Antitumor Activities of Platinum Blues Containing α-Pyrrolidone, 3,3-Dimethylglutarimide, Orotic Acid, Succinamic Acid and Oxamic Acid

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Platinum pyrimidine blues are reported to exhibit antitumor activities against Sarcoma 180 [1]. The advantage of these blue platinum complexes over the well established *cis*-$Pt(NH_3)_2Cl_2$ (DDP) is their low nephrotoxicities [1–4]. Due to poor reproducibility in their syntheses and lack of single crystal X-ray diffraction analysis, they have long been considered as ambiguous unidentified compounds with no definite formulas, and their structures and properties have been left unclarified. The author has over the past few years synthesized a series of model compounds for platinum pyrimidine blues by using a simple cyclic amide ligand, α-pyrrolidone, in place of pyrimidine and has elucidated their amide-bridged tetranuclear structures, $[Pt_4(NH_3)_8(C_4H_6NO)_4]^{n+}$ (n = 5, 6, 8), and novel mixed-valent nature containing Pt(II) and Pt(III) [5–11]. Furthermore, $[Pt_4(NH_3)_8(C_4H_6NO)_4]^{m+}$ (m = 6 and 8) have been found to oxidize water to molecular oxygen, being themselves reduced to $[Pt_2(NH_3)_4(C_4H_6NO)_2]^{2+}$ and $[Pt_4(NH_3)_8(C_4H_6NO)_4]^{6+}$, respectively [11, 12].

With this recently obtained knowledge concerning the redox behavior of these compounds in mind, the antitumor activity against L1210 has been tested and is reported in this paper for several platinum blue compounds. The effects of the platinum oxidation states and differences of counter anions in these compounds are discussed.

Experimental

Syntheses of the Platinum Complexes

cis-Diammineplatinum α-pyrrolidone tan nitrate, $[Pt_4(NH_3)_8(C_4H_6NO)_4](NO_3)_6 \cdot 2H_2O$ [5, 6], and *cis*-diammineplatinum α-pyrrolidone green nitrate, $[Pt_4(NH_3)_8(C_4H_6NO)_4](NO_3)_{5.48} \cdot 3H_2O$ [7], were prepared according to the previously reported procedures. The dodecanesulfonate, tridecanesulfonate and β-naphthalenesulfonate of *cis*-diammineplatinum α-pyrrolidone tan cation were synthesized by adding the sodium salt of each sulfonic acid to an aqueous solution of *cis*-diammineplatinum α-pyrrolidone tan nitrate. Dark red precipitates of each sulfonate salt were immediately obtained. *cis*-Diammineplatinum 3,3-dimethylglutarimide blue, $[Pt_4(NH_3)_8(C_7H_{10}NO_2)_4](PF_6)_4(NO_3) \cdot 8H_2O$ [13], orotic acid blue [14], succinamic acid blue [15] and oxamic acid blue [14] were prepared according to the reported procedures. Each compound was confirmed by elemental analyses (C, H and N). The dodecanesulfonate, tridecanesulfonate and β-naphthalenesulfonate of *cis*-diammineplatinum α-pyrrolidone tan were confirmed by both elemental analyses and UV–Vis spectra (λ_{max} = 478 nm).

Antitumor Activity Measurement

The antitumor activity of each compound was tested on CDF_1 mice injected intraperitoneally with 10^6 cells of L1210. The treatment with the platinum compounds was carried out intraperitoneally on six mice in a group on days 1, 5 and 9. The antitumor activity is expressed as T/C (%), which is a ratio of the life-spans for treated to untreated groups.

Results and Discussion

Elemental analyses of the dodecanesulfonate, tridecanesulfonate and β-naphthalenesulfonate of *cis*-diammineplatinum α-pyrrolidone tan are shown in Table I.

TABLE I. Elemental Analyses

Salts of *cis*-diammineplatinum α-pyrrolidone tan	Analysis, found (calc.) (%)		
	C	H	N
Dodecanesulfonate, $[Pt_4(NH_3)_8(C_4H_6NO)_4](C_{12}H_{25}SO_3)_6 \cdot 5H_2O$	37.29 (37.22)	7.30 (7.33)	5.60 (5.92)
Tridecanesulfonate, $[Pt_4(NH_3)_8(C_4H_6NO)_4](C_{13}H_{27}SO_3)_6$	39.85 (39.74)	7.42 (7.16)	5.94 (5.85)
β-Naphthalenesulfonate, $[Pt_4(NH_3)_8(C_4H_6NO)_4](C_{10}H_7SO_3)_6$	36.52 (36.74)	3.62 (3.66)	6.58 (6.76)

The dodecanesulfonate and tridecanesulfonate are insoluble in water but soluble in CH_2Cl_2, $CHCl_3$ and CCl_4. These are the first platinum blues that are soluble in non-polar organic solvents. These solubility differences are expected to cause different cell membrane permeability and therefore to result in different antitumor activities. The β-naphthalenesulfonate is insoluble in water and all the usual organic solvents. Except for these sulfonates, all the other platinum blues and tans tested in the present study are highly soluble in water and insoluble in organic solvents.

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TABLE II. Antitumor Activity of some Platinum Blues against L1210

Complex	Dose (mg/kg)	*T/C* (%)
α-Pyrrolidone tan nitrate, $[Pt_4(NH_3)_8(C_4H_6NO)_4](NO_3)_6 \cdot 2H_2O$	12.5	102
	25	102
	50	111
	100	115
	200	123
	400	0
α-Pyrrolidone green nitrate, $[Pt_4(NH_3)_8(C_4H_6NO)_4](NO_3)_{5.48} \cdot 3H_2O$	50	113
	100	113
	200	90
α-Pyrrolidone tan dodecanesulfonate, $[Pt_4(NH_3)_8(C_4H_6NO)_4](C_{12}H_{25}SO_3)_6 \cdot 5H_2O$	50	113
	100	109
	200	119
α-Pyrrolidone tan tridecanesulfonate, $[Pt_4(NH_3)_8(C_4H_6NO)_4](C_{13}H_{26}SO_3)_6$	6.25	136
	12.5	136
	25	133
α-Pyrrolidone tan β-naphthalenesulfonate, $[Pt_4(NH_3)_8(C_4H_6NO)_4](C_{10}H_7SO_3)_6$	12.5	104
	25	110
	50	126
3,3-Dimethylglutarimide blue, $[Pt_4(NH_3)_8(C_7H_{10}NO_2)_4](PF_6)_4(NO_3) \cdot 8H_2O$	25	108
	50	108
	100	124
Orotic acid blue	50	120
	100	102
	200	122
	400	107
Succinamic acid blue	50	109
	100	104
	200	120
	400	109
Oxamic acid bluc	50	109
	100	100
	200	122
	400	112

The results of the antitumor activity test are summarized in Table II. Although platinum pyrimidine blues are reported to exhibit high antitumor activity against Sarcoma 180 [1], the platinum blues reported in this paper have generally rather marginal activity against L1210, except for a few complexes. From the comparison of the nitrate salts of α-pyrrolidone tan and green, it seems that the difference in the platinum oxidation state (the average Pt oxidation state is 2.5 for the tan complex [5] and 2.37 for the green [7]) has little effect on antitumor activity. In a comparison of several sulfonates and nitrates on the tan cation, it is noteworthy that only the tridecanesulfonate exhibits high activity at extremely low dose levels. This might be related to the solubility characteristics of the complexes, since only the dodecanesulfonate and tridecanesulfonate are soluble in non-polar organic solvents, which implies that transport of the drug across the cell membrane would be easier for these compounds. However, the low activity of the dodecanesulfonate shows that antitumor activity cannot be explained only by cell membrane transport.

Platinum blues and tans listed in Table II are generally less toxic than DDP, as shown in their higher dose levels than that for DDP. With DDP at dose levels higher than 12.5 mg/kg, only toxicity dominates, which leads to death of the mouse.

The present study shows that variation of the counter anion in platinum blues drastically changes the solubility of the salt, which in some cases leads to higher antitumor activity.

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