SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME MIXED - CIS DIAMINE COMPLEXES OF PT(II) CONTAINING PIPERIDINE AND OTHER AMINES

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Abstract *Five complexes of cis - dichloro (piperidine) (amine) platinum (II) including [Pt (Pip) (Morpholine)Cl_2].H_2O, [Pt(Pip)(Pyridine)Cl_2], [Pt(Pip)(Quinoline)Cl_2], [Pt(Pip)(p-Phenetidine)Cl_2], [Pt(Pip) (α- Naphthylamine)Cl_2)] (Pip = piperidine) have been synthesised and characterized by elemental analysis, molar conductivity, IR and Raman spectral studies. The complexes were tested for biological activities and found to be capable of inhibiting the growth of some human cancer cells.*

Introduction

Many diamine complexes of Pt(II) exhibits high anti-tumor activity. Some of which have been used for treatment of cancer [1]. On the basis of the synthesis of potassium tri chloro piperidine platinate (II), $K[PtPipCl_3]$, (P0), [2], the Pt(II) complexes containing piperidine and aromatic amine or heterocyclic amine (Am) have been synthesised. The structures of complexes have been determined. The complexes were tested for biological activities.

Result and Discussion

Five complexes were prepared according to the Peyrone rule: when a chlorine atom in the P0 is substituted by an amine molecule, the product of *cis* - configuration would be expected. The amines used for synthesis included: morpholine, quinoline, pyridine, p - phenetidine and α - naphthylamine. The synthesis of Pt(II) complexes of mixed cis - diamine were carried out in acidic medium:

$$K[Pt(Pip)Cl_3] + AmH^+ + Cl^- + KOH \rightarrow [Pt(Pip)(Am)Cl_2] + 2KCl + H_2O$$

Or in aqueous solution of free amine:

$$K[Pt(Pip)Cl_3] \quad + \quad Am \quad \rightarrow [Pt(Pip)(Am)Cl_2] + KCl$$

All the above-prepared complexes are in yellow acicular crystals. They show a sharp trace on TLC. The analyses (thermal analysis, spectral analysis...) found out the presence of crystalline - water in P1 complex (Table 1). The results of elemental analysis are in a

good agreement with predicted structures. The molar conductivity (μ) of the complexes in 5.10^{-5} M solution are in the range $10 \div 14\ \Omega^{-1}cm^2.\ mole^{-1}$ indicates their non - electrolytic nature (Table 1)

Table 1: Yield, Rf, Molecular conductivity (μ), Elemental and crystalline - water composition of the complexes

Comp.	Formula	Yield	R_f	μ $\Omega^{-1}.cm^2.mole^{-1}$	Composition (%): found / calcd.				
					Pt	N	Cl	C	H
P1	$[Pt(Pip)(C_4H_8ONH)Cl_2].H_2O$	68	0.673	10.0	41.96	6.03	16.17	23.58	4.82
					42.71	6.13	15.55	23.65	4.84
P2	$[Pt(Pip)(C_5H_5N)Cl_2]$	62	0.698	10.8	45.12	6.29	17.13	28.76	3.92
					45.34	6.51	16.17	27.91	3.74
P3	$[Pt(Pip)(C_9H_7N)Cl_2]$	60	0.701	11.5	41.15	5.62	15.09	35.32	3.82
					40.62	5.80	14.91	35.06	3.75
P4	$[Pt(Pip)(p\text{-}C_2H_5O\text{-}C_6H_4\text{-}NH_2)Cl_2]$	52	0.876	14.0	40.72	5.81	15.96	30.32	4.38
					39.95	5.73	14.55	31.96	4.50
P5	$[Pt(Pip)(\alpha\text{-}C_{10}H_7\text{-}NH_2)Cl_2]$	62	0.821	12.1	38.49	-	15.01	-	-
					39.47	5,66	14.37	36.43	4.04

The main absorption bands in the IR and Raman spectra of the complexes are listed in the table 2. The results show that most of the bands characterizing of the same atomic groups are exhibited in both spectra.

Table2: Main absorption bands in the IR and Raman spectra of the complexes

Comp.		IR (cm^{-1})/RAMAN (Ram) (cm^{-1})										
		ν_{NH}	ν_{CH} (aro.)	ν_{CH} (sat.)	$\nu_{C=C}$ (aro.)	δ_{CH} (sat.)	ν_{C-C} (sat. ring)	ν_{Pt-N}	ν_{Pt-Cl}	ν_{NPtCl}	δ_{PtCl_2}	
P0	IR	3167	-	2939, 2855	-	1446	1209	434	-	-	-	
	Ram	3173	-	2945, 2863	-	1448	1208,1029	436	325	211	187	
P1	IR	3187	-	2945, 2864	-	1454	1228, 1027	541 462	-	-	-	
	Ram	3189	-	2954, 2860	-	1453	1226, 1030	533 475	319	215	166	
P2	IR	3187	3059	2945, 2858	1608	1452	1212, 1027	466	-	-	-	
	Ram	3197	3077	2960, 2867	1607, 1574	1423	1207, 1022	470	326	208	179	
P3	IR	3178	3072	2945, 2849	1626, 1589	1456	1126, 1028	534 513	-	-	-	
	Ram	3184	3055	2950, 2850	1626, 1589	1437	1133, 1015	536 521	326	218	155	
P4	IR	3178, 3155	3061	2924, 2864	1612, 1601	1450	1201, 1043	551 502	-	-	-	
	Ram	3182, 3154	3071	2934, 2862	1616, 1602	1446	1202, 1024	579 498	334	214	183	
P5	IR	3211, 3182	3076	2954, 2858	1610, 1512	1456	1155, 1014	442 484	-	-	-	
	Ram	3220	3071	2966, 2857	1580, 1515	1458	1153, 1014	450 509	318	255	171	

There is one or two absorption bands for ν_{NH} at 3200 -3154 cm^{-1}, in which one band characterizes the stretching vibration of NH group of piperidine and morpholine, other band characterizes the stretching vibration of NH_2 group from aromatic amines in P4 P5. Weak bands at 3077 - 3055 cm^{-1} characterize the stretching vibration of $CH_{(aromatic}$ group. There are several bands exhibiting the stretching vibration of $CH_{(saturated)}$ group at 2966 - 2850 cm^{-1}. Deformation vibrations of NH_2 group (in P4, P5) are mixed with

the stretching vibration of $C{=}C_{(aromatic)}$ group exhibited by bands at 1626 - 1512 cm^{-1}. Deformation vibrations of $CH_{(Saturated)}$ are exhibited at 1458 - 1423 cm^{-1}. In the Raman spectra, the skeletal vibration $\nu_{C\text{-}C}$ of saturated the ring result in strong bands at 1228 - 1014 cm^{-1}. The stretching vibration of Pt - N bond is observed in the 580 - 440 cm^{-1} region, that indicated the coordination of amine to Pt(II). A strong band at 334 - 318 cm^{-1} arises from the stretching vibration of Pt - Cl bond. The medium bands at 255 - 208 cm^{-1} and at 187 - 155cm^{-1} can be assigned to stretching vibration of NPtCl and deformation vibration of $PtCl_2$ group, [3],[4]. Besides, bands at 3479 - 3429 cm^{-1} in the both spectra characterize the stretching vibration of OH group from crystalline water molecule in P1.

Thus, the spectra of studied complexes are in good agreement with the structural formulas suggested in Fig. 1

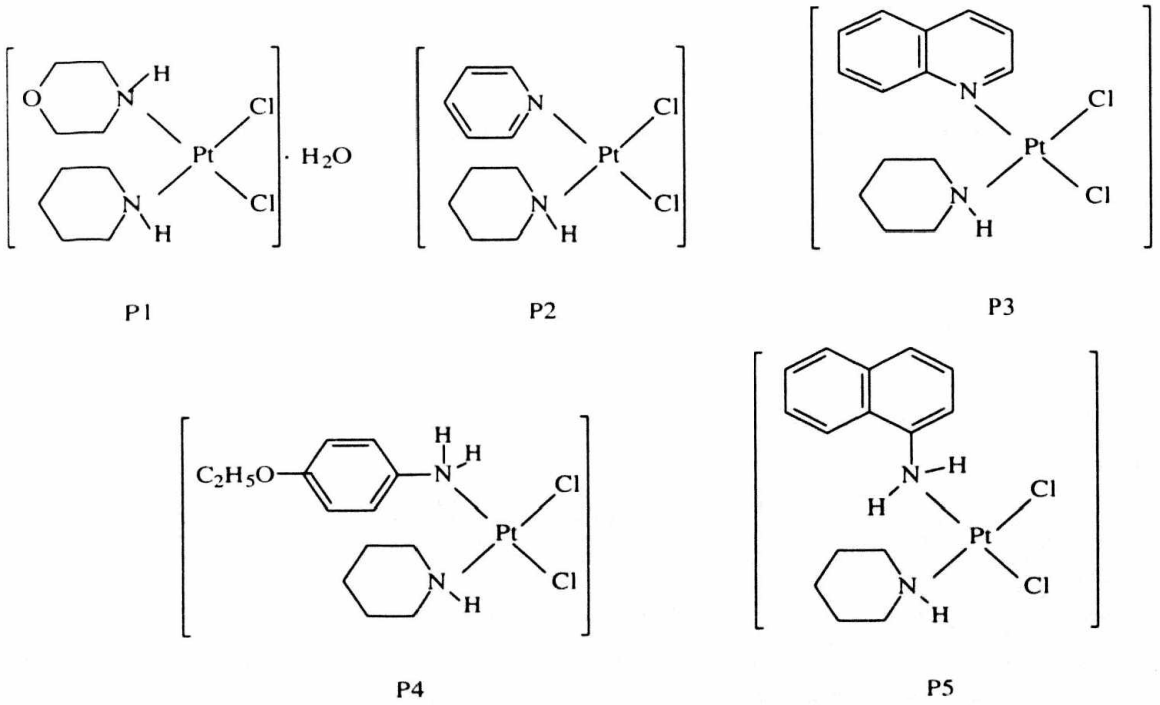

Fig. 1: The structural formulas of the complexes: P1, P2, P3, P4, P5

The test for cell cytotoxicity was carried out on human liver cancer cell (Hep - G_2) and human heart membrance cancer cell (RD). IC_{50} (μg/ml) values for the tested complexes are given in the table 3. $IC_{50} \leq 5$ (with pure sample) and $IC_{50} \leq 20$ (with crude sample) are considered to be positive (+). The results show that P1, P2, P4, P5 are capable of inhibiting the two above cell lines (Hep - G_2 and RD); P3 is capable of inhibiting only cell line (RD).

Table 3: IC_{50} (μ g/ml) values for Hep - G_2 and RD of the tested complexes

Comp.	$P1_{(crude\ sample)}$	P2	P3	P4	P5
Hep - G_2	8.9, (+)	3.2, (+)	> 5.0 (-)	3.9, (+)	3.6, (+)
RD	9.0, (+)	2.8, (+)	2.0 (+)	2.9, (+)	3.1, (+)

Experimental

1. Synthesis

- Synthesis of P1: to an aqueous solution of 2m.mole of morpholine, a solution of 1.m.mole of P0 saturated in water was added. The reaction mixture was tirred at 25 - 30^0C for 3 hours. A yellow precipitate was filtered, washed with cold water and recrystallized from ethanol - water mixture.

- Synthesis of P2: similar to that of P1.

- Synthesis of P3: to a solution of 3.m.mole of quinoline in acidic medium (pH = 6), a solution of 1m.mole P0 satutated in water was added. The resulting solution was tirred and added dropwise with 2N KOH solution. After about 3.5 hours, a yellow pricipitate was filtered, washed with dilute HCl, cold water and recrystallized from ethanol - water mixture.

- Syntheses of P4, P5: similar to that of P3.

2. Apparatus and methods

- TLC chromatograms were obtained on silufol UV - 254 plates (desorption system: acetone/ nitric acid = 10/1), developed by iodine vapors.

- The IR spectra at 4000 - 400 cm^{-1} were recorded in KBr discs on a FTIR - 8700 SNO - SHIMADZU spectrophotometer. The Raman spectra were recorded on a Micro Raman LABRAM at 4000 - 100 cm^{-1}–, using excited radiation at 632,8 nm from heli - neon laser.

- The C, H, N, Cl contents were determined at HCM city Experiment center, using an automatic elemental analyzer. The Pt content carried out by weight method at faculty of Chemistry, Hanoi University of Pedagog. The thermal analysis was recorded on a DSD - 50 instrument and TGA - 50 H instrument (SHIMADZU). The molar conductance values of complex solutions were measured on a conductivity meter HI - 88119 N.

- The cytotoxicity towards cancer cells was tested at the Experimental biological Lab., Institute of Chemistry of natural compounds, based on the method being carried out at Nation Cancer Institute of America (NCI).

Conclusions

Five Pt(II) mixed *cis* - diamine complexes of Pt(II) containing piperidine and other amines have been synthesized including *cis* - Dicholoro (Morpholine) (Piperidine) Platinum (II), *cis* - Dichloro (Piperidine) (Pyridine) Platinum (II), *cis* - Dichloro (Piperidine) (Quinoline) Platinum (II), *cis* - Dichloro (p -Phenetidine) (Piperidine) Platinum (II), *cis* - Dichloro (α- Naphthylamine) (Piperidine) Platinum (II).

The structures of the complexes have been determined on the basis of elemental analysis, thermal analysis, molar conductivity measurement, IR and Raman spectral studies.

The result of testing for cell cytotoxicity shows that P1, P2, P4, P5 are capable of inhibiting two human cancer cell lines (Hep - G_2 and RD); P3 inhibits only cell line (RD).

Rerrerences

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TỔNG HỢP VÀ HOẠT TÍNH SINH HỌC CỦA MỘT SỐ PHỨC CIS - DIAMIN HỖN TẠP CỦA Pt(II) CHỨA PIPERIDIN VÀ CÁC AMIN KHÁC

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Năm phức *cis* - diamin hỗn tạp của platin (II) chứa piperidin và amin khác bao gồm [Pt (Pip) (Morpholine)Cl_2].H_2O, [Pt(Pip)(Pyridine)Cl_2], [Pt(Pip)(Quinoline)Cl_2], [Pt(Pip)(p-Phenetidine)Cl_2], [Pt(Pip) (α- Naphthylamine)Cl_2)] với (Pip = piperidine) đã được tổng hợp và nghiên cứu cấu trúc bởi phương pháp phân tích nguyên tố, đo độ dẫn điện phân tử, phổ IR và Raman.

Kết quả thử nghiệm cho thấy các phức thu được có khả năng ức chế sự phát triển của một số dòng tế bào ung thư người.