Synthesis and Antitumor Activity of Platinum(II) Complexes Containing the Selenito Ligand

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Since the discovery of the antineoplastic agent cisplatin (cDDP) by Rosenberg *et al.* [1], the drug has been in wide-spread use to date. However, because of its toxic side-effects, particularly renal damage, the search for safer platinum complexes and administration methods is still continuing. The combined use of cDDP and other compounds has often been attempted. Imura *et al.* [2] reported that sodium selenite prevented the renal toxicity of cDDP and gave little effect on the antitumor activity to mice carrying Ehrlich ascites tumor cells. Berry *et al.* [3] also reported a similar effect of selenious acid on the treatment of murine fibrosarcoma. Thus, the combination of selenite and cDDP in chemotherapy has become of much interest in recent years. We expected that platinum(II) complexes containing the selenito ligand would show high antitumor activity and lower toxicity than cDDP. There have been reported only a few mononuclear selenito complexes: amine cobalt complexes [4, 5] and *cis*-$Pt(PPh_3)_2SeO_3$ [6]. In this paper we report the synthesis and antitumor activity of some diamineplatinum(II) complexes containing the selenito ligand.

Experimental

As the diamine ligand, we used (1*R*,2*R*)-chxn (chxn = 1,2-cyclohexanediamine), *trans*-cotn (cotn = 1,2-cyclooctanediamine) and ammines. Isomers of chxn were resolved according to the reported method [7]; cotn was prepared according to the reported scheme for cyclopentadiamine synthesis [8]; the *trans*-isomer of cotn was separated by use of nickel(II) chloride in a modification of the published method [9]. Dinitratodiamineplatinum(II) was synthesized via dichlorodiamineplatinum(II) according to the reported method [10].

Synthesis of Pt[1R, 2R)-chxn](SeO$_3$)

Pt[(1*R*,2*R*)-chxn]$(NO_3)_2$ (8.6 mmol) was dissolved in water (100 ml) at 40 °C. The solution was passed through a column packed with anion exchange resin (OH^- type). Selenium dioxide (8.1 mmol) was added to the eluate and the reaction mixture was left overnight at ambient temperature. The resulting solution was concentrated until a small amount of yellow solid appeared, and a further powdery solid was precipitated by the addition of methanol. The precipitate was filtered, washed with cold water, then with methanol, and dried *in vacuo*. An additional crop was obtained from the filtrate. The total yield was 74%.

Pt(*trans*-cotn)(SeO_3) and *cis*-$Pt(NH_3)_2(SeO_3)$ were also synthesized by a similar method.

When selenium dioxide was added in more than the stoichiometric amount of starting platinum complex, an unidentified blue–black solid formed and the yield of selenito complex was lowered. The undesirable formation of blue–black solid was avoided by addition of the dinitrato complex in a small excess or by the further addition of sodium selenite in a small amount.

Antitumor Assay in vivo

L1210 cells (10^5) were transplanted intraperitoneally (i.p.) into $CD2F_1$ mice. The samples were administered i.p. on days 1, 5 and 9 after tumor inoculation. The antitumor activity is expressed as *T/C* (%), the ratio of mean survival days for treated and control groups. Treated and control groups consisted of 6 and 10 mice, respectively. A *T/C* (%) value of over 125 is regarded as significant antitumor activity.

Results and Discussion

All the complexes are yellow powdery solids. We have so far been unsuccessful in attempts to obtain any crystalline substance. Elemental analyses given in Table I show that each compound is represented by the formula Pt(diamine)·SeO_3.

TABLE I. Elemental Analyses (%) of Pt(diamine)(SeO_3) (found (calc.))

Complexes	C	H	N	Se[a]
Pt(chxn)(SeO_3)	16.23 (16.52)	3.45 (3.23)	6.31 (6.42)	18.19 (18.10)
Pt(cotn)(SeO_3)	20.51 (20.70)	3.85 (3.91)	6.03 (6.03)	16.92 (17.01)
$Pt(NH_3)_2(SeO_3)$	0.00 (0.00)	1.78 (1.70)	7.61 (7.87)	21.79 (22.17)

[a]Selenium content was determined by ion chromatography.

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TABLE II. IR Data of Pt(diamine)(SeO_3)[a] (SeO_3 moiety 450–850 cm^{-1}) (KBr pellet)

Complexes	Absorption frequency (cm^{-1})			
	ν_1'	ν_2'	ν_5'	ν_3'
Pt(chxn)(SeO_3)	834m	723s	694s	518m
Pt(cotn)(SeO_3)	838s	730s	693m	520m
$Pt(NH_3)_2(SeO_3)$	828s	742s	720s	522s
	ν_1	ν_3	ν_2	
Na_2SeO_3	792s	740s, br	457s	

[a] s, strong; m, medium; br, broad.

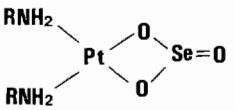

Fig. 1. Proposed structure of selenito complexes: RNH_2 = NH_3; $2RNH_2$ = 1,2-cyclohexanediamine or 1,2-cyclooctanediamine.

The solid-state IR spectrum of each complex exhibited four characteristic absorption bands derived from the SeO_3 moiety in the 500–850 cm^{-1} region (Table II). Fowless and Stranks [4] reported that free selenite exhibited a broad absorption band assigned as degenerate Se–O antisymmetric stretching (ν_3) at 742 cm^{-1} and that the selenite coordinating to cobalt via oxygen exhibited two bands (ν_2' and ν_5') in the region. Our compounds also exhibited two distinct bands in the 690–750 cm^{-1} region, although the splittings were somewhat smaller than those of the cobalt complexes [4]. From the above-mentioned results, we conclude that the selenito ligand coordinates to platinum via oxygen as a bidentate ligand (Fig. 1).

In aqueous solution, Pt(chxn)(NO_3)$_2$ and Pt(chxn)(SO_4)(H_2O) are rapidly hydrolyzed to the cationic diaquo species [11]. The solution of selenitoplatinum complexes which was almost neutral, however, showed much smaller electrical conductivity than the solution of the dinitratoplatinum complex (Table III). Furthermore, Pt[(1*R*,2*R*)chxn](SeO_3) containing an optically active ligand showed longer wavelength shifts of CD bands than Pt[(1*R*,2*R*)-chxn]$(H_2O)_2$ [12]. Thus, we consider that the selenitoplatinum complexes are not readily hydrolyzed. In order to obtain further information in solution, we tried ^{195}Pt or ^{77}Se NMR measurement, but unfortunately could not get any data on the complexes owing to their low solubilities.

The antitumor activity of the selenito complexes is listed in Table IV. The diammine complex had no significant antitumor activity. Both the chxn and cotn complexes, however, had higher antitumor activity than cDDP. Thus, it should be emphasized that selenite is a potent ligand as the leaving group in antitumor diamineplatinum(II) complexes.

TABLE III. Electrical Conductivity of an Aqueous Solution of Pt(diamine)(SeO_3)

Complexes	Λ (Scm^2/mol) (2 mM, 15 °C)
Pt(chxn)(SeO_3)	29
$Pt(NH_3)_2(SeO_3)$	30
Pt(chxn)(NO_3)$_2$	250
Na_2SeO_3	215

TABLE IV. Antitumor Activity against Mouse Leukemia L1210[a]

Complexes	*T/C* (%) at dose (mg kg^{-1})			
	100	20	10	5
Pt(chxn)(SeO_3)	toxic	188P	302P (3/6)	246P (2/6)
Pt(cotn)(SeO_3)		169P (1/6)	329P (4/6)	271P (3/6)
$Pt(NH_3)_2(SeO_3)$		toxic	123	108

[a] P = positive; (*X*/6) = number of cured mice (30 days).

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