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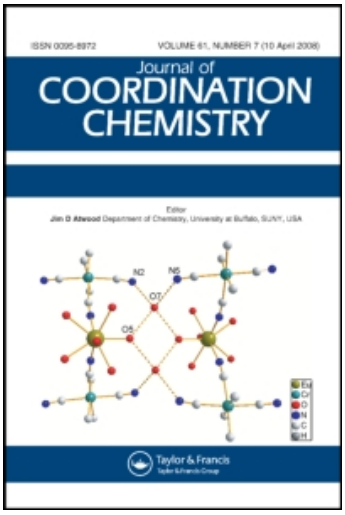

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SYNTHESIS AND CHARACTERIZATION OF A SERIES OF HYDROPHOBIC ANTITUMOR AMINE PLATINUM(II) CARBOXYLATES

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As part of a systematic study, a series of hydrophobic amine platinum(II) carboxylate complexes has been prepared as potential antitumor agents in a liposomal-entrapped form. These complexes have been characterized by elemental analysis, IR, ^{13}C and ^{195}Pt NMR spectroscopic techniques. Effect of ligand donors on NMR chemical shift is briefly discussed.

Keywords: Platinum, amine, carboxylate, hydrophobicity, synthesis

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INTRODUCTION

There has been a growing interest, in the cancer chemotherapy field, in the use of liposomes for transporting certain therapeutic agents.[1-4] Previous attempts to entrap *cis*-diaminedichloroplatinum(II) in liposomes were handicapped by its low entrapment efficiency (7.4%) and poor stability of the liposomal platinum complex.[5] Recently, we successfully designed and synthesized a series of highly lipid-soluble 1*R*,2*R*-diaminocyclohexaneplatinum(II) complexes that have high liposomal entrapment efficiency, stability and excellent antitumor activity.[6-11] Liposomal *cis*-bis(*neo*-decanoato)(*trans*-1*R*,2*R*-diaminocyclohexane)platinum(II) (*L*-NDDP) is currently undergoing clinical trials at the M. D. Anderson Cancer Center.[12] As part of our systematic investigation, we report here the syntheses and characterization of a series of hydrophobic platinum complexes containing ligands such as cyclopentylamine, cyclohexylamine, cycloheptylamine, pyrrolidine, hexamethyleneimine, 1-(2-aminoethyl)pyrrolidine, 1-(2-aminoethyl)piperidine and 4-(2-aminoethyl)morpholine and leaving groups such as *neo*-hexanoic acid, *neo*-heptanoic acid, *neo*-nonanoic acid and *neo*-decanoic acid.

EXPERIMENTAL

Cyclopentylamine, cyclohexylamine, cycloheptylamine, pyrrolidine, 1-(2-aminoethyl)pyrrolidine 1-(2-aminoethyl)piperidine and 4-(2-aminoethyl)morpholine were purchased from Aldrich Chemical Co. (Milwaukee, WI). *Neo*-hexanoic acid (*n*-C6), *neo*-heptanoic acid (*n*-C7), *neo*-nonanoic acid (*n*-C9) and *neo*-decanoic acid (*n*-C10) were obtained from Exxon Chemical Co. (Houston, TX) and K_2PtCl_4 was purchased from Johnson Matthey (Seabrook, NH). All compounds obtained from commercial suppliers were used as received.

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Elemental analyses were performed by Robertson Laboratories (Madison, NJ). ^{13}C NMR spectra of reported complexes were recorded in $CDCl_3$ solutions (reference: $CDCl_3$ peak at 77.00 ppm). ^{195}Pt NMR spectra were measured in $CHCl_3$ solution on an IBM NR 200/AF NMR spectrometer. A 5 mm NMR tube containing a D_2O solution of Na_2PtCl_4 was inserted into the 10 mm sample tube during acquisition of the spectra. The D_2O solution was utilized as a deuterium lock, while the Na_2PtCl_4 served as reference (−1621.0 ppm). Infrared spectra were recorded in KBr pellets using a Beckman 250MX spectrophotometer.

Preparation of Iodo Complexes

All iodo complexes $(A)_2PtI_2$ or $(A')PtI_2$, where A is cyclopentylamine, cyclohexylamine, cycloheptylamine, pyrrolidine or hexamethyleneimine, and A′ is 1-(2-aminoethyl)pyrrolidine, 1-(2-aminoethyl)piperidine or 4-(2-aminoethyl)morpholine were synthesized according to Dhara's method.[13] The preparation of *cis*-bis(cyclopentylamine)diiodoplatinum(II) is given here as an example. Potassium iodide (0.830 g, 5 mmol) was added to a filtered aqueous solution of K_2PtCl_4 (0.415 g, 1 mmol), and the reaction mixture was stirred for 10 min. Then, cyclopentylamine (0.170 g, 2 mmol) was introduced to the resultant K_2PtI_4 solution. After the reaction mixture was left for 1 h at room temperature, an orange precipitate was obtained. This was collected by filtration and repeatedly washed with water. The final product was dried in a vacuum desiccator (Yield: 81%).

Preparation of Complexes $(A)_2Pt(X)_2$

Complexes $(A)_2Pt(X)_2$, where A is cyclopentylamine, cyclohexylamine, cycloheptylamine, pyrrolidine or hexamethyleneimine and X is *neo*-hexanoate, *neo*-heptanoate, *neo*-nonanoate or *neo*-decanoate, were synthesized from their respective $(A)_2PtI_2$ complex along with the corresponding silver salts of *neo*-acids (prepared *in situ* by reacting sodium carboxylate with silver nitrate in the dark) in a light-shielded environment. For instance, *cis*-bis(cycloheptylamine)diiodoplatinum(II) (1.008 g, 1.5 mmol) was dissolved in 500 cm^3 of methylene chloride. To this, silver *neo*-hexanoate (0.666 g, 3 mmol) was added. The reaction mixture was left for 2 days at room temperature. The AgI precipitate was filtered off, and the filtrate was evaporated to dryness using a rotary evaporator. The oily residue obtained was treated with acetone. The resulting solid, *cis*-bis(cycloheptylamine)di-*neo*-hexanoatoplatinum(II), was further purified by treating with acetone/water (Yield: 51%).

Preparation of Complexes $(A')Pt(X)_2$

Bidentate amine platinum(II) complexes, $(A')Pt(X)_2$, where A′ is 1-(2-aminoethyl)-pyrrolidine, 1-(2-aminoethyl)piperidine or 4-(2-aminoethyl)morpholine, were prepared by the reaction of iodo complexes with the corresponding silver carboxylates. A typical experiment is described for the preparation of 4-(2-aminoethyl)morpholine-(di-*neo*-hexanoato)platinum(II) as an example. Silver *neo*-hexanoate (0.805 g, 3.6 mmol) was added to a chloroform solution of 4-(2-aminoethyl)morpholine-diiodoplatinum(II) (1.046 g, 1.8 mmol). The reaction mixture was stirred at room temperature for 2 days in the dark and then filtered. The solvent was evaporated under reduced pressure. The oily residue obtained was treated with acetone to give a white solid which was further purified as described above (Yield: 56%).

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RESULTS AND DISCUSSION

A series of hydrophobic platinum(II) carboxylate complexes has been prepared by using monodentate and bidentate amine ligands and *neo*-acids. A general synthetic method has been utilized to prepare these complexes (*1–5*). For monodentate amine (A):

$$K_2PtCl_4 + 4\,KI \longrightarrow K_2PtI_4 + 4\,KCl \qquad (1)$$

$$K_2PtI_4 + 2\,A \longrightarrow (A)_2PtI_2 + 2\,KI \qquad (2)$$

$$(A)_2PtI_2 + 2\,AgX \longrightarrow (A)_2Pt(X)_2 + 2\,AgI \qquad (3)$$

and for the bidentate amine (A′):

$$K_2PtI_4 + A' \longrightarrow (A')PtI_2 + 2\,KI \qquad (4)$$

$$(A')PtI_2 + 2\,AgX \longrightarrow (A')Pt(X)_2 + 2\,AgI \qquad (5)$$

After the tetrachloroplatinate was converted to tetraiodoplatinate, either two equivalents or one equivalent of amine, depending on the type of amine (*i.e.*, monodentate or bidentate), was added. The orange precipitate, $(A)_2PtI_2$ or $(A')PtI_2$ was collected by filtration and washed with water. Reaction of iodo platinum complex with silver carboxylate in chloroform yields the desired product in solution and a precipitate of AgI. The silver iodide can be separated by filtration. Evaporation of the filtrate results in an oily residue, which can be treated with acetone to yield a white solid product. Complexes can be further purified from acetone/water. Some complexes contain water, as evidenced by a broad O–H stretch near 3400 cm^{-1} in the infrared and by elemental analysis (Table I).

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TABLE I
Elemental analyses for the $(A)_2Pt(X)_2.yH_2O$ and $(A')Pt(X)_2.yH_2O$ complexes.

			Found (Calc.)		
A (or A′)	X	y	%C	%H	%N
cyclopentylamine	*n*-C6	0	44.46(44.36)	6.92(7.39)	4.42(4.71)
cyclohexylamine	*n*-C10	0	49.31(49.71)	8.39(8.80)	3.16(3.62)
cycloheptylamine	*n*-C6	0	47.52(47.90)	7.85(8.00)	4.10(4.30)
	n-C7	0	49.01(49.48)	7.85(8.25)	4.10(4.12)
	n-C9	0	52.02(52.24)	8.98(8.71)	3.67(3.81)
pyrrolidine	*n*-C9	1	46.66(46.67)	7.93(8.13)	3.99(4.19)
hexamethyleneimine	*n*-C6	0	46.10(46.21)	7.97(7.76)	4.46(4.49)
1-(2-aminoethyl)pyrrolidine	*n*-C6	1.5	37.82(38.12)	6.04(6.88)	4.67(4.94)
	n-C7	2	39.60(39.79)	6.85(7.25)	5.09(4.64)
	n-C9	0	45.99(46.20)	7.89(7.70)	4.34(4.50)
1-(2-aminoethyl)piperidine	*n*-C6	1	40.23(40.60)	6.72(7.03)	4.79(4.91)
	n-C7	1.5	41.53(41.47)	7.03(7.46)	4.60(4.61)
	n-C9	0.5	45.94(46.47)	7.83(7.95)	4.35(4.33)
4-(2-aminoethyl)morpholine	*n*-C6	0.5	38.01(38.30)	6.02(6.56)	4.62(4.96)
	n-C7	0	40.87(41.16)	6.76(6.86)	4.86(4.80)
	n-C9	0	44.84(45.06)	7.80(7.51)	4.14(4.38)
	n-C10	1.5	45.33(44.96)	7.64(7.92)	4.15(4.03)

The presence of the alkyl group, R, in the carboxylates (Figure 1) imparts lipid-solubility. Thus, all complexes are highly soluble in chloroform and other organic solvents, but completely insoluble in water. The complexes have been characterized by elemental analysis, infrared and NMR spectroscopy.

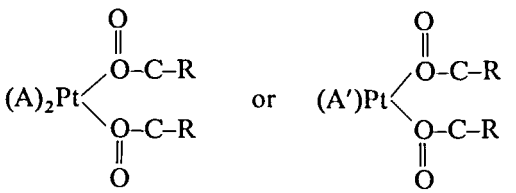

FIGURE 1 Structure of platinum complexes: A = monodentate and A' = bidentate amine and OCOR = *neo*-hexanoate (*n*-C6), *neo*-heptanoate (*n*-C7), *neo*-nonanoate (*n*-C9) or *neo*-decanoate (*n*-C10).

The stoichiometry of two amine ligands and two carboxylate leaving groups per platinum atom for monodentate amines (A) and of one amine ligand and two carboxylate leaving groups per platinum atom for bidentate amines (A') has been confirmed by elemental analysis (Table I). In all cases, the infrared spectra (Table II) display typical patterns expected for carboxylate ligands bound in unidentate fashion. The $\nu_a(COO^-)$ peaks appear in the range 1340 to 1395 cm^{-1}, while the $\nu_s(COO^-)$ bands appear in the range 1600 to 1640 cm^{-1}. Thus $\Delta\nu(=\nu_a(COO^-) - \nu_s(COO^-)) = 200$ to 300 cm^{-1}. These differences are characteristic of unidentate carboxylate ligands.[14-16] The N–H stretch in the region 3090 to 3230 cm^{-1} due to the amine ligands is also observed.

TABLE II
Infrared spectroscopic data[a] for the $(A)_2Pt(X)_2$ and $(A')Pt(X)_2$ complexes.

A (or A')	X	ν(N–H)	ν_a(COO)	ν_s(COO)
cyclopentylamine	*n*-C6	3188	1600	1350
cycloheptylamine	*n*-C6	3200	1600	1345
	n-C7	3215	1600	1395
	n-C9	3210	1600	1370
pyrrolidine	*n*-C9	3222	1600	1350
hexamethyleneimine	*n*-C6	3090	1600	1340
1-(2-aminoethyl)pyrrolidine	*n*-C6	3190	1610	1340
	n-C7	3215	1620	1345
	n-C9	3230	1610	1365
1-(2-aminoethyl)piperidine	*n*-C6	3210	1615	1340
	n-C7	3220	1620	1345
	n-C9	3230	1640	1350
4-(2-aminoethyl)morpholine	*n*-C6	3260	1625	1345
	n-C7	3230	1625	1350
	n-C9	3220	1620	1345
	n-C10	3230	1620	1350

[a] Infrared spectra were recorded in KBr pellets (cm^{-1}).

Other evidence for the structures shown in Figure 1 is obtained from the proton-decoupled carbon-13 NMR data for the carboxyl carbon in $CDCl_3$ (Table III). The

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^{13}C resonances of the carboxylate carbons give a single peak in the carbonyl region 185.1 to 190.1 ppm, which is close to values for carboxylate carbons reported for other platinum carboxylate complexes.[6,16] Therefore, the two carboxylate carbons in the platinum complexes are magnetically equivalent. Because the *neo*-decanoate ligand in the 4-(2-aminoethyl)morpholine complex consists of various different isomers, the $^{13}C\{^1H\}$ NMR spectrum of this complex was very complicated. Full analysis of the carbon-13 spectrum of this complex was not attempted.

These hydrophobic complexes have also been characterized by ^{195}Pt NMR spectroscopy in chloroform solution. The NMR spectra show only singlets in the range -1468.0 to -1834.1 ppm (Table III). Such chemical shift values are not unexpected for platinum(II) complexes that have two nitrogen and two oxygen donors.[17]

TABLE III
NMR spectroscopic data[a] for the $(A)_2Pt(X)_2$ and $(A')Pt(X)_2$ complexes.

A (or A')	X	^{13}C	^{195}Pt
cyclopentylamine	*n*-C6	187.8	−1718.0
cycloheptylamine	*n*-C6	187.6	−1720.8
	n-C7	187.6	−1719.0
	n-C9	188.6	−1700.0
pyrrolidine	*n*-C9	190.1	−1468.0
hexamethyleneimine	*n*-C6	188.4	−1548.6
1-(2-aminoethyl)pyrrolidine	*n*-C6	187.4	−1779.0
	n-C7	187.6	−1779.6
	n-C9	185.1	−1774.7
1-(2-aminoethyl)piperidine	*n*-C6	187.8	−1832.9
	n-C7	187.6	−1834.1
	n-C9	ND[b]	−1800.0
4-(2-aminoethyl)morpholine	*n*-C6	185.7	−1801.7
	n-C7	187.6	−1798.0
	n-C9	ND	−1795.2
	n-C10		−1794.6

[a] δC=O values are given in ppm relative to the $CDCl_3$ peak at 77.0 ppm. ^{195}Pt NMR spectra were recorded in $CHCl_3$ with the platinum-195 chemical shift being referenced to Na_2PtCl_4(−1621.0 ppm). [b] Not determined.

As seen in Table III, the leaving group, carboxylate, has little effect on the ^{195}Pt NMR chemical shift. For example, the chemical shifts for 4-(2-aminoethyl)morpholine complexes with different carboxylates range only from -1794.6 to -1801.7 ppm. On the other hand, various amine ligands exert a significant influence on the ^{195}Pt chemical shift. A downfield shift of the platinum-195 signal in the amine platinum complexes -1800 ppm to -1500 ppm in the imine platinum complexes is observed, and this shift is presumably due to the decreased electron density on the platinum atom bound to the imine ligand. This variation is also found for complexes with the same kind of nitrogen. For instance, the ^{195}Pt signal is shifted downfield from -1548.6 ppm for the hexamethyleneimine complex to -1468.0 ppm for the pyrrolidine complex.

In summary, we have synthesized a novel series of hydrophobic amine platinum(II) carboxylates to be investigated as potential antitumor agents.

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