SYNTHESIS AND ANTITUMOR ACTIVITY OF PLATINUM COMPLEXES WITH CYCLIC THIOAMIDES†

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Abstract —— Platinum(II) complexes with 2-mercaptopyridine, 2-thiouracil, and ethylenethiourea have been synthesized. Some of them showed antitumor activity against Sarcoma 180 in mice.

Since the discovery of antitumor activity of cis-$[PtCl_2(NH_3)_2]$,[1] many researches have been carried out to develop new platinum complexes, being more effective and less toxic.[2,3] It has been suggested that a pair of strongly covalent-bonded ligands in cis-configuration and a pair of moderately labile ligands are required for a potential antitumor platinum complex.[4] As platinum(II) is a soft-acid type metal ion, a sulfur atom being a representative of soft type ligands will strongly coordinate to it. The antitumor activity of few complexes with sulfur-containing ligands has been investigated,[5] and we, thereore, have synthesized ammine platinum complexes with cyclic thioamides and tested their antitumor activity.

Thioamide platinum(II) complexes were synthesized by the following general procedure. To an aqueous solution of $[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ [6] (1 mmol), was added 1 or 2 mmol of thioamide dissolved in water.[7] The pH was adjusted with NH_4OH to 7.0, and immediately yellow or orange precipitates were deposited. The mixture was stirred for 2 hr at room temperature. The precipitates were filtered off and dried in a vacuum desiccator over $CaCl_2$ overnight.

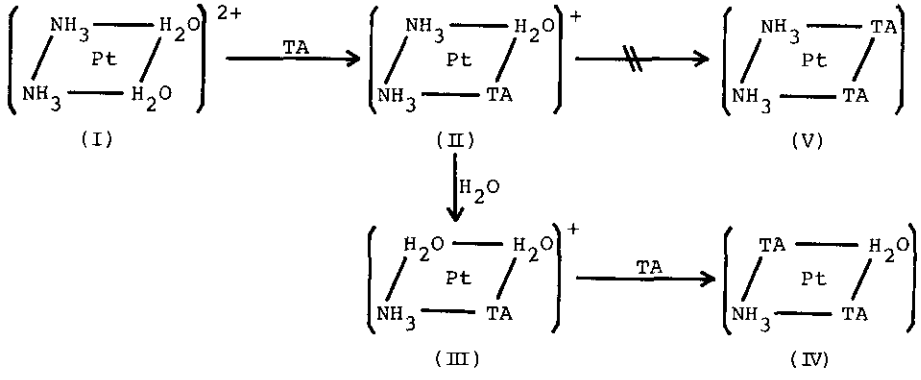
The results of the elementary analysis and yields for the complexes obtained are given in Table 1.

When the equimolar ratio of $[Pt(NH_3)_2(H_2O)_2]^{2+}$ and cyclic thioamide(TA) was reacted, the product obtained was $[Pt(NH_3)(H_2O)_2(TA)]NO_3$, but not $[Pt(NH_3)_2(H_2O)(TA)]NO_3$.

Table 1. Analytical Data and Yields of Platinum Complexes

Compound		Anal. %C	%H	%N	%S	Yield %
2-Mercaptopyridine						
$[Pt(NH_3)(H_2O)_2(C_5H_4NS)]NO_3$	Calcd.	14.9	2.6	10.0	7.6	
	Found	15.0	2.0	10.6	7.8	10.0
$[Pt(NH_3)(H_2O)(C_5H_4NS)_2]$	Calcd.	26.7	2.9	9.3	14.3	
	Found	26.9	2.5	10.0	14.7	90.1
2-Thiouracil						
$[Pt(NH_3)(H_2O)_2(C_4H_3N_2OS)]NO_3$	Calcd.	11.0	2.3	12.8	7.3	
	Found	10.9	2.1	13.1	7.4	43.7
$[Pt(NH_3)(H_2O)(C_4H_3N_2OS)_2]$	Calcd.	19.8	2.3	14.5	13.2	
	Found	19.9	2.3	14.7	13.3	3.1
Ethylenethiourea						
$[Pt(NH_3)(H_2O)_2(C_3H_5N_2S)]NO_3$	Calcd.	8.7	3.0	13.6	7.7	
	Found	8.0	3.1	13.5	6.6	5.4
$[Pt(NH_3)(H_2O)(C_3H_5N_2S)_2]$	Calcd.	16.6	3.5	16.2	14.8	
	Found	15.9	2.7	16.3	14.2	73.9

The pathway of the reaction has been proposed in the following scheme:



At first a labile H_2O molecule in $[Pt(NH_3)_2(H_2O)_2]^{2+}$ (I) will be replaced by a TA anion. The trans-effect of sulfur atoms is so strong that the NH_3 molecule at the

trans-position to the TA ligand in $[Pt(NH_3)_2(H_2O)(TA)]^+$ (II) will dissociate and the solvent H_2O molecule will coordinate to give $[Pt(NH_3)(H_2O)_2(TA)]^+$ (III). The reaction II → III would be too fast to isolate the complex II. When the metal-TA ratio was 1:2, $[Pt(NH_3)(H_2O)(TA)_2]$ (IV) was obtained (Table 1), but cis-dithioamide complex $[Pt(NH_3)_2(TA)_2]$ (V) was not able to be isolated. Because of the strong trans-effect of the sulfur-containing compounds,[8] the reaction II → III will be faster than the reaction II → V. Therefore, the H_2O molecule at the trans-position to the TA ligand in III dissociates and another TA coordinates instead of it to give IV. Type III complexes are very soluble in water, while type IV complexes which belong to an inner complex salt are less soluble in water but easily soluble in organic solvents.

As III has strongly bonded NH_3 and TA ligands of cis-configuration and a pair of labile H_2O molecules, such a type of complexes may be effective against tumor. The antitumor activity of the complexes obtained was tested according to the literature.[9] The results of the animal test are given in Table 2, using five Swiss mice per test. Ascites Sarcoma 180 was transplanted to mice intraperitoneally. Single injection of the saline solution of the complexes was given intraperitoneally on Day 1 only, and the dose range was 50-400 mg/kg.

Table 2. Activity of Platinum Complexes against Sarcoma 180 in Mice

Compound	Toxic Level (mg/kg)	Best ILS* (%)	Dose of best ILS (mg/kg)	Number of Cures
2-Mercaptopyridine				
$[Pt(NH_3)(H_2O)_2(C_5H_4NS)]NO_3$	>100	244	100	0
$[Pt(NH_3)(H_2O)(C_5H_4NS)_2]$	>400	>311	400	1
2-Thiouracil				
$[Pt(NH_3)(H_2O)_2(C_4H_3N_2OS)]NO_3$	>400	44	400	0
$[Pt(NH_3)(H_2O)(C_4H_3N_2OS)_2]$	200	11	100	0
Ethylenethiourea				
$[Pt(NH_3)(H_2O)_2(C_4H_3N_2S)]NO_3$	>400	333	200	1
$[Pt(NH_3)(H_2O)(C_4H_3N_2S)_2]$	100	11	50	0

* ILS means increase in lifespan.

Both of the mono- and bis(2-mercaptopyridine) complexes showed high antitumor activity on 60 day observation. The former was more effective than the latter in the same dose level, but was toxic to kill the mice in the higher dose level. The complexes with 2-thiouracil were less effective. It is interesting that the mono-(ethylenethiourea) complex is so effective in spite of the ineffectiveness of the bis(ethylenethiourea) complex. The complexes of the type, $[Pt(NH_3)(H_2O)_2(TA)]NO_3$, containing 2-mercaptopyridine and ethylenethiourea were effective, expectedly. In order to clarify the relationship between the activity and the structure of the complexes, the studies of platinum complexes with other sulfur-containing compounds are currently in progress.

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References

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