

In situ methanolic solvent synthesis, spectroscopic and thermogravimetric characterizations of three new transition metal complexes of trimethoprim drug

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Trimethoprim drug (TMP) complexes of copper (II), cobalt (II), and nickel (II) were prepared and discussed by using elemental analysis (C, H, N analysis), magnetic, molar conductance, FTIR, Raman spectroscopy, electron spin resonance (ESR) and UV-vis spectroscopy analyses. TMP drug coordinated as a tridentate ligand towards the respected three metal ions through two nitrogen atoms of amino groups and nitrogen atom of pyrimidine ring which flanked between $-NH_2$ groups, these assignments confirmed by spectroscopic, magnetic, ESR and thermogravimetric analyses with formulas $[Cu(TMP)(H_2O)_3]Cl_2$, $[Co(TMP)(H_2O)_3]Cl_2$ and $[Ni(TMP)(H_2O)]Cl_2$. Copper (II) and cobalt (II) complexes have an octahedral geometrical structure included one TMP molecule, three coordinated water molecules and two uncoordinated chlorine atoms while, nickel(II)–TMP complex has a tetrahedral geometric configuration that involved one TMP molecule, one coordinated water molecule and two uncoordinated chlorine atoms. The activation energies and other kinetic thermodynamic parameters were estimated based on the employed of the Coats-Redfern and Horowitz-Metzger equations. The nano-structured form of the synthesized TMP complexes was confirmed dependent on the transmission electron microscopy (TEM).

Keywords: Complexation; trimethoprim; transition metals; TGA; FTIR; ESR; kinetic thermodynamic parameters.

INTRODUCTION

The trimethoprim (TMP; Fig. 1) was classified as one an interesting anti-biotic and anti-parasitic drug¹. The TMP drug is distinguished as a good complexing agent towards different metal ions because it contains three nitrogen atoms on the pyrimidine ring^{2–4}. Trimethoprim has potential binding sites for metal ions. Several authors have studied the interaction of this ligand with biological metal ions and the coordination of TMP *via* a NH_2 nitrogen atom has been inferred based on IR and visible measurements^{5, 6}. However, other authors have shown by X-ray diffraction methods that the coordination site of the TMP molecule is the N_1 of the pyrimidine ring^{7–14}. On the other hand, other research groups^{15–27} have prepared and characterized complexes of TMP with metal(II)/(III) and the spectral and analytical data show that the ligand acts as a monodentate or bidentate. Trimethoprim and isoniazid as a mixed ligand have been coordinated towards some of transition metal ions²⁸. These resulted complexes have coordinated via nitrogen of pyrimidine ring and nitrogen atom of amino group of isoniazid²⁸. Silver(I) complexes of mixed ligand of both trimethoprim and pyrimethamine were synthesized and well-characterized by analytical and spectroscopic analyses. The Ag(I) metal ion was coordinated with trimethoprim and pyrimethamine ligands through the nitrogen atoms of pyrimidine ring with three and four coordination behavior²⁹. Silver(I) trimethoprim complexes were recorded a stronger antibacterial activity in comparison with free TMP drugs. Platinum (II) and Pd (II) complexes of TMP and pyrimethamine mixed ligands have a square planar geometry³⁰. The Cu (II), Zn (II) and Ti(IV)–TMP complexes have been synthesized and

spectroscopically characterized. These complexes have been shown a good antibacterial activity, besides this result, the Ti(IV) and Cu(II) complexes have excellent anticancer efficiency³¹. Mn (II), Fe (III), Co (II), Ni (II), Cu (II), Zn (II), Pb (II) and La (III) complexes of TMP derivative were prepared and the speculated structures were designed using a different physical and chemical tool of analyses. The geometry of these complexes confirmed that the TMP derivative ligand act as a bidentate chelate³². Herein, in this article, the 1:1 molar ratio of Cu (II), Co (II) and Ni (II)–TMP complexes were synthesized, spectroscopic and thermal analysis discussed.

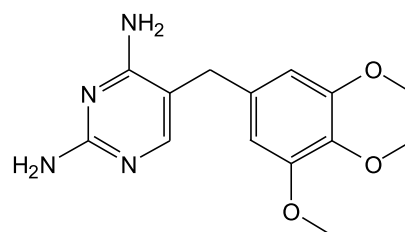


Figure 1. Structure of trimethoprim (TMP) drug

EXPERIMENTAL

Chemicals

Copper (II), cobalt (II) and nickel (II) chloride hydrate salts as well as trimethoprim drug were received from Sigma-Aldrich Chemical Company, USA and used in the preparation without further purification.

Instruments

The type of analyses and their corresponding models can be listed as follows:

1. Elemental analyses; Conductance; FTIR spectra; Raman Spectroscopy; Thermogravimetric; Electronic spectra; Magnetic moment; XRD; ESR.

2. Models: Perkin Elmer CHN 2400; Jenway 4010 conductivity meter; Bruker FTIR Spectrophotometer; Bruker FT Raman with laser 50 mW; TG/DTG-50H, Shimadzu thermogravimetric analyzer; UV2 Unicam UV/Vis Spectrophotometer; Magnetic Susceptibility Balance; X ,Pert PRO PANanalytical, with copper target; Jeol, JES-FE2XG Spectrometer (Frequency 9.44 GHz).

Synthesis

Copper, cobalt and nickel (II)–trimethoprim complexes were prepared by mixing 1.0 mmol of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ in 25 mL methanol with 1.0 mmol TMP in 25 mL methanol. The mixtures were refluxed for ~ 3 hours till the colored precipitates appeared, the solid products were filtered off and washed several times with little amounts of methanol. The solid precipitates were dried and closed in a vacuum desiccator over anhydrous CaCl_2 .

RESULTS AND DISCUSSIONS

Elemental analysis and conductance measurements

The solid products of copper (II), cobalt (II) and nickel (II)–TMP complexes have a yield within the 72–76% range. The solubility of the synthesized complexes is soluble in DMSO and DMF organic solvents but insoluble in most organic solvents and water. The synthesized three Cu (II), Co (II) and Ni (II)–TMP complexes have a melting point at 315°C, 283°C and 260°C respectively, these sharp melting points of the solid complexes have supported the absence of any impurities. The elemental analysis (C, H, N and metal percentages) of the experimental results has a good matched with theoretical data as listed in Table 1. The molar conductance of the 10^{-3} M synthesized Cu(II), Co(II) and Ni(II)–TMP complexes that dissolved in dimethyl sulfoxide (DMSO) solvent have $\Lambda_m = 76, 81,$ and $73 \text{ ohm}^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$ respectively. These results data confirmed that all three TMP complexes have an electrolytic property³³. The appearance of various colored

complexes confirmed the formation of new compositions. The speculated structures of the synthesized 1:1 (M:L) Cu(II), Co(II) and Ni(II)–TMP complexes are shown in Fig. 2 with molecular formula $[\text{Cu}(\text{TMP})(\text{H}_2\text{O})_3]\text{Cl}_2$, $[\text{Co}(\text{TMP})(\text{H}_2\text{O})_3]\text{Cl}_2$ and $[\text{Ni}(\text{TMP})(\text{H}_2\text{O})]\text{Cl}_2$.

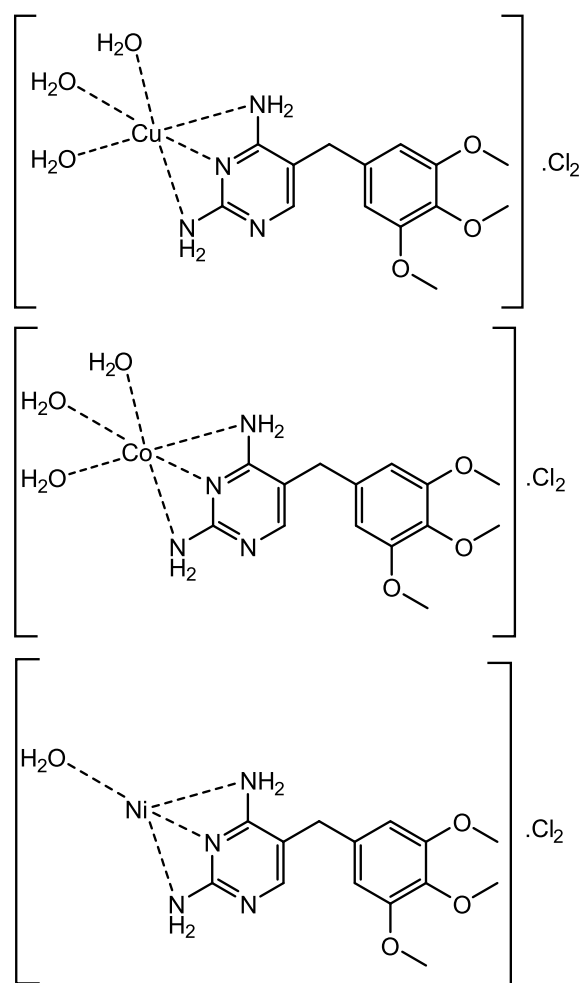


Figure 2. Suggested structures of the synthesized Cu(II), Co(II) and Ni(II)–TMP complexes

FTIR and Raman spectra

Infrared spectra of the copper(II), cobalt(II) and nickel(II) complexes as well as trimethoprim free ligand are displayed in Fig. 3a, 3b, 3c, 3d and their assignments are tabulated in Table 2. The trimethoprim free ligand has an oxygen and nitrogen donating atoms through

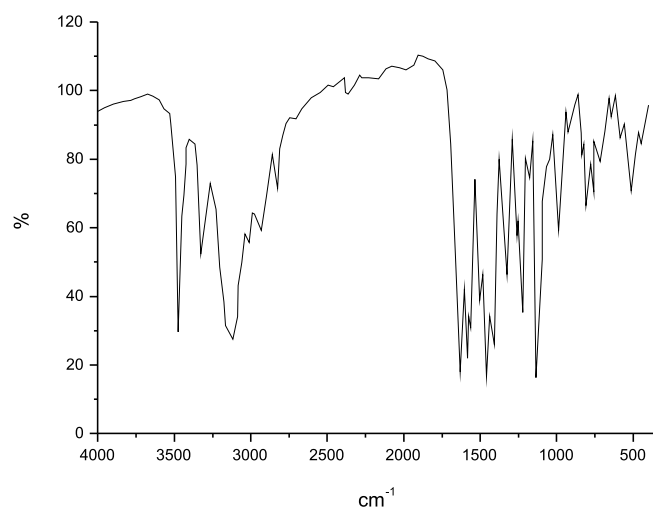
Table 1. Elemental analysis and physical data of Cu^{2+} , Co^{2+} and Ni^{2+} –TMP complexes

Complex	Color	Conductance/ ($\text{ohm}^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$)	Element	Calc./%	Found/%
Cu(II)	Greenish Brown	76	C	35.12	34.68
			H	5.05	4.82
			N	11.70	11.63
			Cl	14.81	14.75
			Cu	13.27	13.21
Co(II)	Blue	81	C	35.46	35.45
			H	5.10	4.62
			N	11.81	11.54
			Cl	14.95	14.91
			Co	12.43	12.35
Ni(II)	Green	73	C	38.40	38.31
			H	4.60	4.39
			N	12.79	12.60
			Cl	16.19	16.14
			Ni	13.40	13.34

Table 2. Infrared spectral data (cm^{-1}) of TMP and its complexes

Compounds	Frequencies, cm^{-1}				
	$\nu_{\text{as}}(\text{NH})$	$\nu_{\text{s}}(\text{NH})$	$\nu(\text{C}=\text{N})$	$\nu(\text{C}=\text{C})$	$\nu(\text{M}-\text{N})$
TMP	3470	3319	1635	1594	–
Cu(II)	3403	3306	1663	1591	514
Co(II)	3404	3303	1674	1590	505
Ni(II)	3404	3302	1674	1588	505

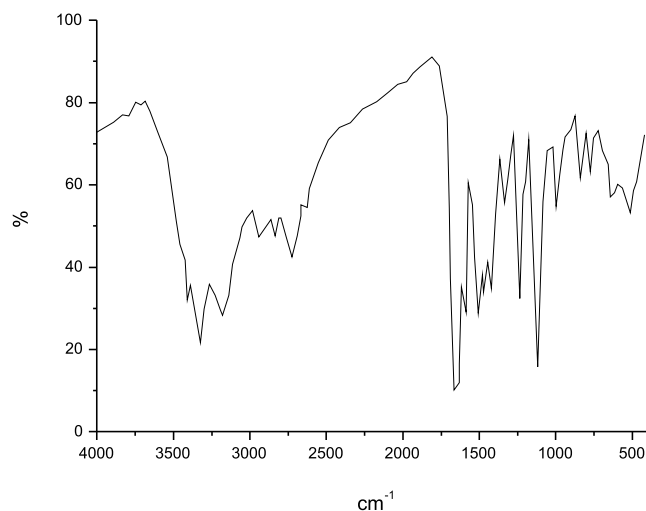
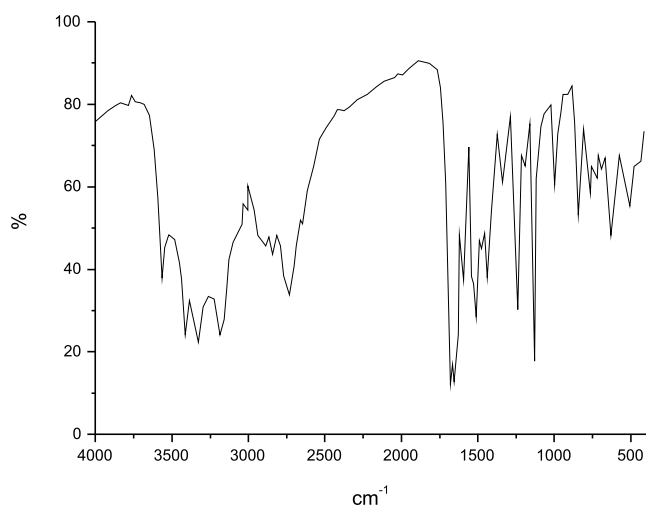
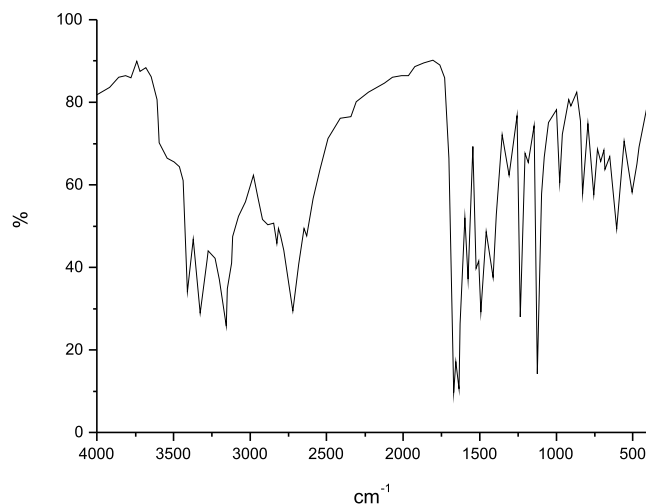
pyrimidine nitrogen atoms ($-\text{NH}_2$ & $-\text{C}=\text{N}$ groups) and oxygen of methoxyl groups. Trimethoprim free drug has a number of characteristic groups with stretching frequencies at 3470, 3319, 1635 and 1594 cm^{-1} due to $\nu_{\text{as}}(\text{NH}_2)$, $\nu_{\text{s}}(\text{NH}_2)$, $\nu(\text{C}=\text{N})$, $\nu(\text{C}=\text{C})$ of pyrimidine and trimethoxy moieties. Regarding the vibration bands of $\nu_{\text{as}}(\text{NH}_2)$, $\nu_{\text{s}}(\text{NH}_2)$ and $\nu(\text{C}=\text{N})$ of the pyrimidine ring are shifted to lower/higher wavenumbers after complexation and exhibited within the range of $3404\text{--}3403 \text{ cm}^{-1}$, $3306\text{--}3302 \text{ cm}^{-1}$ and $1674\text{--}1663 \text{ cm}^{-1}$ respectively, this results supported the coordinated of nitrogen atoms of amino group and $-\text{C}=\text{N}$ towards central metal ions [2-4]. The new frequencies present in the spectra of complexes at $514\text{--}505 \text{ cm}^{-1}$ region are attributed to $\nu(\text{M}-\text{N})$ and [3]. The infrared assignments confirmed that the TMP coordinated to respected metal ions as a tri-dentate ligand through the nitrogen atoms of the $-\text{NH}_2$ & $-\text{C}=\text{N}$ groups for the pyrimidine ring. The Raman spectra (Fig. 4a, 4b, 4c) also agree with infrared spectra of the Cu(II), Co(II) and Ni(II)–TMP complexes. The presence of new frequency bands at around $\sim 430 \text{ cm}^{-1}$ in the case of the synthesized complexes are assigned to the $\nu(\text{M}-\text{N})$ vibration bands. In FTIR spectra of the prepared complexes, there are broad absorption bands of (OH) with a maximum at $3174\text{--}3166 \text{ cm}^{-1}$ and characteristic bands of bending to water hydrated, $\delta(\text{H}_2\text{O})$ at $1645\text{--}1640 \text{ cm}^{-1}$ confirming the presence of coordinated water molecules.

**Figure 3a.** FTIR spectrum of TMP

Electronic spectra and magnetic susceptibility

The electronic spectrum of copper(II)–TMP complex displays two distinguished bands. A low-intensity band at 19.608 cm^{-1} is assigned to ${}^2\text{E}_g \rightarrow {}^2\text{T}_2g$ electronic transition and another low-intensity band at 23.923 cm^{-1} are due to symmetry forbidden $\text{L} \rightarrow \text{M}_{\text{CT}}$. Based on the solid reflectance spectrum, the distorted octahedral geometry of $[\text{Cu}(\text{TMP})(\text{H}_2\text{O})_3]\text{Cl}_2$ is suggested^{34, 35}. The complex displays a higher magnetic moment value (1.88 BM)

than that of spin only moment (1.73 BM). This can support the absence of any metal–metal interaction inside the crystal of the distorted geometry³⁶. The $[\text{Co}(\text{TMP})$

**Figure 3b.** Infrared spectrum of $[\text{Cu}(\text{TMP})(\text{H}_2\text{O})_3]\text{Cl}_2$ complex**Figure 3c.** Infrared spectrum of $[\text{Co}(\text{TMP})(\text{H}_2\text{O})_3]\text{Cl}_2$ complex**Figure 3d.** The infrared spectrum of $[\text{Ni}(\text{TMP})(\text{H}_2\text{O})_3]\text{Cl}_2$ complex

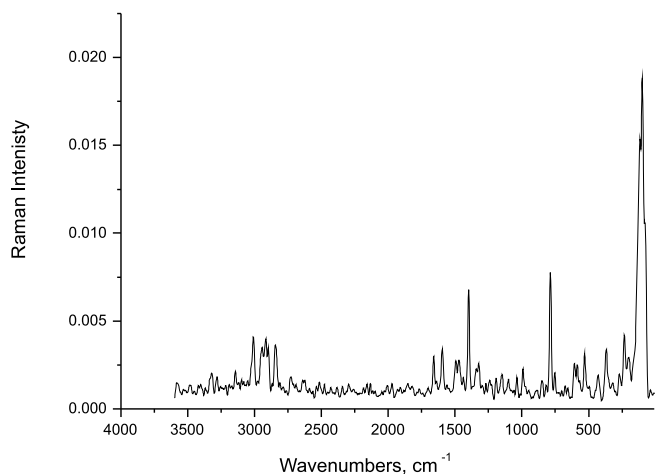


Figure 4a. Raman spectrum of TMP

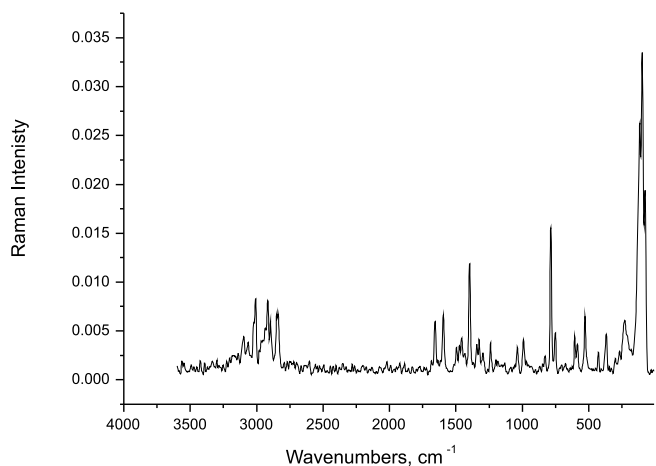


Figure 4b. Raman spectrum of Co(II)-TMP complex

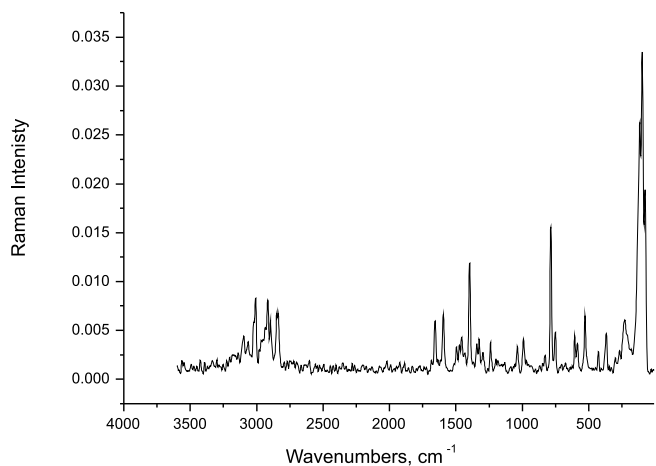


Figure 4c. Raman spectrum of Ni(II)-TMP complex

(H₂O)₃]Cl₂ complex shows a magnetic moment at 3.92 B.M. corresponding to three unpaired electrons. The electronic spectrum of the Co(II) complex displays three bands at 12.195, 15.649 and 24.570 cm⁻¹. These bands are attributed to ⁴T_{1g} → ⁴T_{2g}(F) (ν₁), ⁴T_{1g} → ⁴A_{2g}(F) (ν₂) and ⁴T_{1g} → ⁴T_{1g}(P) (ν₃) electronic transitions, respectively. The band assignments suggest an octahedral geometrical structure for the Co(II)-TMP complex³⁷. The nickel(II) complex shows magnetic moment 2.90 B.M. corresponding to two unpaired electrons³⁸. Electronic spectrum displays bands at 12.315, 15.698 and 21.052 cm⁻¹. These bands may be assigned to ³A₂(F) → ³T₂(F) (ν₁), ³A₂(F) → ³T₁(F) (ν₂) and ³A₂(F) → ³T₁(P) (ν₃) transitions respec-

tively. It suggests tetrahedral geometry of [Ni(TMP)(H₂O)]Cl₂ complex³⁸.

ESR spectrum of copper(II) complex

The ESR spectrum of the [Cu(TMP)(H₂O)₃]Cl₂ complex sample was scanned at room temperature (Fig. 5).

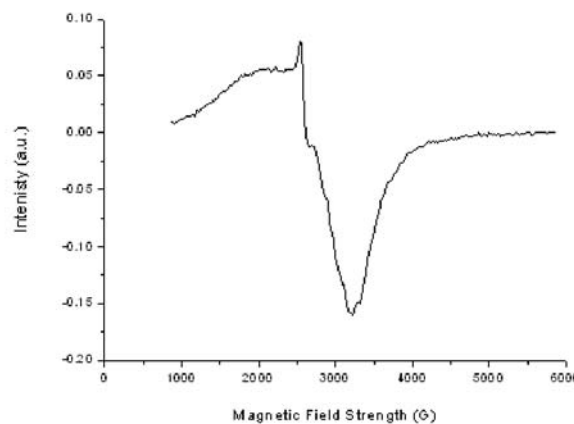


Figure 5. ESR spectrum of copper(II)-TMP complex

The experimental data for the copper(II)-TMP complex are $g_{||} = 2.6831$, $g_{\perp} = 2.1321$ and $G = 5.1711$. The anisotropic G values have been calculated by Kneubuhl's method³⁹. $G = (g_{||}-2)/(g_{\perp}-2)$ which measures the exchange interaction between copper(II) centers. According to Hathaway⁴⁰ if the G value is greater than 4, the exchange interaction is negligible, while a value of less than 4 indicates a considerable exchange interaction in the complexes. As $G = 5.1711$ for the present complex indicates that there is no spin exchange interaction in the copper complex and hence distorted octahedral geometry proposed for the Cu(II) complex.

TGA-DTG analyses

Thermal analysis diagrams (TG/DTG) of the free TMP ligand and its studies copper(II), cobalt(II) and nickel(II)-TMP complexes are represented in Fig. 6. The ligand completely decomposed at 700°C with two differential thermogravimetric peaks at 275°C and 600°C, (Figure 6a). From the TG curve, it appears that the sample decomposes in two stages over the temperature range 125–800°C. The first step occurs at (275°C) with a mass loss of (obs. = 61%, calc. = 62%) due to elimination of 1,2,3-trimethoxy-5-methyl-benzene. The second step starts at 375°C and ends at 800°C with a mass loss (obs. = 39%, calc. = 38%) attributed to elimination of pyrimidine-2,4-diamine moiety.

The thermal decomposition of the [Cu(TMP)(H₂O)₃]Cl₂ complex (Fig. 6b) occurs at three steps. The first degradation step takes place in the range of 75–178°C (DTG_{max} = 132°C) and it is corresponding to the elimination of two coordinated water molecules due to a weight loss of 8% in a good match with a theoretical value 7.5%. The second step fall in the range of 178–430°C (DTG_{max} = 325°C) which is assigned to loss of one water and chlorine gas molecules beside 1,2,3-trimethoxy-5-methyl-benzene moiety with a weight loss 55% and the calculated value is 65%. The third step fall in the range of 430–800°C (DTG_{max} = 612°C) which is assigned to loss of pyrimidine-2,4-diamine moiety with a weight loss 22.5% and the calculated value is 23%. The CuO

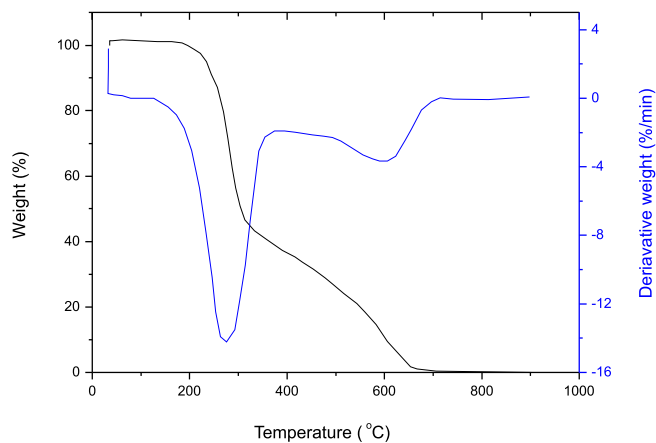


Figure 6a. TG-DTG curves of free TMP

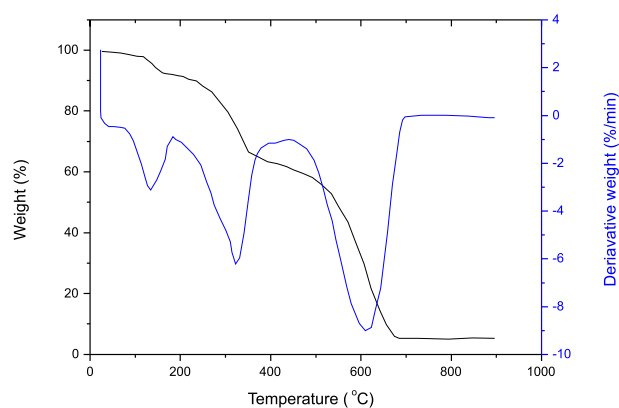


Figure 6b. TG-DTG curves of [Cu(TMP)(H₂O)₃]Cl₂ complex

is the final product that remains stable till 800°C. The thermal decomposition of [Co(TMP)(H₂O)₃]Cl₂ complex (Fig. 6c) completely in four steps. The first step ranged at 55–175°C (DTG_{max} = 116°C) corresponding to the loss of 2H₂O molecules, representing a weight loss of 7% and its calculated value is 7.5%. The second and third steps ranged at 175–509°C (DTG_{max} = 280 & 473°C) corresponding to the loss of also H₂O, Cl₂ and 1,2,3-trimethoxy-5-methyl-benzene molecules, representing a weight loss of 56% and its calculated value is 57%. The fourth step occurring at 509–800°C (DTG_{max} = 568°C) corresponding to the loss of pyrimidine-2,4-diamine moiety, representing a weight loss of 23% and its calculated value is 23%. The CoO is the final product that remains stable till 800°C. The [Ni(TMP)(H₂O)]Cl₂ complex decomposed along two decomposition steps (Fig. 6d). The first extended from 152°C to 365°C (DTG_{max} = 262°C) and can be assigned to the loss of H₂O and Cl₂ molecules, representing a weight loss of 19% and its calculated value is 20%. The second step occurring at 365–800°C (DTG_{max} = 545°C) corresponding to the loss of the 1,2,3-trimethoxy-5-methyl-benzene and other pyrimidine-2,4-diamine moiety moieties, representing a weight loss of 66.5% and its calculated value is 67%. The final products resulted at 800°C contain NiO oxide.

Kinetic thermodynamic results

The calculated thermodynamic parameters from TG and DTG are listed in Table 3. The thermodynamic activation parameters of decomposition processes for dehydrated complexes namely activation energy (ΔE*), enthalpy (ΔH*), entropy (ΔS*) and Gibbs free energy change of the decomposition (ΔG*) were evaluated

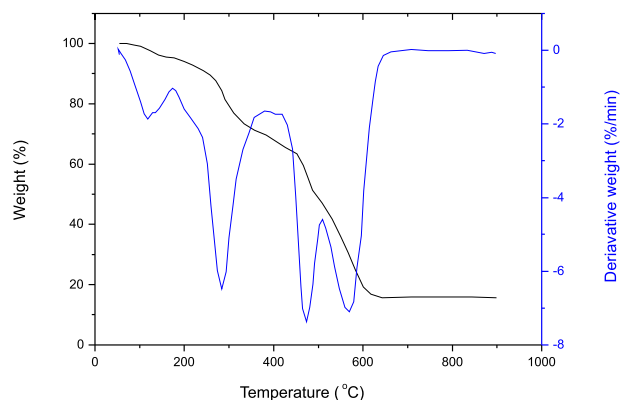


Figure 6c. TG-DTG curves of [Co(TMP)(H₂O)₃]Cl₂ complex

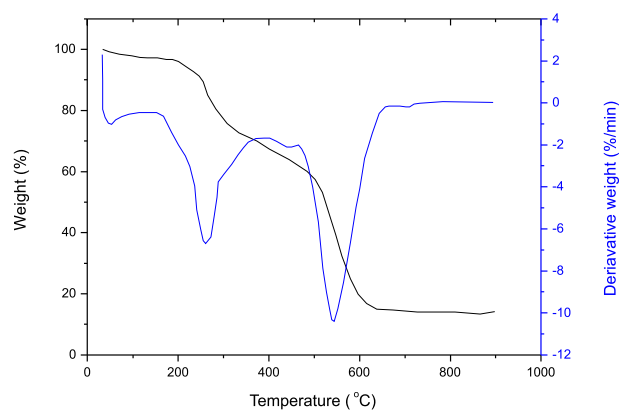


Figure 6d. TG-DTG curves of [Ni(TMP)(H₂O)]Cl₂ complex

graphically by employing the Coats-Redfern and Horowitz – Metzger relations^{41, 42}. To assess the influence of the structural properties of the ligand and the type of the metal on the thermal behavior of the complexes, the order, n , and the heat of activation E of the various decomposition stages were determined from the TG and DTG thermograms.

Coats – Redfern equation

The equations as follow:

$$\ln \left[\frac{1 - (1 - \alpha)^{1-n}}{(1-n)T^2} \right] = \frac{M}{T} + B \quad \text{for } n \neq 1 \quad (1)$$

$$\ln \left[\frac{-\ln(1 - \alpha)}{T^2} \right] = \frac{M}{T} + B \quad \text{for } n = 1 \quad (2)$$

where $M = -E/R$ and $B = \ln AR/\Phi E$; E , R , A , and Φ are the heat of activation, the universal gas constant, pre-exponential factor, and heating rate, respectively. The correlation coefficient, r , was computed using the least square method for different values of n , by plotting the left-hand side of Eqs. (1) or (2) versus $1000/T$.

Horowitz – Metzger equation

The relations derived are as follow:

$$\ln[-\ln(1 - \alpha)] = \frac{E}{RT_m} \Theta \quad (3)$$

Where α is the fraction of the sample decomposed at time t and $\Theta = T - T_m$.

A plot of $\ln[-\ln(1 - \alpha)]$ against Θ , was found to be linear, from the slope of which E , was calculated and Z can be deduced from the relation :

$$Z = \frac{E\varphi}{RT_m^2} \exp\left(\frac{E}{RT_m}\right) \quad (4)$$

Where φ is the linear heating rate, the order of reaction, n , can be calculated from the following relationship:

$$n = 33.64758 - 182.295\alpha_m + 435.9073\alpha_m^2 - 551.157\alpha_m^3 + 357.3703\alpha_m^4 - 93.4828\alpha_m^5$$

The n value which gave the best fit ($r \approx 1$) was chosen as the order parameter for the decomposition stage of interest. From the intercept and linear slope of such stage, the A and E values were determined. The other kinetic parameters, ΔH , ΔS and ΔG were computed using the relationships; $\Delta H = E - RT$, $\Delta S = R[\ln(Ah/kT) - 1]$ and $\Delta G = \Delta H - T\Delta S$, where k is the Boltzmann's constant and h is the Planck's constant. The following remarks can be pointed out: (i) all complexes decomposition stages show the best fit for ($n = 1$) indicating a first-order decomposition in all cases. Other n values (e.g. 0, 0.33 and 0.66) did not lead to better correlations^{43, 44}; (ii) the negative values of activation entropies ΔS indicate a more ordered activated complex than the reactants and/or the reactions are slow⁴⁵; (iii) the positive values of ΔH mean that the decomposition processes are endothermic.

Transmission electron microscopy

TEM image (Fig. 7a, 7b, 7c) shows that Cu(II)–TMP, Co(II)–TMP and Ni(II)–TMP complexes nanoparticles are aggregates of irregular shape. The size of [Cu(TMP)(H₂O)₃]Cl₂, [Co(TMP)(H₂O)₃]Cl₂ and [Ni(TMP)(H₂O)]Cl₂ complexes nanoparticles calculated from TEM images are in the range of 5–20 nm (Fig. 7).

Complexes of trimethoprim with Cu(II), Co(II), and Ni(II) have been synthesized. Then, these complexes have been characterized by spectroscopic techniques involving UV–vis, FTIR, Raman spectroscopy and ESR. The CHN elemental analysis, molar conductance, magnetic susceptibility, and thermal behavior of complexes have also been investigated. The synthesized TMP behaves as tridentate ligand NNN donor via two nitrogen atoms of amino groups and nitrogen atom of pyrimidine ring. The data of UV–vis spectra and the magnetic measurements recommended that the octahedral geometry for copper(II) and cobalt(II) complexes except for Ni(II) which is tetrahedral was suggested. Furthermore, the kinetic and thermodynamic parameters for the decomposition steps were calculated using the Coats-Redfern and Horowitz-Metzger methods. The morphology of the nano-structured form of the TMP metal complexes has been investigated by transmission electron microscopy (TEM).

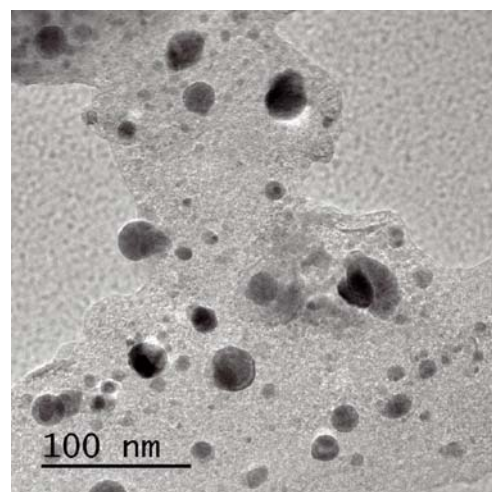


Figure 7a. TEM image of [Cu(TMP)(H₂O)₃]Cl₂ complex

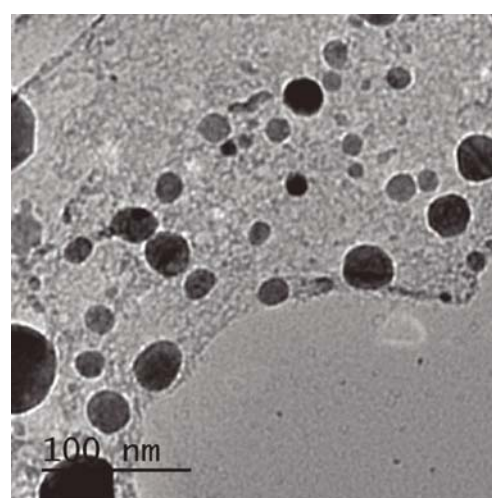


Figure 7b. TEM image of [Co(TMP)(H₂O)₃]Cl₂ complex

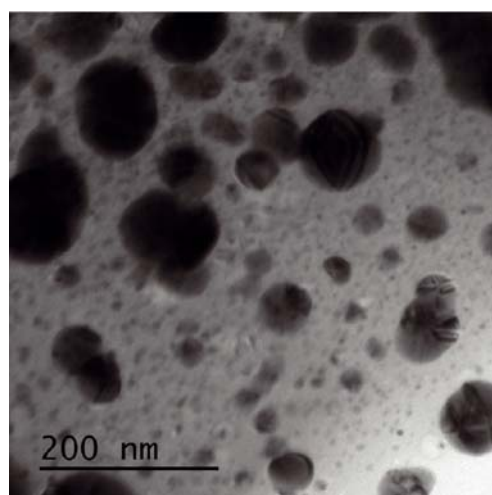


Figure 7c. TEM image of [Ni(TMP)(H₂O)]Cl₂ complex

Table 3. Kinetic parameters of TMP ligand and Cu(II), Co(II) and Ni(II) complexes

Compound	Methods	2 nd step				
		r	E (kJ mol ⁻¹)	ΔS* (J k ⁻¹ mol ⁻¹)	ΔH* (kJ mol ⁻¹)	ΔG* (kJ mol ⁻¹)
TMP	CR	0.9933	2.88*10 ⁴	-1.43*10 ²	2.65*10 ⁴	1.33*10 ⁵
	HM	0.9946	2.92*10 ⁴	-1.37*10 ²	2.71*10 ⁴	1.41*10 ⁵
Cu(II)	CR	0.9959	1.76*10 ⁴	-1.23*10 ²	1.65*10 ⁴	1.44*10 ⁵
	HM	0.9912	1.70*10 ⁴	-1.30*10 ²	1.61*10 ⁴	1.37*10 ⁵
Co(II)	CR	0.9965	1.95*10 ⁴	-1.41*10 ²	1.87*10 ⁴	2.21*10 ⁵
	HM	0.9954	2.10*10 ⁴	-1.32*10 ²	1.69*10 ⁴	1.99*10 ⁵
Ni(II)	CR	0.9972	1.88*10 ⁴	-1.25*10 ²	2.01*10 ⁴	1.43*10 ⁵
	HM	0.9924	1.94*10 ⁴	-1.26*10 ²	1.98*10 ⁴	1.28*10 ⁵

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