SYNTHESIS, STRUCTURAL AND SPECTROSCOPIC STUDY AND CYTOTOXICITY OF TRANS-[$PtCl_2$(METHYL EUGENOXYACETATE)(2-AMINOPYRIDINE)]

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TÓM TẮT

TỔNG HỢP, NGHIÊN CỨU CẤU TRÚC VÀ HOẠT TÍNH CỦA PHỨC CHẤT TRANS-[$PtCl_2$(METHYLEUGENOXYACETATE)(2-AMINOPYRIDINE)]

Bài báo trình bày các kết quả tổng hợp và nghiên cứu cấu trúc của phức chất trans-[$PtCl_2$(Meteug)(2-$NH_2C_5H_4N$)] bằng phương pháp phổ IR, ^{1}H NMR và đặc biệt là phương pháp nhiễu xạ tia X đơn tinh thể. Kết quả cho thấy 2-aminopyridine phối trí với Pt(II) qua nguyên tử N trong vòng pyridine, trong khi đó methyeugenoxyaxetat (Meteug) phối trí qua liên kết đôi của nhánh allyl. Kết quả xác định cấu trúc theo phương pháp nhiễu xạ tia X không những chỉ rõ được phức chất nghiên cứu có cấu hình trans mà còn xác nhận trong phức chất tồn tại một liên kết hidro nội phân tử. Phức chất có khả năng ức chế sự phát triển các tế bào ung thư KB, HepG2, MCF7 và Lu với giá trị IC_{50} tương ứng là 6,80; 14,83, 14,20 và 19,04 μg/mL.

1. INTRODUCTION

Platinum complexes have been known for vital medical applications for along time. The first platinum-based drug was approved for the treatment of some types of human cancers being Cisplatin. There have been two other platinum drugs, Cacboplatin and Oxaliplatin, approved for clinical use worldwide thus far. However, all three generations of these platinum-based anticaner drugs have undesirable side effects and are not effective in all cancer types. Thus, chemists are looking for other platinum complexes as potential anticancer agents [1-3].

Eugenol (4-allyl-2-methoxyphenol), a main component of clove oil, and its derivatives find application in a number of areas because of varied biological properties [4,5]. Recently, some complexes of

transition metal bearing biologically active ligands such as oxicams, omeprazole have been synthesized, characterized and screened for antibacterial activities [6,7].

Considering these findings, we have decided to synthesize followed by the study on structure of platinum(II) complex containing methyleugenoxyacetate (a derivative of eugenol) and 2-aminopyridine. The designed complex is subjected to the investigation of an useful cytotoxicity.

2. EXPERIMENTAL

2.1. Synthesis

Trans-[$PtCl_2$(Meteug)(2-$NH_2C_5H_4N$)] was prepared as follow: 576.5 mg (1 mmol) K[$PtCl_3$(Meteug)] (prepared according to the synthetic protocol of Da *et al.* [8]) was dissolved in 25 mL of aqueous acetone solution (1:1 *v/v*) and filtered. 2-aminopyridine (0.13 g, 1.1mmol) was dissolved in 10 mL of acetone ethanol solution (1:4 *v/v*) and added dropwise while stirring at room temperature for 15 minutes. The reaction mixture was stirred for a further 2 hours to obtain a clear solution. The solvents were removed slowly from the mixture in the air. After 15 hours the brown yellow crystals in thin plates appeared, which consequensely were collected by filtration and washed with ethanol. These crystals were used for X-ray diffraction. The yield of the preparation was 70%. Anal. Calcd for [$PtC_{18}H_{22}N_2O_4Cl_2$]: Pt, 32.72; $H_2O_{crystalized}$, 0.0. Found: Pt, 32.67; $H_2O_{crystalized}$, 0.0.

2.2. Apparatus and methods

Pt and crystalized water were analyzed according to the weight method. The IR spectrum was recorded on an IMPACK-410 NICOLET spectrometer in KBr discs in the range 400-4000 cm^{-1}; the ^1H NMR spectrum was recorded on a Bruker AVANCE 500 MHz, at 298-300K, with TMS as the internal standard at Insititute of Chemistry - Vietnam Academy of Science and Technology.

Single crystal X-ray diffraction of the complex was recorded on Aligent SuperNova diffractometer in KU Leuven, Belgium. The X-ray diffraction experiment details are summarized in Table 1. All H atoms were placed in idealized positions and refined in riding mode, with C–H distances of 0.95 (aromatic), 0.98 (methyl) and 0.99 Å (methylene), and N–H distances 0.92 Å (NH2).

The anticancer activity was tested at Institute of Chemistry - Vietnam Academy of Science and Technology according to the method described in [8]; IC50 values were calculated based on OD values taken on an Elisa instrument at 515–540 nm.

Table 1. X-ray diffraction experimental details.

Crystal data	
Chemical formula	$C_{18}H_{22}N_2O_4Cl_2Pt$
M_r	596.37
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	100.15
a, b, c (Å)	11.2739(14), 16.9232(5), 11.368(3)
α, β, γ (°)	90.00, 107.67(2), 90.00
V (Å^3)	2066.7(7)
Z	4
Radiation type	Mo $K\alpha$

Crystal data	
Crystal size (mm^3)	0.3 × 0.2 × 0.13
Data collection	
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	42051, 4226, 4064
R_{int}	0.0413
$(\sin \theta/\lambda)_{max}$ ($Å^{-1}$)	0.625
Refinement	
$R[F^2 > 2\ \sigma(F^2)]$, $wR(F^2)$, S	0.0213, 0.0448, 1.312
No. of reflections	4226
No. of parameters	344
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	0.876, - 0.636

Computer programs: CrysAlis PRO [9], SHELXS97 and SHELXL97 [10] and OLEX2 [11].

3. RESULTS AND DISCUSSION

Complex trans-[PtCl2(Meteug)(2-NH2C5H4N)] was prepared by replacement a Cl ligand from K[PtCl3(Meteug)] by a 2-aminopyridine ligand in the quite high yield, 70%, according to the trans-e□ect. The neutral complex precipitates out and can be easily isolated. The reaction equation is described as follow:

$K[PtCl_3(Meteug)] + 2\text{-}NH_2C_5H_4N \rightarrow$ *trans*-$[PtCl_2(Meteug)(2\text{-}NH_2C_5H_4N)] + KCl$The resulting compound are high soluble in acetone, chloroform, low soluble in ethanol and insoluble in water. The composition of the complex showed a good agreement between the theoretical and actual values. The complex was further characterized by IR and ^1H NMR spectroscopies and single crystal X-ray diffraction. The X-ray structure of the complex is illustrated in Fig. 1 and Table 2. All results of IR and ^1H NMR analysis are unambiguously assigned and shown in Table 3 and Fig. 2.

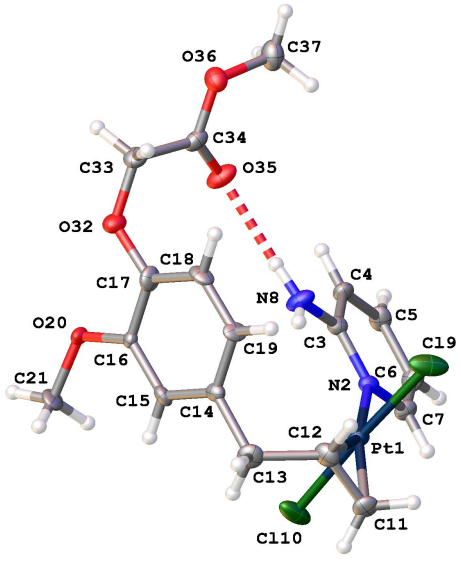


Figure 1. The X-ray structure of the complex with displacement ellipsoids drawn at 50% probability level.

Table 2. Selected bond lengths (Å) and angles (°) and hydrogen bond geometry (Å, °)

Bonds		**Angles**	
Pt1–N2	2.078(3)	N2–Pt1–Cl9	89.26(8)
Pt1–Cl9	2.2966(11)	N2–Pt1–Cl10	88.37(8)
Pt1–Cl10	2.2981(11)	N2–Pt1–C11	167.83(13)
Pt1–C11	2.168(3)	N2–Pt1–C12	155.1(3)
Pt1–C12	2.207(8)	Cl9–Pt1–Cl10	175.52(4)
		C11–Pt1–Cl9	91.34(11)
		C11–Pt1–Cl10	90.19(11)
		C11–Pt1–C12	36.4(3)
		C12–Pt1–Cl9	80.2(3)
		C12–Pt1–Cl10	103.5(3)

Hydrogen bond geometry				
D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
N8–H8A···O35	0.92	2.09	2.98	170

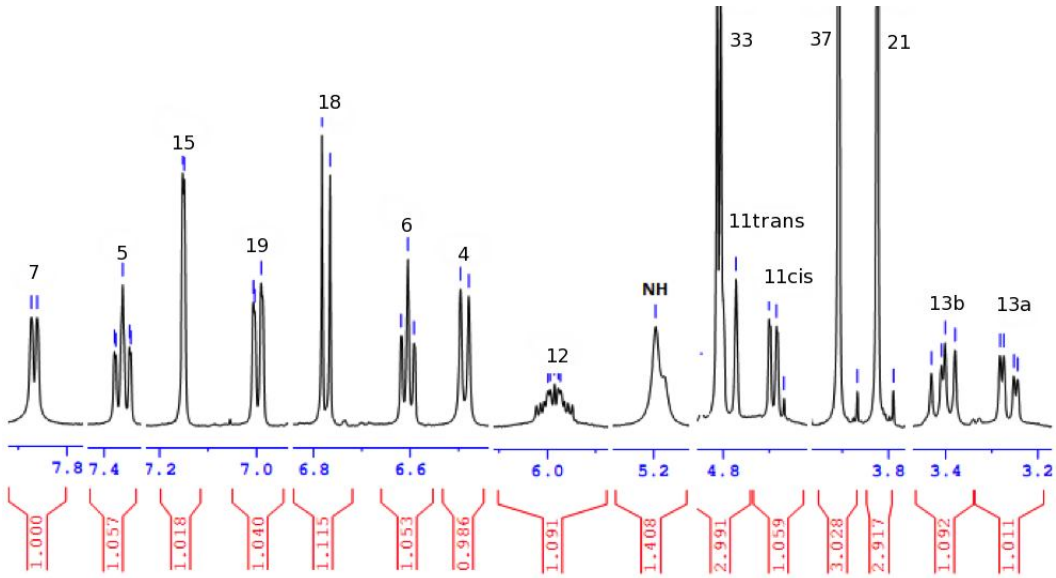
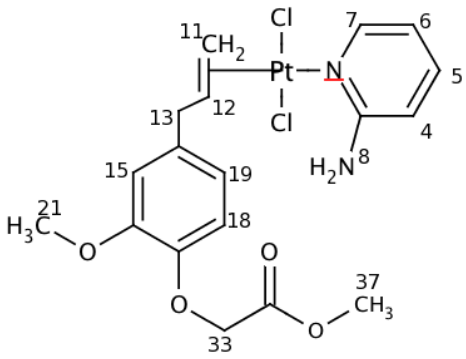


Figure 2. Assigned ^{1}H NMR spectrum of trans-[$PtCl_2$(Meteug)(2-$NH_2C_5H_4N$)]

Table 3. Main bands in IR spectra (cm^{-1}) and ^{1}H NMR signals of the examined complex, δ (ppm), J (Hz). For clarity only numbers of non-hydrogen atoms consisting H atoms are visible; hydrogen atoms are numbered according to the parent atoms.



Main bands in IR spectra of examined complex, cm^{-1}				
ν_{NH}	ν_{CH} aromatic	ν_{CH} aliphatic	$\nu_{C=O}$	δ_{NH}
3439 3356	3063	2920 2863	1748	1626
$\nu_{C=C,}$ $\nu_{C=N}$	$\nu_{C-C,}$ ν_{C-O}	ν_{Pt-N}	$\nu_{(Pt-C=C)}$	
1560 1488	1251 1057	514	440	

^{1}H NMR signals of Meteug and 2-aminopyridine in the examined complex, δ (ppm), J (Hz)

Solvent: $CDCl_3$	H15	H19	H18	H33	H21	H37	H13a	H13b	H12	H11*cis*	H11*trans*
Meteug	7.15 d ^{4}J 1.5	7.00 dd ^{3}J 8.0 ^{4}J 1.5	6.77 d ^{3}J 8.0	4.81 s 4.80 s	3.82 s	3.91 s	3.26 dd ^{2}J 15.0 ^{3}J 4.0	3.41 dd ^{2}J 15.0 ^{3}J 11.0	5.98 m	4.68 d ^{3}J 8.0	4.78 d ^{3}J 12.0
2-aminopyridine	H7		H6		H5		H4		NH(H8)		
	7.87 d ^{3}J 6.0		6.61 t ^{3}J 8.0		7.36 td ^{3}J 8.0; ^{4}J 1.5		6.49 d ^{3}J 8.0		5.19 br		

The Pt(II) atom shows a usual square-planar coordination in which two Cl atoms are bonded with the Pt(II) in a *trans* arrangement [Cl9–Pt1–Cl10 = 175.52(4)°]. The Pt–Cl bond lengths are of 2.2966(11) Å and 2,2981(11) Å, which are in good agreement with the related complex, *trans*-$[PtCl_2(C_5H_{11}N)(C_6H_6N_2O_2)]$ [12]. One of the two coordination is via a heterocyclic N atom of the 2-aminopyridine ligand. The coordination of 2-aminopyridine with Pt(II) is only via heterocyclic N atom, sp^2 N atom, but not amine N atom, sp^3 N atom. This is because that electron density of sp^2 N atom is richer than that of sp^3 N atom. Consequently, the IR spectrum shows two intense bands at 3439 and 3356 cm^{-1} corresponding N-H stretching frequency of non-coordinated amino group of 2-aminopyridine. The pyridine ring is tilting an angle of 70.69° with the mean square plane of Pt (II) coordination. This could be due to the repulsion between two Cl atoms with H7 and the amine group. The other coordination is placed for ethylenic group of the Meteug ligand. The C=C bond is coordinated almost perpendicular to the mean square plane of Pt(II) with an angle of 80.63°. This η^2 manner coordination of Meteug ligand also exhibits in the IR and ^{1}H NMR spectroscopic data. In the IR spectrum, this results in the appearance of $\nu_{(Pt-C=C)}$ band at 440 cm^{-1} and the absence of a band at 1640 cm^{-1} from the C=C double bond of allyl group in the non-coordinated Meteug molecule [8]. In the ^{1}H NMR

spectrum, the resonances of H11*cis* and H11*trans* (Table 3) are upfield in comparison to those of non-coordinated Meteug with Δδ being 0.33 and 0.30 ppm respectively. Additionally, two protons of CH_2 of allyl group (H13) in non-coordinated Meteug give rise to a doublet at 3.29 ppm with ^3J = 7.0 Hz but in the complex, one doublet of doublets centered at 3.26 ppm and another doublet of doublets centered at 3.41 ppm are observed for H13a and H13b, respectively (Table 3).

Interestingly, the X-ray structure reveals that there is an intra hydrogen bond between amine group of the 2-aminopyridine ligand and carbonyl group of the Meteug ligand, Table 2. This could enhance the stability and hinder a *cis-trans* isomerization of the complex that could be favorable for the antitumor activity [1].

The examined complex was tested for cell in *vitro* cytotoxicity on human cancer cells KB, HepG2, MCF7 and Lu. The IC50 values are 6.80, 14.83, 14.20 and 19.04 μg/mL, respectively.

4. CONCLUTIONS

The comprehensive structural studies of the designed complex by spectroscopic methods and single X-ray diffraction show consistently that the two ligand was introduced successfully into the complex of Pt(II). Particularly, the X-ray structure reveals that 2-aminopyridine in the complex occupies the *trans*-position with the ethylenic group of the Meteug ligand and the intra hydrogen bond between these two ligands. The complex exhibits a promising cytotoxicity on human cancer cell lines KB, HepG2, MCF7 and Lu with IC_{50} values of 6.80, 14.83, 14.20 and 19.04 μg/mL, respectively.

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