[Chem. Pharm. Bull. 34(9)3563—3572(1986)]

Synthesis and Antitumor Activity of *cis*-Dichloroplatinum Complexes Coordinating Nitrogen Cyclic or Sulfur Compounds

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(Received January 8, 1986)

cis-Dichloroplatinum complexes of nitrogen cyclic compounds and sulfur-containing compounds were synthesized through the reaction of K_2PtCl_4 with the corresponding ligands in water or an interfacial layer between water and an organic solvent. The effect of substituents of pyridine derivatives on the synthesis of the *cis*-platinum complexes depended greatly on their position. The coordination of 2-substituted pyridines required a long reaction time and the yields were low. That of 3- or 4-substituted pyridines proceeded smoothly in high yields. The complexes coordinating dimethyl- or trimethyl-substituted pyridines were obtained in low yields, but a methyl group at the *para* position increased the coordination activity of pyridines. The reactivity of other nitrogen cyclic compounds depended greatly on their structures and no clear correlation between structure and reactivity was observed. In some cases, polynuclear or unidentified complexes were formed. Sulfur-containing compounds reacted smoothly in high yields.

Three synthesized *cis*-dichloroplatinum(II) complexes coordinating di(3-methylpyridine), di(quinoline) and di(isoquinoline) and a polynuclear platinum piperidine complex ($Pt_4Cl_5(OH)_3$-$(C_5H_{11}N)_6 \cdot 3H_2O$) had high antitumor activities against Sarcoma 180 ascites in female ICR/CRJ mice. The required platinum weight of these effective complexes for antitumor activity was in the range of 23—94 mg/kg in mice compared with 5 mg/kg in the case of *cis*-dichlorodiammine-platinum.

Keywords——platinum complex; *cis*-dichlorodiammineplatinum(II); antitumor activity; toxicity; interfacial reaction; Sarcoma 180 tumor; *cis*-dichlorodi(3-methylpyridine)platinum(II); *cis*-dichlorodi(quinoline)platinum(II); *cis*-dichlorodi(isoquinoline)platinum(II)

The antitumor activity of *cis*-dichlorodiammineplatinum(II) ($[PtCl_2(NH_3)_2]$, **1**) was discovered by Rosenberg *et al.*,[1] and since then many platinum complexes have been synthesized and their antitumor activities examined against many tumor cell lines. However, antitumor platinum complexes which are more active at a small dosage and less toxic than **1** have not been reported.

In a series of Pt complexes of heteroaromatic and heterononaromatic ligands, only the ethyleneimine and pyrrolidine complexes showed antitumor activity. Other Pt complexes of O, S or P donors were almost inactive.[2]

In the previous paper, we reported the synthesis and antitumor activity of *cis*-platinum complexes coordinating aromatic amines.[3] In this paper we will report the synthesis and antitumor activity of platinum complexes coordinating nitrogen cyclic compounds and sulfur-containing compounds.

Experimental

Synthesis of *cis*-Platinum Complexes——Various ligand compounds were dissolved in the following solvents and

the solutions prepared were stoichiometrically added to 2 ml of an aqueous solution containing 0.207 g (0.5 mmol) of K_2PtCl_4 (**2**). The solvent was water (A), ethyl acetate (B), benzene (C), dichloromethane (D), 0.2 M (mol/dm^3) KOH aqueous solution (E) or 1 M (mol/dm^3) HCl (F) aqueous solution. The complex formation in A, E or F was performed without agitation, whereas that in B, C or D was done with agitation. All reactions were carried out in a dark room at room temperature. The resultant precipitates were filtered off, washed with small amounts of water and the organic solvent used, and then dried in a $CaCl_2$ desiccator.

Tables I—V summarize the reaction conditions and results (the kind of ligands, the amount of solvents, the reaction time, and the yield of products). The results of the elemental analyses and absorption peaks in the range of 400—600 cm^{-1} of the complexes synthesized are listed in Table VI. The platinum complexes synthesized gave reproducible values, compatible with those expected, in elemental analyses.

Antitumor Activity Test——The antitumor activity of the platinum complexes was determined against ascites Sarcoma 180 tumor in mice. One million cells of Sarcoma 180 were transplanted intraperitoneally (i.p.) into female ICR/CRJ mice on day 0 of each test. On the next day (day 1), a saline suspension containing an arbitrary amount of platinum complex at a dosage of 10 ml/kg saline was injected i.p. into mice by single administration and the life spans of mice were observed for 60 d. Antitumor activity was expressed as T/C (%), which was calculated by means of the following equation.

$$T/C\ (\%) = L_T/L_C \times 100$$

L_T: average survival time of treated animals in days.
L_C: average survival time of untreated controls in days.

Five mice were used in each group. The antitumor activity was evaluated as follows: (+), T/C 150—199%; (++), 200—299%; (+++), >300%; (−), <150%. No evaluation was performed with animal groups in which deaths occurred due to toxicity. Such deaths were evaluated as the number of mice which died within 5 d.

Results and Discussion

Synthesis of *cis*-Platinum Complexes

The generalized structure of most of the platinum complexes synthesized in this work can be expressed as (*cis*-$[PtCl_2L_2]$, **3**) (L = ligand). Formation of *cis*-geometry of Pt complexes is

TABLE I. Reaction Conditions and Yields of Coordination Products of Pyridine Derivatives to **2**[a]

No.	R	Position of substituent group	Solvent[b]	(ml)	Reaction time (d)	Yield (%)
1	OH	2	A	3	8	—[c]
2		3	A	2	2	67
3		4	A	2	19	31
4	NH_2	2	A	1	1	74
5		3	A	2	2	72
6		4	A	2	2	78
7	CH_3	2	A	2	2	47
8		3	A	2	1	86
9		4	A	2	1	87
10	C_2H_5	2	C	2	37	65
11		3	C	2	4	68
12		4	C	2	6	80
13	CN	2	B	2	2	77
14		3	A	2	2	88
15		4	A	2	2	87
16	C_5H_4N	2	B	2	1	38
17		4	B	3	3	85
18	$2CH_3$	3, 4	C	2	6	77

a) **2** (0.5 mmol) was dissolved in 2 ml of H_2O. *b*) A, H_2O; B, ethyl acetate; C, benzene. *c*) No reaction product was formed.

due to the *trans* effect originating from the platinum metal: *cis* complexes are usually stable at room temperature, but at higher temperature, the *cis* form isomerizes to the *trans* one.[4] The infrared (IR) spectra of the synthesized Pt complexes showed weak absorptions at 400—600 cm^{-1} (Pt–N stretching). This absorption is due to *cis*-form platinum complex.[5] In some cases, polynuclear platinum complexes were formed, as discussed later.

As shown in Table I, the substituent effect of hydroxy (Nos. 1—3), amino (Nos. 4—6), methyl (Nos. 7—9), ethyl (Nos. 10—12) and cyano (Nos. 13—15) groups depended greatly on their position in pyridine derivatives. The *cis*-platinum complexes coordinating 2-substituted pyridines were generally obtained in low yields in spite of a long reaction time, perhaps due to steric hindrance of the *ortho* substituents. However, the complex coordinating 2-aminopyridine (No. 4) was obtained in a high yield in a short time. This may suggest accelerated

Table II. Reaction Conditions and Yields of Coordination Products of Quinoline, Isoquinoline and Indole Derivatives to **2**[a]

No.	Ligand	Solvent[b]	(ml)	Reaction time (d)	Yield (%)
19	Quinoline	C	2	2	43
20	3-Aminoquinoline	C	2	5	81
21	8-Aminoquinoline	A	1	4	38
22	Quinaldine	B	2	13	47
23	Quinoline-8-sulfonylchloride	C	10	1	59
24	1,2,3,4-Tetrahydroquinoline	C	1	8	41
25	Quinidine	D	2	16	17
26	Quinine	D	5	28	54
27	Isoquinoline	B	2	1	62
28	Papaverine	A	10	2	96
29	Indole	C	2	4	22
30	Indoline	B	2	3	53
31	Strychnine	D	7	3	63
32	Brucine	B	16	1	78

a) **2** (0.5 mmol) was dissolved in 2 ml of H_2O. *b*) A, H_2O; B, ethyl acetate; C, benzene; D, CH_2Cl_2.

Table III. Reaction Conditions and Yields of Coordination Products of Pyrimidine, Imidazole, Purine and 1,3,5-Triazine Derivatives to **2**[a]

No.	Ligand	Solvent[b]	(ml)	Reaction time (d)	Yield (%)
33	Pyrimidine	A	1	4	93
34	4-Hydroxypyrimidine	A	2	24	77
35	Cytosine	A	14	4	38
36	Imidazole	A	1	8	87
37	2-Imidazolidinethione	A	3	2	100
38	Purine	A	2	3	90
39	Adenine	A	5	1	62
40	Hypoxanthine	F	2	8	68
41	Xanthosine	E	8	18	59
42	1,3,5-Triazine	A	2	19	16
43	Acetoguanamine	A	10	2	37
44	Benzoguanamine	F	10	2	91
45	Melamine	E	10	7	66

a) **2** (0.5 mmol) was dissolved in 2 ml of H_2O. *b*) A, H_2O; E, 0.2 M KOH; F, 1 M HCl.

coordination by the amino group. On the other hand, the complexes coordinating 3- or 4-substituted pyridines (except No. 3) were obtained within a short time in high yields. 4-(2,2′-Diamino)ethylpyridine, 4-dimethylaminopyridine and nicotine (not shown in Table I) formed unidentified Pt complexes. Shorter reaction time and higher yields in the reactions of **2** with 3- or 4-substituted pyridines may be attributable to the reduced steric hindrance compared with the case of 2-substituted pyridines.

In the reactions of **2** with dimethyl- or trimethyl-substituted pyridines, the 3,4-dimethylpyridine complex (No. 18) was obtained in a satisfactory yield (77%). 2,3-Dimethylpyridine complex was obtained in a low yield (29%), as were the complexes of 2-substituted pyridine derivatives, but needed only a short reaction time (2 d). 2,6-Dimethylpyridine did not react, probably due to the steric hindrance at both *ortho* positions. 2,4,6-Trimethylpyridine gave an unidentified platinum complex. These results also suggested that a methyl group at the *para* position increased the coordination activity of pyridine derivatives. However, the reaction of **2** with 2,4-dimethylpyridine needed a fairly long reaction time (23 d) and gave a low yield (48%), perhaps due to steric hindrance.

Table II summarizes the reactions between **2** and quinoline, isoquinoline, or indole derivatives. In general, quinoline derivatives coordinated **2** in low yields. However, the complex coordinating 3-aminoquinoline (No. 20) was obtained in a high yield. This may suggest coordination by an amino group. The complexes coordinating 2,2′-biquinoline and cinchonidine were not identified. The complexes coordinating isoquinoline (No. 27) and isoquinoline derivative of papaverine (No. 28) were obtained in high yields within a short

TABLE IV. Reaction Conditions and Yields of Coordination Products of Nitrogen Cyclic Compounds to **2**[a]

No.	Ligand	Solvent[b]	(ml)	Reaction time (d)	Yield (%)
46	2,9-Dimethyl-1,10-phenanthroline	B	2	1	34
47	Methylene blue	A	10	6	98
48	Piperidine	A	1	1	71
49	Piperazine	A	0.5	2	79
50	4-Aminoantipyrine	A	2	1	77
51	1,4-Diazabicyclo[2.2.2]octane	A	2	2	76
52	1,8-Diazabicyclo[5.4.0]undecene-7	C	2	1	76
53	1,4,8,11-Tetraazacyclooctadecane	B	15	1	86
54	Hexamethylenetetramine	A	2	2	100

a) **2** (0.5 mmol) was dissolved in 2 ml of H_2O. *b*) A, H_2O; B, ethyl acetate; C, benzene.

TABLE V. Reaction Conditions and Yields of Coordination Products of Sulfur Compounds to **2**[a]

No.	Ligand	Solvent[b]	(ml)	Reaction time (d)	Yield (%)
55	Diethyldithiocarbamate[c]	A	2	1	83
56	Xanthogenate[d]	A	2	2	90
57	*O,O′*-Dimethyl dithiophosphate	B	2	7	76
58	3,6-Dithiaoctane	B	2	1	77
59	Dimethyl disulfide	C	2	1	73

a) **2** (0.5 mmol) was dissolved in 2 ml of H_2O. *b*) A, H_2O; B, ethyl acetate; C, benzene. *c*) Sodium salt. *d*) Potassium salt.

TABLE VI. Elemental Analysis of Obtained Complexes

No.	Formula	Analysis (%) Calcd (Found)						IR (cm^{-1}) Pt–N
		C	H	Cl	N	Pt	S	
2	$[PtCl_2(C_5H_5NO)_2]^{a)}$	26.33	2.21	15.54	6.14	42.76		430
	$C_{10}H_{10}Cl_2N_2O_2Pt$	(27.83	2.32	13.87	6.43	42.16)		
3	$[PtCl_2(C_5H_5NO)_2]$	26.33	2.21	15.54	6.14	42.76		505
	$C_{10}H_{10}Cl_2N_2O_2Pt$	(26.63	2.25	14.10	6.60	41.94)		
4	$[PtCl_2(C_5H_6N_2)_2]$	26.44	2.66	15.61	12.34	42.95		450
	$C_{10}H_{12}Cl_2N_4Pt$	(26.75	2.59	14.73	12.10	45.87)		
5	$[PtCl_2(C_5H_6N_2)_2]^{a)}$	26.44	2.66	15.61	12.34	42.95		545
	$C_{10}H_{12}Cl_2N_4Pt$	(26.14	2.75	13.74	13.08	40.54)		
6	$[PtCl_2(C_5H_6N_2)_2]^{a)}$	26.44	2.66	15.61	12.34	42.95		525
	$C_{10}H_{12}Cl_2N_4Pt$	(26.26	2.64	14.88	11.70	41.61)		
7	$[PtCl_2(C_6H_7N)_2]\cdot H_2O^{a)}$	30.65	3.43	15.08	5.96	41.49		400
	$C_{12}H_{16}Cl_2N_2OPt$	(29.04	2.49	14.47	5.42	45.44)		
8	$[PtCl_2(C_6H_7N)_2]$	31.87	3.12	15.68	6.19	43.14		420
	$C_{12}H_{14}Cl_2N_2Pt$	(31.72	3.01	15.69	6.16	39.14)		
9	$[PtCl_2(C_6H_7N)_2]^{a)}$	31.87	3.12	15.68	6.19	43.14		505
	$C_{12}H_{14}Cl_2N_2Pt$	(30.80	2.88	16.49	6.02	41.98)		
10	$[PtCl_2(C_7H_9N)_2]^{a)}$	35.01	3.78	14.76	5.83	40.62		455
	$C_{14}H_{18}Cl_2N_2Pt$	(36.19	4.05	13.82	5.66	39.39)		
11	$[PtCl_2(C_7H_9N)_2]\cdot H_2O$	33.74	4.05	14.23	5.62	39.15		430
	$C_{14}H_{20}Cl_2N_2OPt$	(34.37	3.74	14.98	5.58	38.72)		
12	$[PtCl_2(C_7H_9N)_2]$	35.01	3.78	14.76	5.83	40.62		420
	$C_{14}H_{18}Cl_2N_2Pt$	(34.31	3.68	14.86	5.56	40.99)		
13	$[PtCl_2(C_6H_4N_2)_2]\cdot H_2O$	29.28	2.05	14.40	11.38	39.63		415
	$C_{12}H_{10}Cl_2N_4OPt$	(28.88	1.86	14.80	11.15	29.21)		
14	$[PtCl_2(C_6H_4N_2)_2]$	30.39	1.70	14.95	11.82	41.14		570
	$C_{12}H_8Cl_2N_4Pt$	(30.05	1.40	14.92	11.64	41.51)		
15	$[PtCl_2(C_6H_4N_2)_2]\cdot H_2O$	29.28	2.05	14.41	11.38	39.63		560
	$C_{12}H_{10}Cl_2N_4OPt$	(29.44	1.45	15.13	11.40	38.29)		
16	$[PtCl_2(C_{10}H_8N_2)]\cdot H_2O$	27.29	2.29	16.11	6.36	44.32		410
	$C_{10}H_{10}Cl_2N_2OPt$	(27.02	1.70	17.06	6.37	44.42)		
17	$[PtCl_2(C_{10}H_8N_2)_2]\cdot 2H_2O$	39.10	3.28	11.54	9.12	31.75		500
	$C_{20}H_{18}Cl_2N_4OPt$	(39.11	2.73	12.02	9.16	31.32)		
18	$[PtCl_2(C_7H_9N)_2]^{a)}$	35.01	3.78	14.76	5.83	40.62		430
	$C_{14}H_{18}Cl_2N_2Pt$	(34.55	3.70	14.78	5.55	22.55)		
19	$[PtCl_2(C_9H_7N)_2]\cdot H_2O^{a)}$	39.87	2.97	13.07	5.17	35.97		410
	$C_{18}H_{16}Cl_2N_2OPt$	(42.35	2.83	13.44	4.78	33.92)		
20	$[PtCl_2(C_9H_8N_2)_2]^{a)}$	39.00	2.91	12.79	10.11	35.19		500
	$C_{18}H_{16}Cl_2N_4Pt$	(40.18	3.07	13.13	9.98	33.64)		
21	$[PtCl_2(C_9H_8N_2)]^{a)}$	26.36	1.97	17.29	6.83	47.56		535,
	$C_9H_8Cl_2N_2Pt$	(27.47	1.90	16.87	7.12	46.60)		440
22	$[PtCl_2(C_{10}H_9N)_2]^{a)}$	43.49	3.29	12.84	5.07	35.32		420
	$C_{20}H_{18}Cl_2N_2Pt$	(42.07	3.32	12.12	4.83	36.70)		
23	$[Pt_2Cl_3(OH)(C_9H_6NO_2SCl)_3]\cdot 4H_2O^{c)}$	25.56	2.15	16.77	3.31	30.76	7.58	420
	$C_{27}H_{27}Cl_6N_3O_{11}Pt_2S_3$	(26.29	1.53	16.62	3.45	27.70	6.65)	
24	$[PtCl_2(C_9H_{11}N)_2]$	40.60	4.17	13.32	5.26	36.64		430,
	$C_{18}H_{22}Cl_2N_2Pt$	(39.72	4.04	13.50	5.09	36.03)		410
25	$[Pt_3Cl_6(C_{20}H_{24}N_2O_2)_4]\cdot H_2O^{c)}$	44.70	4.78	9.90	5.21	27.23		
	$C_{80}H_{98}Cl_6N_8O_9Pt_3$	(44.88	4.71	10.80	5.18	23.06)		
26	$[PtCl(OH)(C_{20}H_{24}N_2O_2\cdot HCl)_2\cdot 2H_2O^{b)}$	47.79	5.51	10.58	5.57	19.41		430
	$C_{40}H_{55}Cl_3N_4O_7Pt$	(48.01	5.24	10.25	5.52	20.06)		
27	$[PtCl_2(C_9H_7N)_2]^{a)}$	41.23	2.69	13.52	5.34	37.21		480
	$C_{18}H_{14}Cl_2N_2Pt$	(37.99	2.45	14.78	4.95	36.92)		

TABLE VI. (continued)

No.	Formula	Analysis (%) Calcd (Found)						IR (cm^{-1}) Pt–N
		C	H	Cl	N	Pt	S	
28	$[PtCl_2(C_{20}H_{22}NO_4Cl)_2]$	47.21	4.36	13.94	2.75	19.17		465
	$C_{40}H_{44}Cl_4N_2O_8Pt$	(46.53	4.26	13.60	2.66	21.08)		
29	$[PtCl_2(C_8H_7N)_2]$	38.41	2.82	14.17	5.60	39.00		440
	$C_{16}H_{14}Cl_2N_2Pt$	(38.70	2.70	13.68	5.45	40.60)		
30	$[PtCl_2(C_8H_9N)_2]$	38.11	3.60	14.06	5.56	38.68		420
	$C_{16}H_{18}Cl_2N_2Pt$	(38.15	3.57	14.16	5.54	36.71)		
31	$[Pt_2Cl(OH)_3(C_{21}H_{22}N_2O_2 \cdot HCl)_4]^{c)}$	51.47	4.89	9.04	5.72	19.91		420
	$C_{84}H_{95}Cl_5N_8O_{11}Pt_2$	(51.10	4.57	9.48	5.57	20.08)		
32	$[PtCl(OH)(C_{23}H_{26}N_2O_4 \cdot HCl)_2] \cdot 4H_2O^{b)}$	46.76	5.38	9.00	4.74	16.51		465
	$C_{46}H_{63}Cl_3N_4O_{13}Pt$	(46.48	4.74	9.44	4.54	15.82)		
33	$[PtCl_2(C_4H_4N_2)_2]$	22.55	1.89	16.64	13.15	45.78		460
	$C_8H_8Cl_2N_4Pt$	(21.56	1.71	17.11	12.29	45.40)		
34	$[Pt_2Cl_3(C_4H_3N_2O)(C_4H_4N_2O)_3] \cdot H_2O^{c)}$	21.40	1.91	11.85	12.48	43.45		470
	$C_{16}H_{17}Cl_3N_8O_5Pt_2$	(20.86	1.97	11.83	12.01	44.73)		
35	$[Pt_2Cl_3(OH)(C_4H_5N_3O)_4] \cdot 2H_2O^{a)}$	19.33	2.54	10.70	16.91	39.25		420
	$C_{16}H_{25}Cl_3N_{12}O_7Pt_2$	(18.53	2.22	11.78	16.06	39.34)		
36	$[PtCl_2(C_3H_4N_2)_2]$	17.92	2.01	17.63	13.93	48.51		610
	$C_6H_8Cl_2N_4Pt$	(18.33	1.97	17.26	14.10	51.75)		
37	$[PtCl_2(C_3H_6N_2S)_2]$	15.32	2.57	15.08	11.91	41.48	13.64	595
	$C_6H_{12}Cl_2N_4PtS_2$	(15.45	2.44	15.04	11.83	40.22	13.74)	
38	$[Pt_2Cl_3(OH)(C_5H_4N_4)_3]^{c)}$	20.62	1.50	12.17	19.23	44.65		
	$C_{15}H_{13}Cl_3N_{12}OPt_2$	(21.28	1.36	11.27	19.74	42.90)		
39	$[Pt_2Cl_4(C_5H_5N_5 \cdot HCl)_3] \cdot 2H_2O^{c)}$	16.64	2.05	22.92	19.40	36.04		535
	$C_{15}H_{22}Cl_7N_{15}O_2Pt_2$	(15.95	1.51	22.93	18.79	37.38)		
40	$[Pt_3Cl_6(C_5H_4N_4O)_4 \cdot HCl] \cdot 8H_2O^{c)}$	15.77	2.18	16.30	14.72	38.43		560
	$C_{20}H_{33}Cl_7N_{16}O_{12}Pt_3$	(15.77	1.24	15.46	14.64	36.93)		
41	$[Pt_2Cl_3(OH)(C_{10}H_{12}N_4O_6)_3] \cdot 8H_2O^{c)}$	23.86	3.54	7.04	11.13	25.83		520
	$C_{30}H_{53}Cl_3N_{12}O_{27}Pt_2$	(23.81	2.60	6.97	11.18	24.22)		
42	$[Pt_3Cl_4(OH)_2(C_3H_3N_3)_4] \cdot 5H_2O^{c)}$	12.26	2.06	12.06	14.30	49.79		420
	$C_{12}H_{24}Cl_4N_{12}O_7Pt_3$	(11.85	2.24	12.12	14.06	49.06)		
43	$[Pt_4Cl_5(OH_3)(C_4H_7N_5)_5] \cdot 7H_2O^{c)}$	13.65	2.98	10.07	19.89	44.33		610
	$C_{20}H_{52}Cl_5N_{25}Pt_4$	(13.54	2.07	10.86	20.42	43.33)		
44	$[PtCl_2(C_9H_9N_5 \cdot HCl)_2]$	30.31	2.83	19.88	19.64	27.35		400
	$C_{18}H_{20}Cl_4N_{10}Pt$	(30.23	2.77	19.55	19.63	27.79)		
45	$[Pt_4Cl_2(OH)_6(C_3H_6N_6)_5] \cdot 7H_2O^{c)}$	10.54	2.95	4.15	24.57	45.63		540
	$C_{15}H_{50}Cl_2N_{30}Pt_4$	(11.30	2.35	3.82	25.57	44.87)		
46	$[Pt_3Cl_6(C_{14}H_{12}N_2)_4]^{c)}$	41.23	2.97	13.04	6.87	35.88		400
	$C_{56}H_{48}Cl_6N_8Pt_3$	(41.63	3.07	13.36	6.89	30.99)		
47	$[PtCl_2(C_{16}H_{18}N_3SCl)_2] \cdot 2H_2O$	40.81	4.29	15.06	8.93	20.71	6.81	450
	$C_{32}H_{40}Cl_4N_6O_2PtS_2$	(40.80	3.55	15.22	9.36	20.62	6.90)	
48	$[Pt_4Cl_5(OH)_3(C_5H_{11}N)_6] \cdot 3H_2O^{c)}$	22.89	4.81	11.26	5.31	49.59		495
	$C_{30}H_{75}Cl_5N_6O_6Pt_4$	(23.45	4.23	11.36	5.31	50.28)		
49	$[Pt_3Cl_6(C_4H_{10}N_2)_4] \cdot H_2O^{c)}$	16.56	3.56	18.32	9.66	50.43		420
	$C_{16}H_{42}Cl_6N_8OPt_3$	(16.68	3.48	17.54	9.45	51.06)		
50	$[PtCl_2(C_{11}H_{13}N_3O)_2]$	39.29	3.90	10.54	12.50	29.01		440
	$C_{22}H_{26}Cl_2N_6O_2Pt$	(39.90	3.90	9.58	12.93	25.93)		
51	$[Pt_2Cl_3(OH)(C_4H_5N_3O)_4] \cdot 2H_2O^{a,c)}$	19.33	2.54	10.70	16.91	39.25		540
	$C_{16}H_{25}Cl_3N_{12}O_7Pt_2$	(18.53	2.22	11.78	16.06	39.34)		
52	$[PtCl(OH)(C_9H_{16}N_2)] \cdot H_2O$	25.87	4.58	8.49	6.71	46.69		465
	$C_9H_{19}ClN_2O_2Pt$	(26.81	4.41	7.50	6.17	47.27)		
53	$[PtCl_2(C_{10}H_{24}N_4 \cdot 2HCl)] \cdot H_2O^{a)}$	21.55	5.07	25.45	10.05	35.01		520
	$C_{10}H_{28}Cl_4N_4OPt$	(22.33	4.82	24.35	10.48	34.08)		

TABLE VI. (continued)

No.	Formula	Analysis (%) Calcd (Found)						IR (cm^{-1}) Pt–N
		C	H	Cl	N	Pt	S	
54	$[Pt_3Cl_6(C_6H_{12}N_4)_4]$[c]	21.22	3.56	15.66	16.50	43.07		460
	$C_{24}H_{48}Cl_6N_{16}Pt_3$	(21.24	3.51	15.80	16.88	38.68)		
55	$[Pt(C_5H_{10}NS_2)_2]$[b]	24.43	4.10		5.70	39.68	26.09	360
	$C_{10}H_{20}N_2PtS_4$	(24.27	4.13		5.72	27.35	26.22)	
56	$[Pt(C_3H_5OS_2)_2]$[b]	16.47	2.30			44.59	29.32	335
	$C_6H_{10}O_2PtS_4$	(16.45	2.16			44.99	29.83)	
57	$[Pt(C_4H_{10}O_2PS_2)_2]$[b]	16.99	3.57			34.50	22.68	400
	$C_8H_{20}O_4P_2PtS_4$	(17.26	3.48				23.30)	
58	$[PtCl_2(C_6H_{14}S_2)]$	17.31	3.39	17.03		46.86	15.40	390
	$C_6H_{14}Cl_2PtS_2$	(17.27	3.25	17.03		45.41	15.05)	
59	$[PtCl_2(C_2H_6S_2)]$[a]	6.67	1.68	19.69		54.16	17.80	390
	$C_2H_6Cl_2PtS_2$	(6.61	1.35	18.73		53.58	13.96)	

a) These complexes are not pure judging from the elemental analysis data. *b*) The structure is different from that of **3**. *c*) Polynuclear complex.

reaction time. Quinine (No. 26) formed a *cis*-$[PtCl(OH)L_2]$ complex. The structures of these complexes were assigned as *cis*-Pt complexes on the basis of elemental analyses and IR spectral examination. However, judging from the elemental analysis, the following ligands were suggested to form polynuclear complexes: quinoline-8-sulfonylchloride (No. 23) and quinidine (No. 25). The IR spectral results support the partial presence of *cis* conformation of the ligands to Pt metal.

Indole (No. 29) and its derivative indoline (No. 30) reacted to yield the expected *cis*-Pt complexes. Brucine (No. 32) formed a *cis*-$[PtCl(OH)L_2]$ complex like quinine (No. 26). Strychnine (No. 31) was suggested to form a polynuclear complex. The other indoles, such as reserpine and indigocarmine, reacted to yield unidentified Pt complexes. Isatin and yohimbine did not react even when the reactions were carried out for more than one month.

Table III summarizes the reactions between **2** and pyrimidine derivatives. In this series of reactions, pyrimidine (No. 33) and cytosine (No. 35) reacted to yield the expected *cis*-Pt complexes. 4-Hydroxypryrimidine (No. 34) probably formed a polynuclear complex. The other pyrimidines, such as 2-hydroxypyrimidine, uracil, 2-thiouracil, dithiouracil, thymine, and barbituric acid, reacted to yield unidentified Pt complexes.

The reactions between **2** and imidazole (No. 36) or its derivative 2-imidazolidinethione (No. 37) are also shown in Table III. In general, imidazole derivatives reacted to give the expected complexes in high yields. For instance, 2-methylimidazole, *N*-methylimidazole and 2-methylbenzimidazole produced the *cis*-Pt complexes in yields of 63, 81 and 57%, respectively. The other imidazoles such as 1,2-dimethylimidazole, histidine and 2-imidazolidinone reacted to yield unidentified Pt complexes. Hydantoin and parabanic acid did not react.

As shown in Table III, the reaction products between **2** and purine derivatives were generally obtained in high yields after a long reaction time. The structures of these complexes were assigned as polynuclear complexes. Caffeine reacted to give the *cis*-Pt complex in low yield (16%) after a long reaction time (11 d). In some cases (such as theobromine and quanine), unidentified complexes were obtained. Xanthine and uric acid did not react.

The reactions between **2** and 1,3,5-triazine derivatives are also included in Table III. 1,3,5-Triazine derivatives (except No.42) reacted to give the expected complexes in good

yields. The complex coordinating 1,3,5-triazine (No. 42) alone was obtained in a low yield in spite of a long reaction time. Benzoguanamine (No. 44) formed a *cis*-Pt complex, but the others formed polynuclear complexes. The complex coordinating 1,2,4-triazole could not be identified and cyanuric acid did not react.

Table IV lists the results for **2** and the other nitrogen cyclic compounds. Methylene blue (No. 47), 4-aminoantipyrine (No. 50) and 1,4,8,11-tetraazacyclooctane (No. 53) reacted with **2** within a short reaction time and gave the desired complexes in high yields. 1,8-

Table VII. Antitumor Activity of Platinum Complexes against Sarcoma 180

No.	Dose (mg/kg)	*T/C* (%)	Toxic death	Evaluation	No.	Dose (mg/kg)	*T/C* (%)	Toxic death	Evaluation
5	25	105	0	−	29	50	140	0	−
	50	146	0	−		100	100	0	−
	100	150	0	+		200	200	0	++
6	25	185	0	+		400	290	0	++
	50	212	0	++	30	25	90	0	−
	100	189	0	+		50	145	0	−
7	200	212	0	++		100	170	0	+
8	100	375	0	+++		200	—	4	Toxic
	200	193	0	+	31	2	140	0	−
9	100	225	0	++		10	160	0	+
	200	175	0	+		50	—	5	Toxic
10	25	99	0	−	32	50	182	0	+
	50	103	0	−		100	194	0	+
	100	171	0	+		200	—	5	Toxic
11	10	115	0	−		400	—	5	Toxic
	25	114	0	−	33	50	232	0	++
	50	159	0	+		100	264	0	++
	100	178	0	+		200	264	0	++
12	25	209	0	++		400	—	2	Toxic
	50	249	0	++	36	50	250	0	++
	100	218	0	++		100	200	0	++
13	25	146	0	−		200	—	1	Toxic
	50	195	0	+		400	—	4	Toxic
	100	222	0	++	47	25	105	0	−
14	200	176	0	+		50	222	0	++
15	200	272	0	++	48	50	110	0	−
16	200	182	0	+		100	330	0	+++
18	25	133	0	−		200	400	0	+++
	50	192	0	+		400	310	0	+++
19	100	137	0	−	49	50	200	0	++
	200	300	0	+++		100	140	0	+
20	50	109	0	−		200	130	0	+
	100	200	0	++		400	180	0	+
	200	164	0	+	51	25	107	0	−
	400	127	0	−		50	221	0	++
21	50	180	0	+		100	250	0	++
	100	100	0	−		200	192	0	+
	200	230	0	++	53	10	161	0	+
	400	170	0	+		50	184	0	+
23	50	100	0	−	54	25	170	0	+
	100	200	0	++		50	160	0	+
	200	—	5	Toxic		100	90	0	−
27	100	375	0	+++		200	90	0	−
	200	144	0	−	59	200	290	0	++

Table VIII. Antitumor Activity

No.	Dose (mg/kg)	Platinum (mg/kg)	Weight (%)	Evaluation for antitumor activity
8	100	39	39.14	+++
	200	78	39.14	+
19	100	34	33.92	−
	200	68	33.92	+++
27	100	37	36.92	+++
	200	74	36.92	−
48	50	12	23.45	−
	100	23	23.45	+++
	200	47	23.45	+++
	400	94	23.45	+++
cis-DDP	7	5	65.00	+++

Diazabicyclo[5.4.0]undecene-7 (No. 52) formed a *cis*-[PtCl(OH)L] complex. The structures of these complexes were assigned as *cis*-Pt complexes on the basis of elemental and IR spectral analyses. However, as judged from elemental analysis, ligands Nos. 46, 48, 49, 51 and 54 were considered to form polynuclear complexes. Nitrogen cyclic compounds such as carbazole, acridine, maleimide, thiamine, proline or homatropine produced unidentified complexes with **2**. These complexes seemed to be different in geometry even from the above polynuclear complexes. On the other hand, nitrogen cyclic compounds such as phenazine, guanosine, 5′-cytidylic acid, 5′-uridyric acid, riboflavin, 2-pyrrolidone, succinimide, quinuclidine and D-(+)-biotin did not reacted with **2**.

Table V summarizes the reactions between **2** and sulfur-containing compounds. 3,6-Dithiaoctane (No. 58) and dimethyl disulfide (No. 59) reacted to produce the expected *cis*-Pt complexes in high yields within a short reaction time. Diethyldithiocarbamate (No. 55), xanthogenate (No. 56), and *O*,*O*′-dimethyl dithiophosphate (No. 57) formed *cis*-[PtL_2] complexes, in which these ligands, L, acted as bidentate ones. However, in some cases (dibenzyldithiocarbamate, DL-α-lipoic acid, toluene-3,4-dithiol, 1,2-ethanedithiol, carbon disulfide and ethylene bis(diphenylphosphine), unidentified compounds were obtained. Di(5,5-dimethylhexyl) disulfide did not react.

As shown in Table VI, there was good coincidence between the elemental analysis values of most Pt complexes and the calculated ones. The exceptions are marked by *a*). Structures which differ from **3** are marked by *b*). Polynuclear complexes are marked by *c*).

The complexes Nos. 10—13, 16—20, 22—27, 29—32, 46, 52, 53, 57—59 were obtained by means of an interfacial reaction. The complexes Nos. 26 and 57 were soluble in organic solvents such as ethyl acetate, benzene or dichloromethane.

Antitumor Activities of Synthesized Platinum Complexes

The antitumor activities of the synthesized Pt complexes evaluated in terms of T/C (%) in the ascites Sarcoma 180 tumor system are listed in Table VII. The complexes Nos. 8, 19, 27 and 48 had high antitumor activities. No well-defined correlation was observed between antitumor activities and the kind or substitution position of ligands.

The antitumor activity of each effective complex (Nos. 8, 19, 27 and 48) and the platinum weight (mg/kg) for each dosage are shown in Table VIII. The required platinum weight of the dosed complexes was more than 4 times larger than that of **1** to obtain (+++) evaluation, for example, *ca.* 23—94 mg/kg for No. 48, 37 mg/kg for No. 27, 39 mg/kg for No. 8, and 68 mg/kg for No. 19.

cis-Platinum complexes of pyridine derivatives, in general, showed lower antitumor

activity than those of aniline derivatives.

Acknowledgement We are grateful to Dr. Masao Arakawa, Biological Laboratories, Sankyo Co., Ltd., for carrying out some antitumor activity tests.

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