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SYNTHESIS, CHARACTERIZATION, AND ANTITUMOR ACTIVITY OF PLATINUM(II) COMPLEXES OF MIXED AMMINE/AMINE WITH BIDENTATE CARBOXYLATES

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SYNTHESIS, CHARACTERIZATION, AND ANTITUMOR ACTIVITY OF PLATINUM(II) COMPLEXES OF MIXED AMMINE/AMINE WITH BIDENTATE CARBOXYLATES

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ABSTRACT

Complexes of the type $Pt(II)(CH_3NH_2)(NH_3)[(OC)_2-(CH_2)_n]\cdot 0.5H_2O$ [(**1**)–(**3**)] (n = 0, 1 and 2) have been synthesized for the first time. At the same time, we also have synthesized three precursor complexes. They were characterized by elemental analyses, molar conductance, differential thermal analyses and spectral (IR, UV, ^1H NMR) studies. *In vitro* antitumor activity results indicate that these complexes have significant activity against HL-60 and U937, but show poor activity against K562, (HL-60, U937 and K562 are human leukemic tumor cell lines).

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INTRODUCTION

Cisplatin and carboplatin are the presently used antitumor platinum drugs, but they have the disadvantages of exhibiting cross-resistance, requiring intravenous administration and producing severe acute and chronic toxicity. The requirement to circumvent acute nephrotoxicity and emesis frequently necessitates hospitalisation.

At the early stage of drug development, cisplatin analogs with either bis(alkylamine) or diamine as their non-leaving ligands and various anionic groups as their leaving groups were the main choice in this development effort. Recently some mixed ammine/amine platinum complexes have appeared in the literature. Preliminary results indicated that these new drugs were less toxic than the parent cisplatin[1–2]. Carboxylate (especially bidentate) platinum(II) complexes seem to be quite promising because they were less toxic and more soluble than the corresponding chloro analogs[3]. But few carboxylate platinum(II) complexes are reported.

Therefore, we synthesized three new mixed ammine/amine platinum complexes $Pt(CH_3NH_2)(NH_3)[(OCO)_2(CH_2)_n]\cdot 0.5H_2O$ ($n = 0$, 1 and 2). Also discussed are the properties and structures of these complexes.

EXPERIMENTAL

Materials

All chemicals used in this work were of analytical grade and purchased from the Shanghai Chem. Co. or Zhejiang Chem. Co.

Physical Measurements

C, H and N were analyzed using a Carlo Erba 1106 elemental analyzer. IR spectra were recorded in the region 4000–200 cm^{-1} (in KBr pellets) on a model-683 Perkin-Elmer infrared spectrophotometer. Electronic spectra were taken on an UV-3400 Toshniwal spectrophotometer. ^1H NMR spectra were obtained on a JEOL FX-90Q spectrometer at 90 MHz. Molar conductances were measured with a DDS-11A conductivity meter at 25 °C. TG-DTA were recorded on a RIGAKU 8150 thermal analyses meter.

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Antitumor Evaluation

Human leukemic tumor cells were maintained in a plastic culture flask containing RPMI 1640 culture medium (RPMI 1640 is a powder with Lglutamine without sodium bicarbonate) supplemented with PSN antibiotics (PSN is penicillin and streptomycin) mixture and 10% fetal bovine serum.

The cytotoxic activity of complexes was measured by an MTT assay (MTT is thiazoyl blue tetrazolium bromide). Briefly, a 96-well culture plate was dispensed in triplicate with 200 μL of culture medium containing the platinum complexes at several concentrations. The complexes were dissolved in normal saline solution as appropriate for maximal stability, and sterilized through 0.22 μm filter discs. Aliquots (0.1 mL) of a cell suspension (1×105 cells/mL) were then added, and after incubating for sixtyeight hours at 37 °C in 5% CO_2, 1×10^{-2} mL of a MTT solution (5×10^{-3} g/mL) was added to each well. After four hours of incubation, the medium was carefully removed, and replaced by 0.25 mL of 100% dimethyl sulfoxide to dissolve MTT formazan crystals. The plates were then agitated on a shaker for 5 min and absorbances were measured at 570 nm in a multiwell scanning spectrophotometer (model DG 3022A). The cytotoxicity was determined by expressing the mean optical densities for drug-treated cells at each concentration as a percentage of that of untreated cells, and IC_{50} values were calculated according to median effect analysis.

Preparation of Platinum Complexes

The precursor complexes *cis*-$Pt(CH_3NH_2)_2I_2$, $[Pt(CH_3NH_2)I_2]_2$ and *cis*-$Pt(CH_3NH_2)(NH_3)I_2$ were synthesized according to the literature[3].

$Pt(CH_3NH_2)(NH_3)[(OCO)_2(CH_2)_n]\cdot0.5H_2O$ (**1**)

Solid Ag_2CO_3 (1 mmol, 0.275 g) was added to an aqueous solution 40 mL of oxalic acid (1 mmol, 0.900 g) and 5 mL of methanol, followed by an equimolar amount of *cis*-$Pt(CH_3NH_2)(NH_3)I_2$. The mixture was stirred in the dark for 40 h, filtered twice through Celite, and the solution evaporated to dryness *in vacuo* and washed with diethyl ether and acetone. The pale yellow compound was dried under vacuum over P_4O_{10}. The synthetic procedures for $Pt(CH_3NH_2)(NH_3)[(OCO)_2(CH_2)_n]\cdot0.5H_2O$ (**2**) and $Pt(NH_3)(CH_3NH_2)[(OCO)_2(CH_2)_n]\cdot0.5H_2O$ (**3**) were similar.

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RESULTS AND DISCUSSION

All data of the precursor complexes are collected in Table I.

The formation of the complexes may be represented by the following equations:

$$K_2PtCl_4 \xrightarrow[CH_3NH_2]{KI} \textit{cis}\text{-}Pt(CH_3NH_2)_2I_2$$

$$Pt(CH_3NH_2)_2I_2 \xrightarrow{HClO_4} [Pt(CH_3NH_2)_2I_2]_2$$

$$[Pt(CH_3NH_2)_2I_2]_2 \xrightarrow{NH_3\cdot H_2O} \textit{cis}\text{-}Pt(CH_3NH_2)(NH_3)I_2$$

$$Pt(CH_3NH_2)(NH_3)I_2 \xrightarrow[\text{dicarboxylic acid}]{Ag_2CO_3} Pt(CH_3NH_2)(NH_3)[(OCO)_2(CH_2)_n]\cdot 0.5H_2O]$$

$$n = 0\ (\mathbf{1}); \qquad n = 1\ (\mathbf{2}); \qquad n = 2\ (\mathbf{3})$$

The physical and analytical data of the complexes (**1**)–(**3**) are presented in Table II. The new complexes are sparingly soluble in water, but insoluble in ethanol, ether and methanol. The molar conductivity of the complexes (**1**)–(**3**) in nitrobenzene indicated that they are non-electrolytes[4].They are quite stable in air and the thermal behaviour is similiar (see Table II).

Table I. Analyses and Other Data of the Precursor Complexes

Complex/Emprical Formula	Colour (Formula Wt.)	Decomp. Temp.(°C)	Found (Calcd.) (%) C	N	H	Yield (%)
cis-$Pt(CH_3NH_2)_2I_2$	Yellow	140	4.61	5.47	1.98	70
($C_2H_{10}N_2I_2Pt$)	(511.0)		(4.70)	(5.48)	(1.97)	
$[Pt(CH_3NH_2)I_2]_2$	Red brown	150	2.48	2.94	1.09	90
($C_2H_{10}N_2I_4Pt$)	(960.0)		(2.50)	(2.91)	(1.05)	
cis-$Pt(CH_3NH_2)(NH_3)I_2$	Yellow	125	2.56	5.72	1.68	70
($CH_8N_2I_2Pt$)	(497.0)		(2.42)	(5.64)	(1.62)	

Table II. Physical, Analytical, and Conductivity Data of the Complexes

No.	Complex/Empircal Formula	Colour (Formula Wt.)	Yield (%)	Decomp. Temp. (°C)	Λ_m ($S \cdot cm^2 \cdot mol^{-1}$)	Found (Calcd.) (%) C	N	H
(**1**)	$Pt(NH_3)(CH_3NH_2)[(OCO)_2]\cdot 0.5H_2O$ ($C_3H_9N_2O_{4.5}Pt$)	Pale yellow (340.2)	60	220	4.10	10.74 (10.59)	7.84 (8.24)	2.43 (2.37)
(**2**)	$Pt(NH_3)(CH_3NH_2)[(OCO)_2(CH_2)]\cdot 0.5H_2O$ ($C_4H_{11}N_2O_{4.5}Pt$)	Pale yellow (354.2)	60	210	4.86	14.06 (13.56)	7.71 (7.91)	3.07 (3.18)
(**3**)	$Pt(NH_3)(CH_3NH_2)[(OCO)_2(CH_2)_2]\cdot 0.5H_2O$ ($C_5H_{13}N_2O_{4.5}Pt$)	Pale yellow (368.3)	60	200	2.20	16.72 (16.31)	7.45 (7.61)	3.54 (3.56)

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IR Spectra

The important IR frequencies are listed in Table III. The υ(N-H) stretching frequencies of the precursor and new complexes show two medium strong bands at ~ 3240 and $\sim 3270\,cm^{-1}$. A new band appearing at 460–480 cm^{-1} is assigned to Pt-N stretching, confirming the presence of coordinated amines. The υ(Pt-I) stretching vibrations absorb below 200 cm^{-1} and were not observed as expected.

The carboxylate groups of the new complexes (**1**)–(**3**) show two bands, and intense antisymmetric carboxylate stretching $\upsilon_{as}(OCO^{-})$ and symmetric stretching $\upsilon_{as}(OCO^{-})$, at about 1650 and 1400 cm^{-1}, respectively.

Trends in the positions and the separation between these bands are the most useful tools in assigning structures from infrared spectra. The data of Table III show that the values of $\Delta\upsilon = \upsilon_{as}(OCO^{-}) - \upsilon_{s}(OCO^{-})$ of the complexes (**1**)–(**3**) are in the range 240–280 cm^{-1}, which is greater than Δv of the corresponding sodium oxalate, malonate or succinate. According to the literature, we may suggest that the carboxylate groups act as monodenate ligands in the complexes (**1**)–(**3**)[5]. At the same time, a new band appeared at about 580 cm^{-1} and is assigned to Pt-O stretching. This indicates that the carboxylate group takes part in coordination. Morever, the υ(O-H) band of the compexes (**1**)–(**3**) occurs as broad shoulder centered at 3500 cm^{-1}. Therefore, we suggest that the complexes (**1**)–(**3**) include water, and this is also confirmed by TG-DTA.

UV Spectra

The UV spectra of malonic acid and succinic acid in water show no absorption, while oxalic acid shows one absorption maximum at 212 nm. The complexes (**1**) and (**3**) did not show any absorption. Complex (**2**) had a new peak at about 193.18 nm.

^{1}H NMR Spectra

The important ^{1}H NMR spectral data are listed in Table IV. The ^{1}H NMR spectra (in D_2O as solvent) of the complexes (**1**)–(**3**) show doublets at about 2.30 and 4.70 ppm. They are assigned to the hydrogen atoms of the methyl group of the methylamine and the exchanging water (HOD). The shift of the methylene group of the complexes (**1**)–(**3**) is greater than that of free malonic acid and succinic acid. The ^{1}H NMR spectra also confirm the coordination of the ligands to platinum.

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Table III. Main IR Spectral Data of the Complexes

Compound	υ(O-H)	υ(N-H)	$\upsilon_{as}(COO^-)$	$\upsilon_{s}(COO^-)$	$\Delta\upsilon(COO^-)$	υ(Pt-N)	υ(Pt-O)
cis-$Pt(CH_3NH_2)_2I_2$		3240 s, 3270 s				470 w, 480 w	
$[Pt(CH_3NH_2)I_2]_2$		3230 s, 3270 s				480 w	
cis-$Pt(CH_3NH_2)(NH_3)I_2$		3240 s, 3280 s				470 w	
(**1**)	3500[a] m	3220 s, 3190 s	1680 s	1400 s	280	460 w	575 w
(**2**)	3500[a] m	3160 s, 3260 s	1650 s	1400 s	250	460 w	580 w
(**3**)	3500[a] m	3240 s, 3260 s	1640 s	1400 s	240	465 w	585 w

[a]Broad.

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Table IV. ^{1}H NMR Spectral Data of the Ligands and Complexes (**1**)–(**3**)

Compound	CH_3NH_2	$-CH_2$	HOD
Malonic acid		3.37 (s, 2H)	
Succinic acid		2.43 (s, 4H)	
(**1**)	2.20 (s, 3H)		4.70
(**2**)	2.37 (s, 3H)	3.71 (s, 2H)	4.70
(**3**)	2.30 (s, 3H)	2.51 (s, 4H)	4.70

Based on the above physical data, we conclude that in the dicarboxylate chelates with platinum(II) each carboxylate group coordinates to platinum(II) as monodentate ligand. The complexes (**1**)–(**3**) may have the following structure as shown in Fig. 1.

Antitumor Properties

Cytotoxicity data for the complexes (**1**)–(**3**) are presented in Table V. These data indicate a dose-dependent activity. The activity increases at higher doses. Complex (**3**) shows the highest activity against the three kinds of tumors. Complex (**2**) has the poorest antitumor activity. Morever, we find that according to the experimental results the complexes are sensitive to U937 and HL-60, but insensitive to K562.

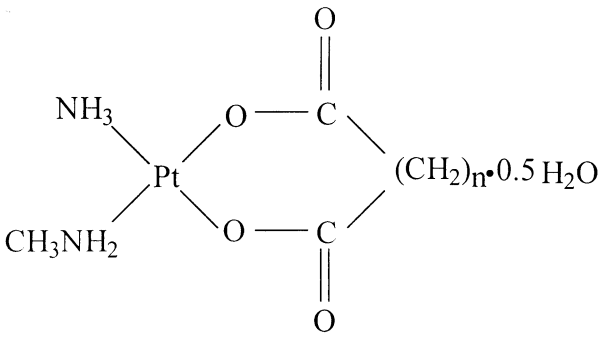

Figure 1. Suggested Structure of the Complexes. (n = 0 (**1**); n = 1 (**2**) and n = 2 (**3**)).

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Table V. *In Vitro* Antitumor Activities to HL-60, U937, and K562 Tumour Cell Lines

	HL-60	U937	K562
Compound	IC_{50} (μg/mL)		%Inhibition of 160 μg/mL
(**1**)	19.05	17.57	14.615
(**2**)	24.32	21.87	1.79
(**3**)	16.21	14.45	22.30

This class of platinum complexes seems to be quite promising, according to the experimental results and the literatures, since they have good antitumor activites and solubility in water. Accordingly, rapid development of this class of platinum complexes toward clinical trials is expected.

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