and 15, respectively.

Acknowledgements

This work was supported by grant CA41581 from the National Cancer Institute.

References

1. S.K. Carter, in M.P. Hacker, E.B. Douple and I.H. Krakoff (eds.), "Platinum Coordination Complexes in Cancer Chemotherapy", (Martinus Nijhoff Publishing, Boston, MA, 1984), p. 359.
2. J.R. Durant, in A.W. Prestayko, S.T. Crooke and S.K. Carter (eds.), "Cisplatin, Current Status and New Developments", (Academic Press, New York, 1980), p. 317.
3. P.J. Loehrer and L.H. Einhorn, *Ann. Internt. Med.*, **100**, 704 (1984).
4. M.J. Cleare, P.C. Hydes, D.R. Hepburn and B.W. Melerbi, in A.V. Prestayko, S.T. Crooke and S.K. Carter (eds.), "Cisplatin, Current Status and New Developments", (Academic Press, New York, 1980), p. 149.
5. T.A. Connors, M.J. Cleare and K.R. Harrap, *Cancer Treat. Rep.*, **63**, 1499 (1979).
6. K.R. Harrap, in F.M. Muggia (ed.), "Cancer Chemotherapy", (Martinus Nijhoff Publishing, Boston, MA, 1983), Vol. 1, p. 171.
7. P.C. Hydes, in M.P. Hacker, E.B. Douple and I.H. Krakoff (eds.), "Platinum Coordination Complexes in Cancer Chemotherapy", (Martinus Nijhoff Publishing, Boston, MA, 1984), p. 216.
8. J.P. Macquet and J.L. Butor, *J. Natl. Cancer Inst.*, **70**, 899 (1983).
9. A.H. Calvort, in D.C.H. McBrien and T.F. Slater (eds.), "Biochemical Mechanisms of Platinum Antitumor Drugs", (IRL Press, Washington, D.C., 1986), p. 307.
10 A.H. Calvert, S.J. Harland, D.R. Newell, Z.H. Siddik and K.R. Harrap, *Cancer Treat. Rev.*, **12** (suppl. A), 51 (1985).
11 (a) R. Perez-Soler, G. Lopez-Berestein, J. Lauterszatin, et al., *Cancer Res.*, **50**, 4254 (1990); (b) M.C. Christian, *Semin. Oncol.*, **19**, 720 (1992); (c) R.B. Weiss and M.C. Christian, *Drugs*, **46**, 360 (1993).
12 (a) M.L. Tobe and A.R. Khokhar, *J. Cli. Hemat. Oncol.*, 7, 114 (1973); (b) P.D. Braddock, T.A. Cannors, M. Jones, A.R. Khokhar, D.H. Melzack and M.L. Tobe, *Chem. Biol. Interact.*, **11**, 145 (1975).
13 P. Braddock, A.R. Khokhar, R. Romeo and M.L. Tobe, in T.A. Connors and J.J. Roberts (eds.), "Recent Results in Cancer Research: Platinum Coordination Complexes in Cancer Chemotheraphy", (Springer-Verlag, Berlin, 1973), Vol. 40, p.
14 (a) V. Fimiani and D. Minniti, *Anticancer Drugs*, **3**, 9 (1992); (b) P. Bitha, G.O. Morton, T.S. Dunne, E.F. Santos, Y. Lin, S.R. Boone, R.C. Haltiwanger and C.G. Pierpont, *Inorg. Chem.*, **29**, 645 (1990); (C) N. Farell, D.M. Kiley, W. Schmidt and M.P. Hacker, *Inorg. Chem.*, **29**, 397 (1990); (d) J. Landi, M.P. Hacker and N. Farell, *Inorg. Chim. Acta.*, **202**, 79 (1992).
15. M.J. Cleare and J.D. Hoeschele, *Bioinorg. Chem.*, **2**, 187 (1973).
16. (a) A.R. Khokhar, S. Al-Baker, T. Brown and R. Perez-Soler, *J. Med. Chem.*, **34**, 325 (1991); (b) A.R. Khokhar, S. Al-Baker and Z.H. Siddik, *J. Inorg. Chem.*, **54**, 39 (1994); (c) S. Al-Baker, Z.H. Siddik and A.R. Khokhar, *J. Coord. Chem.*, **21**, 109 (1994).
17. M.M. Jones, M.A. Basinger and M.A. Holscher, *Anticancer Res.*, **11**, 449 (1991).
18. P.S. Pregosin, *Coord. Chem. Rev.*, **44**, 247 (1982).