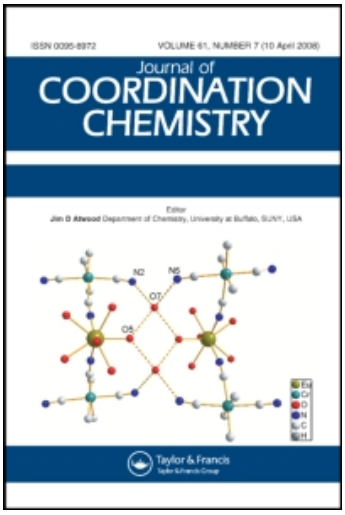

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Synthesis and Characterization of Novel *Trans*-Mixed Diamine Platinum(II) and Platinum(IV) Complexes

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SYNTHESIS AND CHARACTERIZATION OF NOVEL *TRANS*-MIXED DIAMINE PLATINUM(II) AND PLATINUM(IV) COMPLEXES

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A series of novel *trans*-mixed diamine platinum(II) and platinum(IV) complexes of type *trans*-[Pt^{II}(R-NH_2)(R′-NH_2)Cl_2] and *trans*-[Pt^{IV}(R-NH_2)(R′-NH_2)Cl_4] (where R-NH_2 = ethylamine or butylamine and R′-NH_2 = methylamine, propylamine, isopropylamine, pentylamine, or hexylamine) was synthesized and characterized using elemental analysis and infrared and ^{195}Pt nuclear magnetic resonance spectroscopic techniques.

Keywords: *Trans*-mixed diamine complexes; Platinum(II) complexes; Platinum(IV) complexes

INTRODUCTION

Since the discovery of cisplatin as an effective anticancer drug [1], a wide variety of platinum complexes have been synthesized and tested against tumor cells [2–4]. These efforts were basically focused on two areas: (1) altering the leaving groups and non-leaving amine ligands to modify the pharmacokinetics of cisplatin [5–7], and (2) preparing platinum(IV) analogs by oxidizing corresponding platinum(II) complexes and modifying their properties by changing axial ligands [8–10]. The principal feature of the structure–activity relationship of platinum antitumor complexes having the general formula Pt(amine)$_2$$Cl_2$ is that the *cis*-isomers are active, whereas the corresponding *trans*-isomers are inactive [11–13]. However, recent reports showed that in some *trans*-isomers a planar ligand, such as pyridine, greatly enhances the cytotoxicity to a level equivalent to that of the analogous *cis*-isomer and, indeed, cisplatin itself [14–16]. These results are very important because complexes that are structurally different from cisplatin and its analogues may have clinically important differences in activity or toxicity due to the difference in cellular biochemical pharmacology. Thus,

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these active *trans*-isomers may result in an altered spectrum of antitumor activity in cisplatin-resistant tumors. On the other hand, there has been an interest in the mixed amines and amine/amine platinum complexes in our group and others because these complexes are more active against some tumors but less toxic than cisplatin [17,18]. In this paper we report the synthesis and characterization of the *trans*-isomers of mixed amine platinum complexes.

EXPERIMENTAL

Chemicals

Methylamine, ethylamine, propylamine, isopropylamine, butylamine, pentylamine, hexylamine and thiourea were purchased from Aldrich Chemical Co., Milwaukee, WI. Potassium tetrachloroplatinate(II) was purchased from Johnson Matthey, Seabrook, NH. Methanol and silver nitrate were purchased from Fischer (Pittsburgh, PA). All chemicals were used as received without further purification.

Physical Measurements

Elemental analyses were performed by Robertson Laboratory Inc., Madison, NJ. Infrared spectra ranging from 4000–650 cm^{-1} and from 600–200 cm^{-1} were recorded in KBr and polyethylene pellets, respectively, using a Perkin-Elmer FT-IR spectrophotometer. ^{195}Pt nuclear magnetic resonance (NMR) spectra were recorded at 43.055 MHz on an IBM NR200/AF spectrometer using a 10 mm tunable probe. The chemical shifts were collected in acetone at room temperature and measured relative to an external standard of 1 M Na_2PtCl_6 in D_2O at 0.0 ppm. The purity of the complexes was evaluated using high-pressure liquid chromatography (HPLC) on a Waters Nova-Pak C18 column (3.9 mm × 300 mm) with methanol as a mobile phase, at a flow rate of 1 mL/min.

Synthesis of Platinum Complexes

Trans-[Pt^{II}(ethylamine)(methylamine)Cl_2] (complex 1)

K_2PtCl_4 (8.30 g, 20 mmol) was dissolved in 200 mL of water and filtered. Potassium iodide (27 g, 160 mmol) in 100 mL of water was added to the solution and stirred for 10 min. Ethylamine ($C_2H_5NH_2$) was added dropwise to the solution until a yellow precipitate was formed while stirring, which was continued for another hour. The yellow compound *cis*-[$Pt(C_2H_5NH_2)_2I_2$] was formed, filtered, washed with water, and dried under vacuum (yield: 9.47 g, 88%). *cis*-[$Pt(C_2H_5NH_2)_2I_2$] (9.47 g, 17.62 mmol) was added as a solid to an aqueous solution of $AgNO_3$ (5.91 g, 35.14 mmol). The reaction mixture was stirred in the dark overnight. Afterward, the AgI precipitate was filtered off, and methylamine (4.21 g, 3.8 mL, 105.42 mmol) was added in excess (~20 mL) to the filtrate. The reaction mixture was refluxed at 100°C for 5 h and cooled to room temperature; 15 mL of concentrated HCl was then added to the mixture, which was refluxed for another 5 h. A yellow precipitate was obtained after cooling the reaction mixture; it was filtered, washed thoroughly with water, and dried under vacuum.

It was then redissolved in acetone and filtered. Next, the filtrate was concentrated to a minimum volume and precipitated with water. The precipitate was then filtered, washed with water, and dried under vacuum (yield: 4.52 g, 75%). Platinum(II) dichloro complexes **2**, **5**, and **6** and platinum(IV) tetrachloro complexes **10** and **11** (see Table I) were prepared according to the method described above.

trans-[Pt^{IV}(ethylamine)(methylamine)Cl_4] (complex 7)

Ten milliliters of a 30% hydrogen peroxide solution was added to a suspension of *trans*-[Pt^{II}(ethylamine)(methylamine)Cl_2] (1.71 g, 5.0 mmol) in 100 mL of water. The mixture was stirred at 70°C for 1 h and then at room temperature for 24 h. The resulting pale yellow solution was concentrated to 5 mL under reduced pressure and precipitated with acetone; a light yellow precipitate was formed. Next, the mixture was left standing for 2 h and then filtered. The resulting solid, *trans*-[Pt^{IV}(ethylamine)(methylamine)$Cl_2(OH)_2$], was washed with acetone and dried under vacuum (yield: 1.3 g, 70%). *trans*-[Pt^{IV}(ethylamine)(methylamine)$Cl_2(OH)_2$] (1.13 g, 3.0 mmol) was then suspended in 20 mL of water and 10 mL of concentrated HCl was added. The reaction mixture was stirred at room temperature for 15 h. First the suspended material was dissolved and formed a clear yellow solution and then a yellow solid was slowly formed; the compound was filtered and washed several times with water. Finally, the solid was dissolved in 25 mL of warm acetone and kept in the refrigerator overnight.

TABLE I Elemental analysis of *trans*-mixed amine platinum(II) and platinum(IV) complexes

Complex no.	*Complex name*	*Found (calculated)*		
		C%	*H%*	*N%*
1	*trans*-[Pt^{II}(ethylamine)(methylamine)Cl_2]	10.71 (10.52)	3.40 (3.50)	8.00 (8.10)
2	*trans*-[Pt^{II}(ethylamine)(isopropylamine)Cl_2]	16.44 (16.22)	4.27 (4.32)	7.49 (7.57)
3	*trans*-[Pt^{II}(ethylamine)(pentylamine)Cl_2]	21.17 (21.11)	5.06 (5.03)	6.91 (7.04)
4	*trans*-[Pt^{II}(ethylamine)(hexylamine)Cl_2]	22.29 (22.34)	4.83 (4.78)	6.79 (6.45)
5	*trans*-[Pt^{II}(propylamine)(butylamine)Cl_2]	21.25 (21.10)	4.98 (5.02)	6.86 (7.02)
6	*trans*-[Pt^{II}(butylamine)(pentylamine)Cl_2]	25.89 (25.35)	5.80 (5.63)	6.76 (6.57)
7	*trans*-[Pt^{IV}(ethylamine)(methylamine)Cl_4]	9.02 (8.72)	2.79 (2.91)	6.59 (6.78)
8	*trans*-[Pt^{IV}(ethylamine)(propylamine)Cl_4]	13.79 (13.59)	3.66 (3.62)	6.42 (6.34)
9	*trans*-[Pt^{IV}(ethylamine)(isopropylamine)Cl_4]	12.76 (12.56)	3.52 (3.56)	6.07 (5.86)
10	*trans*-[Pt^{IV}(ethylamine)(pentylamine)Cl_4]	16.44 (16.62)	3.95 (4.15)	5.97 (5.54)
11	*trans*-[Pt^{IV}(ethylamine)(hexylamine)Cl_4]	19.76 (19.88)	4.55 (4.60)	5.80 (5.79)
12	*trans*-[Pt^{IV}(butylamine)(methylamine)Cl_4]	13.58 (13.61)	3.61 (3.63)	6.25 (6.35)
13	*trans*-[Pt^{IV}(butylamine)(propylamine)Cl_4]	18.08 (17.91)	4.31 (4.29)	5.90 (5.97)
14	*trans*-[Pt^{IV}(butylamine)(pentylamine)Cl_4]	21.53 (21.73)	4.69 (4.83)	5.58 (5.63)

A crystalline yellow material, *trans*-[Pt^{IV}(ethylamine)(methylamine)Cl_4] was obtained, which was filtered and dried under vacuum (yield: 0.87 g, 70%).

Complexes **8**, **9**, and **13–15** were prepared in a similar manner.

trans-[Pt^{II}(ethylamine)(pentylamine)Cl_2] (complex 3)

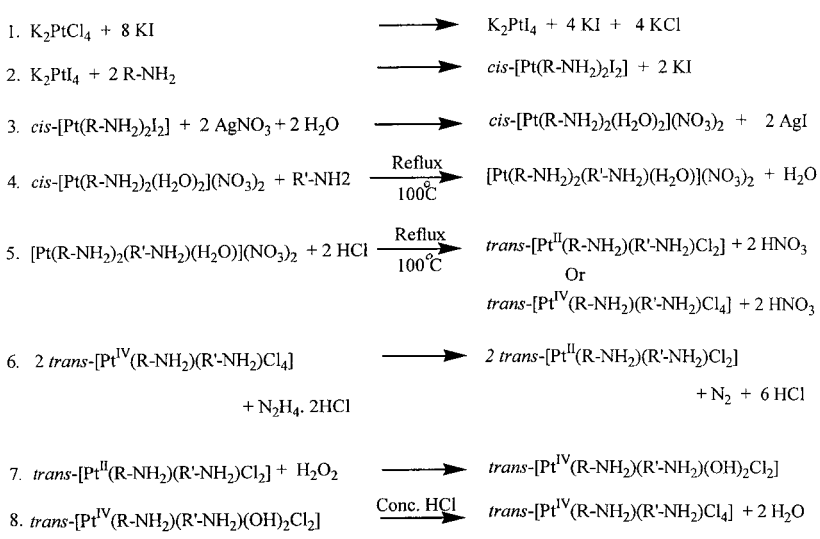
trans-[Pt^{IV}(ethylamine)(pentylamine)Cl_4] (1.88 g, 4 mmol) was dissolved in 100 mL of acetone. An aqueous solution consisting of hydrazine dihydrochloride ($N_2H_4 \cdot 2HCl$) (0.21 g, 2 mmol) in 100 mL of water was added to it and refluxed for 15 h. The acetone was then removed under reduced pressure at room temperature, and the reaction mixture was further refluxed for 5 h. A clear yellow solution formed, which was cooled and evaporated to dryness under reduced pressure. The residue obtained was dissolved in acetone, and an insoluble white material was filtered off. Next, the filtrate was concentrated to a minimum volume and precipitated with water to obtain yellow solid *trans*-[Pt^{II}(ethylamine)(pentylamine)Cl_2]. The solid was filtered, washed with water, and dried under vacuum (yield: 1.47 g, 92%).

Complex **4** was prepared in a similar manner from the corresponding tetrachloro complex.

RESULTS AND DISCUSSION

Synthesis of Platinum Complexes

Trans-mixed diamine platinum(II) and platinum(IV) complexes were prepared according to the steps shown in Scheme 1. K_2PtCl_4 was reacted with an excess of KI (1), which was followed by the addition of the primary amine ligand R-NH_2 (where



where R-NH_2 = ethylamine, or butylamine and R'-NH2 = methylamine, ethylamine, propylamine, isopropylamine, pentylamine, or hexylamine.

SCHEME 1

R-NH_2 = ethylamine or butylamine) to obtain *cis*-[Pt^{II}(R-NH_2)$_2I_2$] (2). *cis*-[Pt^{II}(R-NH_2)$_2I_2$] was then reacted with $AgNO_3$ to form *cis*-[Pt^{II}(R-NH_2)$_2$(H_2O)$_2$](NO_3)$_2$ in solution (3). *cis*-[Pt^{II}(R-NH_2)$_2$ (H_2O)$_2$](NO_3)$_2$ was refluxed in the presence of another ligand, R′-NH_2 (where R′-NH_2 = methylamine, ethylamine, propylamine, isobutylamine, pentylamine, or hexylamine) to obtain the mixed triamine complex *cis*-[Pt^{II}(R-NH_2)$_2$(R′-NH_2)H_2O](NO_3)$_2$ in solution (4). The ^{195}Pt NMR of this solution showed a singlet at -2200 ppm confirming the triamine formation. *cis*-[Pt^{II}(R-NH_2)$_2$(R′-NH_2)H_2O](NO_3)$_2$ was again refluxed in the presence of concentrated HCl to obtain the *trans*-dichloroplatinum(II) complex *trans*-[Pt^{II}(R-NH_2)(R′-NH_2)Cl_2] (5) as a crystalline yellow powder. In some cases, reaction with concentrated HCl led to the formation of *trans*-tetrachloroplatinum(IV) complexes of the type *trans*-[Pt^{IV}(R-NH_2)(R′-NH_2)Cl_4]. The reason for the oxidation of platinum is not clear. In such cases, *trans*-tetrachloroplatinum(IV) complexes were reacted with $N_2H_4 \cdot 2HCl$ to obtain corresponding *trans*-dichloroplatinum(II) complexes (6). Finally, platinum(II) complexes were oxidized with 30% H_2O_2 to obtain the *trans*-hydroxy platinum(IV) complex *trans*-[Pt^{IV}(R-NH_2)(R′-NH_2)$(OH)_2Cl_2$] (7), which was then reacted with concentrated HCl to form corresponding tetrachloro complexes (8).

Additionally, *trans*-mixed diamine platinum complexes were prepared by following a well-established route that uses the difference in the *trans* effect of halide and amine ligands in platinum(II) complexes to achieve selective substitution and thus control of stereochemistry [19,20]. Platinum(II) complexes were oxidized to platinum(IV) complexes by following a reported procedure [21]. Reduction of *trans*-tetrachloro platinum(IV) complexes was carried out by modifying a previously reported procedure [19].

Finally, the *trans* geometry of platinum(II) complexes was confirmed using Kurnakow's test [22], which involves the addition of thiourea (tu) to the aqueous suspension of the sample. Upon gentle heating, *trans*-[Pt(amine)$_2Cl_2$] produced *trans*-[Pt(tu)$_2$(amine)$_2$]Cl_2, which is colorless, while the *cis*-isomer produced yellow [Pt(tu)$_4$]Cl_2. Complexes **1–6** showed no color.

TABLE II Infra red and ^{195}Pt NMR data for *trans*-mixed amine platinum complexes

Complex no.	*IR*, cm^{-1}			*^{195}Pt NMR*[c], ppm
	ν(N-H)[a]	*ν(Pt-N)*[b]	*ν(Pt-Cl)*[b]	
1	3140	617	352	−2232
2	3220	614	348	−2223
3	3240	610	353	−2216
4	3210	616	350	−2216
5	3217	612	356	−2196
6	3198	611	348	−2220
7	3248	619	348	−341
8	3192	620	351	−351
9	3175	619	352	−356
10	3237	612	349	−355
11	3218	610	350	−360
12	3216	618	347	−354
13	3225	622	351	−346
14	3222	621	355	−368

[a]Recorded in KBr pellets.
[b]Recorded in polyethylene pellets.
[c]Recorded in acetone.

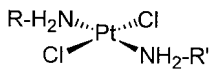


FIGURE 1 Chemical structure of *trans*-[Pt^{II}(R-NH_2)(R′-NH_2)Cl_2] where R = ethylamine or butylamine and R′ = methylamine, propylamine, isopropylamine, pentylamine, or hexylamine.

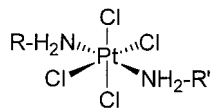


FIGURE 2 Chemical structure of *trans*-[Pt^{IV}(R-NH_2)(R′-NH_2)Cl_4] where R = ethylamine or butylamine and R′ = methylamine, propylamine, isopropylamine, pentylamine or hexylamine.

Characterization of the Platinum Complexes

The composition of each complex was determined using elemental analysis. There was good agreement between the calculated and found values (Table I). Also, the compounds were characterized using FT-IR and ^{195}Pt NMR spectroscopic techniques (results summarized in Table II). Additionally, Fig. 1 shows the general structure of platinum(II) complexes **1–6**. As expected, in the infrared spectra of mixed *trans*-amine platinum(II) complexes **1–6**, the N–H stretching vibrations were observed from 3140–3240 cm^{-1}. Also, the Pt–N stretching frequencies were observed ranging from 610–617 cm^{-1}. The single peaks observed in the range from 348–356 cm^{-1} were assigned for Pt–Cl stretching vibrations. Presence of single peaks in this region clearly indicates that chlorides are *trans* [23]. ^{195}Pt NMR spectra further confirmed the structures of these compounds; the ^{195}Pt NMR spectra of complexes **1–6** showed signals ranging from -2196 to -2232 ppm, which is characteristic of platinum(II) complexes that contain two nitrogen and two chlorine donor atoms [24].

In addition, the tetrachloroplatinum(IV) complexes **7–14** had a general structure (Fig. 2). The FT-IR spectra of these complexes did not show much difference as compared with platinum(II) complexes. The N–H stretching vibrations were observed from 3175–3248 cm^{-1}; the Pt–N stretching vibrations showed absorption ranging from 612–622 cm^{-1}, and the Pt–Cl stretching frequencies were observed ranging from 347–355 cm^{-1}. However, ^{195}Pt NMR spectra clearly differentiated platinum(IV) complexes **7–14** from platinum(II) analogs **1–6**. As oxidation of platinum(II) to platinum(IV) leads to large chemical shifts, the ^{195}Pt NMR spectra of complexes **7–14** showed signals ranging from -341 to -368 ppm, confirming the system in which platinum is surrounded by two nitrogen atoms and four chloride ions [24,25].

In summary, we have synthesized and characterized a series of new *trans*-mixed diamine platinum(II) dichloride complexes and their platinum(IV) tetrachloride analogs. The preliminary data, which we will publish elsewhere, indicate that these complexes show very good *in vitro* activity.

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