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Synthesis and spectroscopic characterizations on the nano structured complexes of platinum(IV) and palladium(II) with sulfamethoxazole drug anticancer therapy

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Abstract

A new two complexes of Pt(IV) and Pd(II)sulfamethoxazole (SMZ) were synthesized by the 1:2 (M: SMZ) molar ratio. We characterized complexes by IR spectra and thermal analysis. By measurement elemental analysis and molar conductance for complexes proved that obtained results these complexes have an electrolytic behavior. From IR spectra appeared form the results sulfamethoxazole antibiotic chelate play as a monobasic bidentate chelate this by Participate nitrogen atom for anilino with nitrogen atom of sulfonamido groups. Forever, from spectroscopic results suggests square planar geometry for Pt(IV) and Pd(II) sulfamethoxazole (SMZ). Thermal decomposition mechanisms for each Pt(IV) and Pd(II) complexes have been studied applying TG-DTG measurements. Employed kinetic thermodynamic parameters it is very necessary for DTGmax analysis form it can be determined decomposition steps for complexes. By transmittance electronic microscopy (TEM) images show nano-size particles appearance for Pt(IV) and Pd(II)complexes. The X-ray powder diffraction (XRD) patterns suggest the nano-sized structures for the SMZ complexes. The evaluation of cytotoxicity of Pt(IV) and Pd(II)complexes against HCT-116 cell line were performed. Also, it can be used in many antibacterial diseases.
Keywords: Pt(IV); Pd(II); sulfamethoxazole; chelation; anticancer; spectra; nano-sized.

1. INTRODUCTION

The literature survey has been revealed that the sulfa drugs and metal of sulfonamide compounds, sulfamethoxazole one of derivatives of sulfa drugs. Sulfamethoxazole (SMZ) have chemical formula ($C_{10}H_{11}N_3O_3S$) this show in (Fig. 1). SMZ has a molecular weight 253.28 (g/mol). Sulfa drugs are synthetic organic compounds derived from sulfanilamide. The synthesized metal complexes of sulfa drugs have been engaged for biological as antibacterial and antifungal entities, it can be employed for catalytic activity as ex. Olefin Polymerization [1-3]. Sulfa drugs are basis of several groups of drugs, which are called sulfa drugs or sulpha drugs. The original antibacterial sulfonamides are synthetic antimicrobial agents that basis essentially contain sulfonamide group it is (nonantibiotic drugs) and sulfonamide drugs the first antimicrobials used systematic. Sulfamethoxazole (SMZ) have composition [4-amino-N-(5-methyl-3-isoxazolyl) benzene sulfonamide is a sulfonamide, where sulfonamide is a class of chemical compounds that contain the -SO2NH group in its structure [4-7]. Sulfa drugs usually used as antimicrobial diseases for known it have antibacterial activity, such as sulfonylureas, anticovulsant sultiame and the newer drug is called thiazide diuretics this is based upon antibacterial sulfonamides. Sulfa drugs are characterized cheap, safe and effective; also it used in wide range in all countries the most used in Republic of Ireland as antimicrobial medications [8-10]. When occur preparations of some derivatives of sulfonamides such as (sulfadiazine or sulfamethoxazole) are mixed with Trimethoprim drug, which acts against dihydrofolate reductase. One of Sulfa

drugs called sulfathiazole is widely used to treatment of various bacterial infections, Sulfa drugs is important antimicrobial drugs, it have many derivatives used in developing countries because it have high effective, so it used as bacteriostatic and for inhibition growth and multiplication of bacteria, sulfa drugs such as sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthase (DHPS), an enzyme involved in folate synthesis[11-14]. sulfa drugs have many uses in treatment diseases such as allergies, cough, as well as antifungal and antimalarial functions. Therefore, sulfa drugs have uses in other medications such as thiazide diuretics including hydrochlorothiazide, indapamide and metolazone and other drugs, loop diuretics including bumetanide, furosemide and torsemide, acetazolamide,sulfonylureas including (glipi zide, glyburide and other drugs) and some COX-2 inhibitors such as celecoxib. Sulfasalazine antibiotic can be employed for treatment inflammatory bowel disease [15-18]. sulfonamide compounds have antibacterial activity against Gram-positive bacteria such as Staphylococcus aureus, Bacillus subtilis, Clostridium sporogenes,and other types Gram-negative bacteria such as Pseudomonas aeruginosa, Escherichia coli and therefore, sulfonamide compounds antifungal activity against Aspergillus fumigatus, Penicillium chrysogenum, Fusarium oxysporum, Candida albicans. Recently, there have been increases in studies regarding sulfonamides because have been potential applications in chemistry, biology and medicine [19-25].

2. Experimental

2.1. Chemicals and reagents

In this Study all chemicals reported in this paper, $PtCl_4$ and $PdCl_2$were of analytically reagent grade with high purity, Sulfamethoxazole used pure, sulfamethoxazole (SMA) have chemical formula ($C_{10}H_{11}N_3O_3S$) as shown in (Fig. 1). Sulfamethoxazole (SMA) was received from the Aldrich chemical company. All chemicals used without previous purification like $PtCl_4$ and $PdCl_2$.

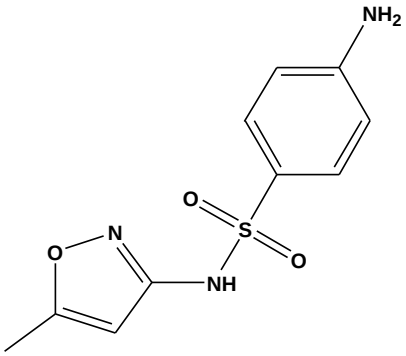


Fig. 1: Chemical structure of sulfamethoxazole (SMZ) drug

2.2. Preparation of Pt(IV) and Pd(II) complexes

The Pt(IV) and Pd(II) complexes were prepared by ratio 1:2 (M: SMZ), the mixture have molar ratio (1 mmol) Pt(IV) or Pd(II) chlorides with (2mmol) of sulfamethoxazole drug but in solvent of 95% methanol all of mixture on a hotplate it take about 5 hrs at temperature about 60 ^oC. These mixtures we left its stable 12 hours until observed volumes decreased to 1/2 quantity after that the precipitates formed immediately. We observed brown solid precipitations present after that filtered off and washed by a very low drops of methanol solution, diethyl ether after that at last step dried in a vacuum desiccator's both over anhydrous $CaCl_2$. We obtain final product of yields about 75-82%.

3. Results and discussions

3.1. Micro analytical and molar conductance study

The micro-analysis of (%C, %H, %N and %metal) elements are indicate high agreement with molar ratio 1:2 stoichiometry ($M^{II,IV}$: SMZ) shown mentioned in Table 1. Observed brown complexes Pd(II)/Pt(IV) both of them have an electrolytic nature [26] this is present narrow range for molar conductance information with scale about(85-112 µS), the results refers to indicate presence chloride ion in outside coordination sphere of complexes.

Table 1: Elemental analyses and physical data of Pt(IV) and Pd(II) complexes.

Complexes	Mp/ ^oC	Content ((calc.) found)				Λm ($\Omega^{-1}cm^{-1}mol^{-1}$)
		% C	% H	% N	% M	
$[[Pt(SMZ)_2].4Cl$	>300	(28.48) 28.39	(2.63) 2.55	(9.96) 9.87	(23.13) 23.09	112
$[Pd(SMZ)_2].2Cl$	>300	(35.13) 35.07	(3.24) 3.19	(12.29) 12.18	(15.56) 15.43	85

3.2.Infrared spectral study

The infrared spectra of SMZ complexes, present symmetric band of anilino group νs(NH) is existed at 3365-3250 cm^{-1}or not present, this lower shifts of of νas(NH) and νs(NH) anilino group (NH_2) or not present it because this group(-NH) involved in chelation toward metal ions as shown in suggested in(Fig. 2). The bending vibration of $–NH_2$ group $\delta(NH_2)$ were existed at 1635-1595 cm^{-1} for free NH_2 group of compound of sulfa drugs this is characterized by lower shifted wave numbers of SMZ complexes in range between 1602-1590 cm^{-1} [27].

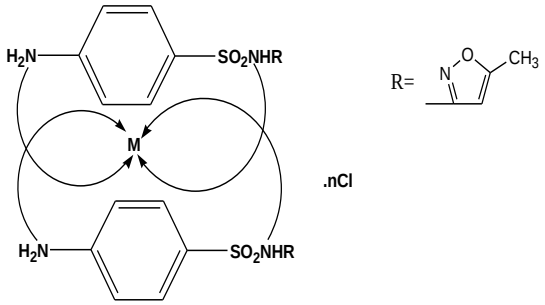


Fig. 2: Suggested formulas of $[Pt(SMZ)_2].4Cl$ and $[Pd(SMZ)_2].2Cl$ complexes.

Represent (–NH) band of sulfonamide group (–SO2NH) it was appeared at 3270-3240 cm-1 this is special by free sulfamethoxazole drug (SMZ)drug, present disappear or shifted to lower wave numbers upon complexation. These shifted in wave numbers indicated that (–NH2) anilino with sulfonamide (–NH) groups were shared in coordination mode toward metal ions of Ligand (Fig. 3). Significant bands at (1330-1302) cm-1 and other bands at (1152-1144) cm-1 for free ligands were referred asymmetric and symmetric stretching vibrations of sulfonyl group (–SO2) for (SMZ)drug, On other hand, it happen in complexes these observed bands showed in the same location or can be shifted higher wave numbers as IR spectra shown. From our result it chelation happen without shared from sulfonyl group (–SO2) [27].

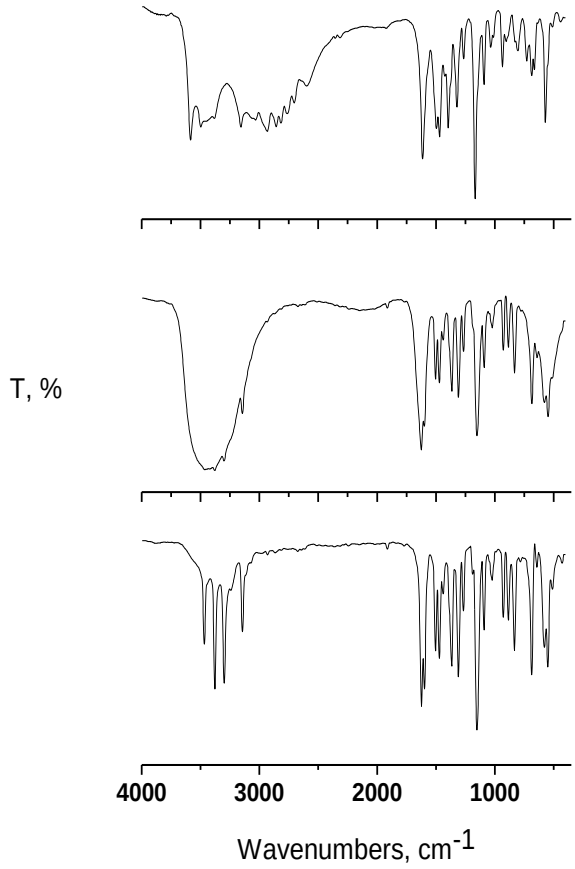


Fig. 3: Infrared spectra of (I): SMZ ligand, (II): $[Pt(SMZ)_2].4Cl$ and (III): $[Pd(SMZ)_2].{}_2Cl$ complexes

3.3.Thermo gravimetric analysis study

The thermal decompositions of Pt(IV) and Pd(II) SMZ complexes take place in two-to-three steps (Fig. 4). The first stage occurs at 50-300 ^oC corresponding to loss of chlorine atoms. Second decomposition step happens at 300-800 ^oC, and represents the loss of two SMZ moieties. However, the remaining organic moiety is decomposed at third and last step at 800 ^oC, leaving metal oxide as a residue. The last step corresponding to the formation of PtO_2 and PdO is endothermic in nature.

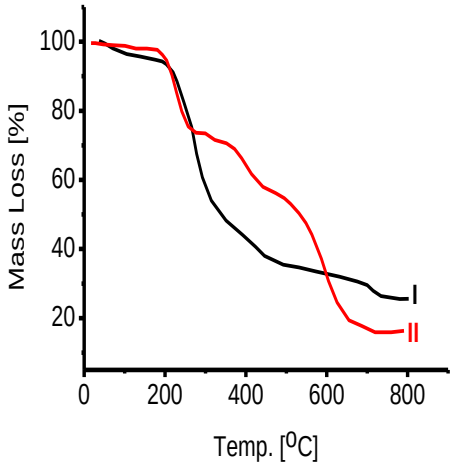


Fig. 4: TGA curves of (I): $[Pt(SMZ)_2].4Cl$ and (II): $[Pd(SMZ)_2].2Cl$ complexes

3.4. Kinetic thermodynamic parameters calculations

In case of non-isothermal decomposition reactions, the determination kinetic thermodynamic parameters were performed based on the analysis of TGA curves. Many equations [28-35] have been employed for the analyses of a TGA curve and calculating data for the kinetic thermodynamic parameters.

Most commonly methods for this purpose are Coat and Redfern [25] and Horowitz and Metzger approximation method [33]. Thermal characterization of SMZ complexes in terms assigned to stability ranges, the peak of temperatures and kinetic parameters values, can be shown in Fig. $5_{a,b}$ and Table 2.

Coats- Redfern equation (CR):

The Coats-Redfern equation, which is a typical integral method, able to be represented as shown:

$$\ln[-\frac{\ln(1-\alpha)}{T^2}] = -\frac{E^*}{RT} + \ln[\frac{AR}{\varphi E^*}] \qquad (1)$$

A plot of left-hand side (LHS) adverse 1/T was drawn. E^* is refers to energy of activation by (J mol^{-1}) unit and from it calculated the slop also A in (s^{-1}) from intercept value.

Horowitz-Metzger equation:

The Horowitz-Metzger equation is explained of the approximation methods. These authors derived the relation as shown following:

$$\log[\log(w_\alpha / w_\gamma)] = E^*\theta/2.303RT_s^2 - \log 2.303 \qquad (2)$$

where $\theta = T - T_s$, $w_\gamma = w_\alpha - w$, w_α = mass loss at reaction achieved; w = mass loss up to time t. The plot of $\log[\log(w_\alpha$

/ w_γ)] vs θ was drawn and present linear from the slope of which E^* able to calculated.

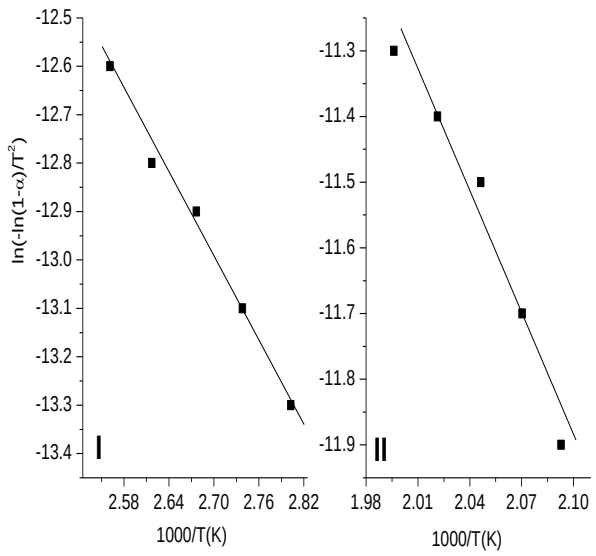


Fig. 5a: Coats–Redfern of the first step of the (I): Pt(IV) and (II): Pd(II) SMZ complexes.

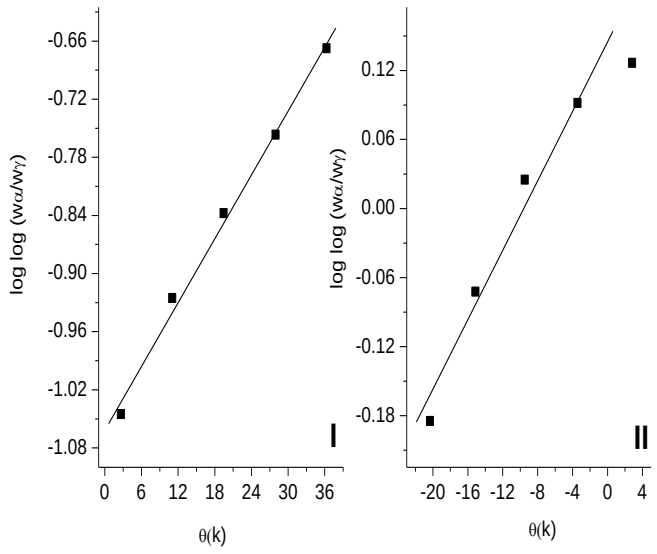


Fig. 5b: Horowitz–Metzger of the first step of the (I): Pt(IV) and (II): Pd(II) SMZ complexes

Table 2: Kinetic parameters using the Coats–Redfern (CR) and Horowitz–Metzger (HM) operated for the Pt(IV) and pd(II) SMZ complexes.

complex	stage	method	parameter					r
			E (kJ mol^{-1})	*A* (s^{-1})	Δ*S* (J mol^{-1} K^{-1})	Δ*H* (kJ mol^{-1})	Δ*G* (kJ mol^{-1})	
Pt(IV)	1st	CR	2.20×10^{4}	1.92×10^{5}	-1.42×10^{2}	1.91×10^{4}	7.21×10^{4}	0.9960
		HM	2.51×10^{4}	3.30×10^{2}	-2.14×10^{2}	2.18×10^{4}	9.89×10^{4}	0.9951
	2nd	CR	4.11×10^{5}	2.12×10^{33}	4.23×10^{2}	4.21×10^{4}	1.45×10^{5}	0.9952
		HM	4.09×10^{5}	4.88×10^{33}	4.31×10^{2}	4.11×10^{4}	1.60×10^{5}	0.9965
Pd(II)	1st	CR	5.19×10^{4}	4.40×10^{3}	-1.87×10^{2}	4.56×10^{4}	1.32×10^{5}	0.9810
		HM	6.22×10^{4}	3.91×10^{4}	-1.75×10^{2}	5.87×10^{4}	1.45×10^{5}	0.9726
	2nd	CR	2.34×10^{5}	3.69×10^{17}	0.86×10^{2}	2.34×10^{5}	1.87×10^{5}	0.9949
		HM	2.39×10^{5}	2.22×10^{15}	0.44×10^{2}	2.22×10^{5}	1.90×10^{5}	0.9960

3.5.XRD and TEM investigations

The XRD of Pt(IV) and Pd(II) for complexes to determined both diffraction patterns with intense and also defined sharp characters of these complexes, it is proved that crystalline phase (Fig. 6). By Debye-Scherrer equation can be determined total average crystallite sizes [37], in width peak of half height it referred to intense peak (FWHM) was found to be 18-20 nm. The TEM images (Fig. $7_{a,b}$) of the Pt(IV) and Pd(II) for two complexes observed particles and present a nano- shape. However, present average particle diameter of SMZ drug complexes can be detected from information showed by images from TEM investigation by a normal apparatus. From result of images, we observed the particle sizes have range between (20-25 nm). From images of TEM shown spherical shapes with a dark spots not large, present high mono and disperse and others uniform in sizes particles.

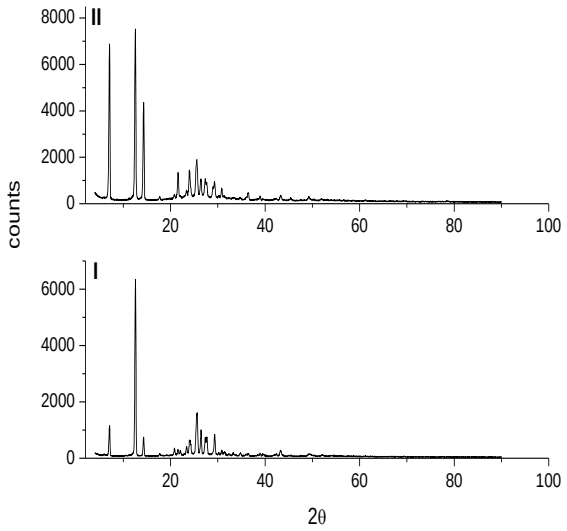
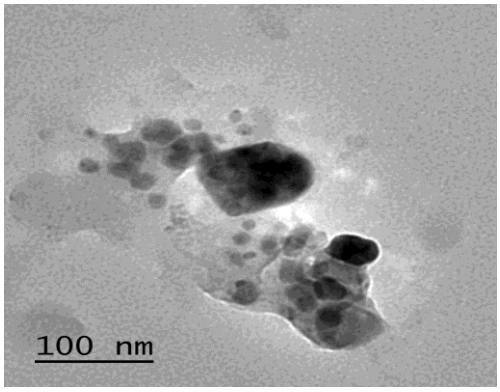
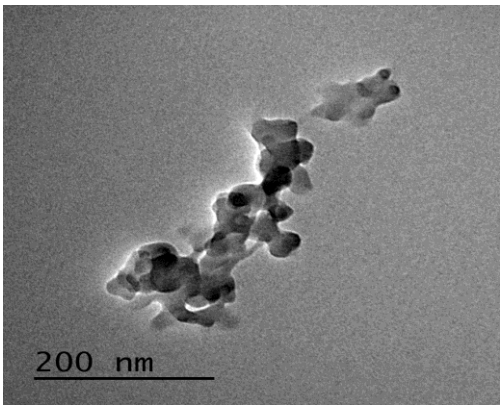


Fig. 6: XRD patterns of the (I): Pt(IV) and (II): Pd(II) SMZ complexes.



A



B

Fig. 7: TEM images of A: $[Pt(SMZ)_2].4Cl$ and B: $[Pd(SMZ)_2].2Cl$ complexes

3.6.Cytotoxicity assessment

From VACSERA Tissue Culture Unit we can obtain mammalian cell lines: HepG-2 cells (human Hepatocellular carcinoma). Also, the chemicals we enable to employed for preparation analysis: crystal violet, dimethyl sulfoxide (DMSO) and trypan blue dye were paid from Sigma (St. Louis, Mo., USA). Fetal Bovine serum, DMEM, RPMI-1640, HEPES buffer solution, L-glutamine, gentamycin and 0.25% Trypsin-EDTA were paid from Lonza. Crystal violet stain (1%): It composed of 0.5% (w/v) crystal violet and 50% methanol then made up to volume with ddH_2O and filtered through a Whatmann No.1 filter paper. Cell line Propagation:The cells were propagated in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum, 1% L-glutamine, HEPES buffer and gentamycin about 50µg/mL. All cells were kept at 37 ºC in atmosphere have humidified with 5% CO_2 and were subcultured in week make two times. Cytotoxicity evaluation using viability assay [38,39]. We used famous known technique called Cytotoxicity assay. At last the concentration required to cause toxic effects in 50% of intact cells, was determined by graphic plots of the dose response curve for each of conc. by used Graphpad Prism software (San Diego, CA. USA).

In final of this research the Complexes of sulfamethoxazole (SMZ) used in vitro cytotoxicity Activities; it can be tested adverse colon carcinoma (HCT-116) cell line human with essentially as standard drug (doxrubcin). From final data of results can be defined to inhibitiory concentration of (IC_{50}). When comparison between information of SMZ complexes and standard doxrubcin, complexes of Pt(IV) and Pd(II) have IC_{50} equal 12 and 8 µg against colon carcinoma (HCT-116) cell line, respectively. From information we reach to it we able to indicate that Pd(II) complex can be used as anti-tumor drug.

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