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Synthesis, Chemical Structure Elucidation, and Biological Studies on the Effect of Some Vital Metal Ions on Sulfadoxine[1]

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Abstract—Complexes of sulfadoxine as a pharmaceutical ligand with Ca(II), Mg(II), Zn(II), Fe(III), and VO(II), were synthesized and characterized by microanalysis, conductance, infrared and thermogravimetric (TGA/DTG and DTA) measurements. The ligand can be coordinate as a bidentate feature via (C=N) and (S=O) groups. Sulfadoxine ligand as well as their complexes has been checked against some kinds of bacteria and fungi which gave a significant effect. The kinetic thermodynamic parameters such as: activation of E^*, ΔH^*, ΔS^*, and ΔG^* were estimated using Coats–Redfern as well as Horowitz–Metzger equations.

Keywords: sulfadoxine complexes, infrared spectra, electronic spectra, thermal analysis, antimicrobial activity

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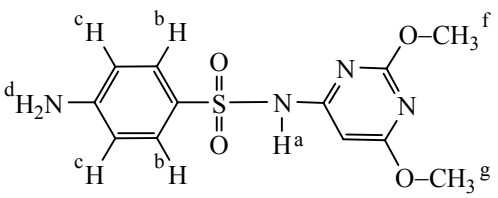
INTRODUCTION

Metal–organic frameworks became interesting field in the last two decades, not only for the physical applications in the areas such as catalysis, molecular adsorption, magnetism, nonlinear optics, and molecular sensing, but also from their novel topologies and intriguing structural diversities [1–3]. On the other hand, many organic drugs, which possess modified pharmacological and toxicological properties administered in the form of metallic complexes [4], have the potential to act as ligands and the resulting metal–drug complexes are particularly important both in coordination chemistry and biochemistry [5–8], however, the study of metal–drug complexes is still in its early stages, thus representing a great challenge in current synthetic chemistry, coordination chemistry and medicinal bioinorganic chemistry [9–11]. Sulfa drugs have attracted special attention for their therapeutic importance as they were used against a wide spectrum of bacterial diseases [12–14]. Also, some sulfa drugs were used in the treatment of cancer, malaria, leprosy and tuberculosis [14].

Sulfadoxine [4-Amino-*N*-(5,6-dimethoxy-4-pyrimidinyl) benzene-sulfonamide, Fig. 1], was proved to be an effective, slow-acting blood schizontocide in clinical trials [15–18]. Subsequent studies revealed more rapid clinical response and faster action when combining sulfadoxine with pyrimethamine against falciparum and vivax malaria, including chloroquine resistant strains, in Southeast Asia and Africa [19–38]. In the literature survey, the synthesis and characterization of sulfa drugs complexes with some metal ions have been described [39–48]. In this article, the coordination mode of sulfadoxine chelating via metal ions such as Ca(II), Mg(II), Zn(II), Fe(III), and VO(II) have been investigated. The antibacterial and antifungal activities of sulfadoxine and its complexes were also evaluated.



Sulfadoxine

Fig. 1. Structural scheme of sulfadoxine (Sdx).

[1] The text was submitted by the authors in English.

Table 1. Elemental analysis and physical data of sulfadoxine complexes

Complex	M_w, g/mol	mp, °C	Color	Elemental analysis data								Λ_m, $\Omega^{-1}cm^2mol^{-1}$
				C, %		H, %		N, %		M, %		
				calculated	found	calculated	found	calculated	found	calculated	found	
$[Ca(Sdx)(Cl)_2(H_2O)_2]$ ($C_{12}H_{18}N_4O_6SCl_2Ca$)	457	226	Yellowish white	31.51	31.00	3.94	4.25	12.25	12.69	8.75	8.63	18
$[Mg(Sdx)(Cl)_2(H_2O)_2]\cdot 5H_2O$ ($C_{12}H_{28}N_4O_{11}SCl_2Mg$)	531	228	Yellow	27.12	27.83	5.27	5.90	10.55	10.93	4.52	4.31	22
$[Zn(Sdx)(SO_4)]\cdot H_2O$ ($C_{12}H_{16}N_4O_9S_2Zn$)	489.4	217	Yellowish white	29.42	30.74	3.27	3.19	11.44	11.42	13.36	13.12	10
$[Fe(Sdx)(NO_3)_3(H_2O)]\cdot H_2O$ ($C_{12}H_{18}N_7O_{15}SFe$)	588	220	Brown	24.49	24.27	3.06	3.33	16.67	16.06	9.52	9.35	49
$[VO(Sdx)(SO_4)(H_2O)]\cdot 3NH_3$ ($C_{12}H_{25}N_7O_9S_2VO$)	542	211	Dark green	26.57	25.98	4.61	4.71	18.08	17.16	12.36	12.14	9

EXPERIMENTAL

Materials and methods. All chemicals used in this investigation were of highest purity grade (Merck). Selected metal salts like $CaCl_2$, $MgCl_2\cdot 6H_2O$, $ZnSO_4\cdot H_2O$, $Fe(NO_3)_3\cdot 9H_2O$, and $VOSO_4\cdot H_2O$ were used. Sulfadoxine was received from Egyptian International Pharmaceutical Industrial Company (EIPICO).

Carbon, hydrogen and nitrogen content were determined using a Perkin-Elmer CHN Elemental Analyzer model 2400. The metal content was found gravimetrically by converting the compounds into their corresponding carbides or oxides. Molar conductivities of freshly prepared 1.0×10^{-3} M DMSO solutions of the complexes were measured using Jenway 4010 conductivity meter. IR spectra were recorded on Bruker FTIR Spectrophotometer (4000–400 cm^{-1}) in KBr pellets. The UV–Vis spectra of 1.0×10^{-3} M DMSO solutions were recorded using Jenway 6405 spectrophotometer with 1 cm quartz cell, in the range 200–900 nm. ^1H NMR spectra of the free ligands and their complexes were recorded on a Varian Gemini 200 MHz Spectrophotometer using DMSO-d_6 as solvent and TMS as internal reference. Thermogravimetric analysis (TGA, DTG, and DTA) was carried out in the temperature range from 25 to 800°C in a steam of nitrogen atmosphere by using Shimadzu TGA-50 H thermal analyzer. The experimental conditions were: platinum crucible, nitrogen atmosphere with a 30 mL/min flow rate and a heating rate of 10°C/min.

Microbiological investigation. The hole well method according to Gupta et al. [49] was applied. The investigated isolates of bacteria and fungi were seeded in tubes with nutrient broth (NB) and Dox's broth (DB), respectively. The antimicrobial activities of the investigated compounds were tested against some kinds of bacteria such as *Escherichia coli* (Gram –ve) and *Staph. albus* (Gram +ve) as well as some kinds of fungi such as *Aspergillus flavus* and *Aspergillus niger*. In the same time with the antimicrobial investigations of the complexes, the pure solvent also was tested as a blank. Commercial DMSO was used to prepare 1.0×10^{-3} M samples.

Preparation of solid complexes. Sulfadoxine complexes: $[Ca(Sdx)(Cl)_2(H_2O)_2]$ **(I)**, $[Mg(Sdx)(Cl)_2(H_2O)_2]\cdot 5H_2O$ **(II),** $[Zn(Sdx)(SO_4)]\cdot H_2O$ **(III)**, $[Fe(Sdx)\cdot(NO_3)_3(H_2O)]\cdot H_2O$ **(IV)**, and $[VO(Sdx)(SO_4)(H_2O)]\cdot 3NH_3$ **(V)** were prepared, using a 1 : 1 (metal : Sdx) ratio. The complexes were prepared by mixing equal volumes (20 mL) of aqueous solution of an appropriate salt (1.0 mmol) with a methanol solution of sulfadoxine (0.310 gm, 1.0 mmol). The mixtures were neutralized by titrated against 5% alcoholic ammonia solution to adjust the pH to 7.0–9.0, then warmed at about ~60°C for about 30 min. and left to evaporate slowly at room temperature overnight. The obtained precipitates were filtered off, washed several times with minimum amount of hot methanol and dried at 60°C over anhydrous $CaCl_2$.

Table 2. IR frequencies (cm^{-1}) of sulfadoxine and its metal complexes.

Compound	ν(H_2O)	ν(NH_2)	ν(N–H)	δ(NH_2, H_2O)	δ(NH)	ν(C=N)	ν(S=O)	ν(SO_2N)	ν(M–O)	ν(M–N)
Sulfadoxine	–	3351	3232	1651	1488	1596	1382	1145	–	–
I	3460	3379	3239	1638	1479	1590	1314	1158	554	445
II	3459	3379	3237	1640	1482	1590	1314	1157	555	455
III	3463	3374	3237	1640	1482	1590	1314	1157	554	422
IV	3462	3373	3235	1639	1477	1590	1316	1157	554	422
V	3463	3374	3237	1649	1480	1589	1313	1157	554	421

RESULTS AND DISCUSSION

The reactions of sulfadoxine (Sdx) with the metal ions Ca(II), Mg(II), Zn(II), Fe(III), and VO(II) gave a colored solid complexes in moderate to good (65–75%) yields. The physical and analytical data, colors, percentage (carbon, hydrogen and nitrogen) and melting/decomposition temperatures of the compounds are presented in Table 1. The found and calculated percentage of CHN is in a well agreement with each other and proves the suggested molecular formula of the resulted sulfadoxine complexes. The complexes have high melting points (211–228°C). The sulfadoxine ligand behaves as bidentate ligand and coordinates to the metal ions via C=N and S=O groups. The isolated sulfadoxine complexes are 1 : 1 molar ratio of (M : Sdx) where M = Ca(II), Mg(II), Zn(II), Fe(III), and VO(II).

Molar conductivities. The molar conductivity values for the Ca(II), Mg(II), Zn(II), Fe(III) and VO(II) complexes of sulfadoxine in DMSO solutions were found to be in the range of 9–49 Ω^{-1} cm^2 mol^{-1} at 25°C, suggesting them to be non-electrolytes [50] as shown in Table 1. Hence the molar conductance values indicate that no ions are presented outside the coordination sphere so the Cl^-, SO_4^{2-}, and NO_3^- ions may be exhibit inside the coordination sphere or absent. The obtained results were strongly matched with the elemental analysis data where Cl^-, SO_4^{2-}, and NO_3^- ions were detected in case of Ca(II), Mg(II), Zn(II), Fe(III), and VO(II) complexes after degradation of these complexes with nitric acid. NO_3^- ions were detected using infrared spectral data. The low conductivity values [51] are in agreement with the low solubility of the above complexes in water, alcohol, chloroform, acetone and most of organic solvents. On the other hand, they are soluble in DMSO, DMF, and concentrated acids.

Electronic absorption spectra. Electronic spectra of the sulfadoxine complexes were recorded in the 200–900 nm region in DMSO. There are two detected absorption bands at 202 and 271 nm in the electronic spectrum of the free sulfadoxine ligand, these bands assigned to π–π* transitions [52, 53], these bands were observed to have undergone bathochromic shift (red shift) clearly in the spectra of the metal complexes as a result of complexation, where the electronic spectra of Mg(II) and Fe(III) complexes show two bands at 223 and 277 nm and at 246 and 276nm, respectively. This bathochromic change in Mg(II) and Fe(III) complexes combining with spectral data, elemental analyses and analytical data were used to elucidate the proposed structure.

Infrared spectra. The results of IR studies are summarized infrared in Table 2. The spectra of free ligand and complexes are similar but there are some differences which could give indication on the type of coordination. The infrared spectra of free sulfadoxine shows a very strong absorption band observed at 1596 cm^{-1} which can be assigned to ν(C=N) group, this peak got downward shift from 1596 to ~1590 cm^{-1} with a significant decrease in its intensity in the spectra of the complexes. This observation suggests that C=N group is one of the coordination sites [46]. The infrared spectra of free sulfadoxine also reveals a strong absorption band observed at 1382 cm^{-1} which can be assigned to the ν(S=O) group this strong band got shifted downward from 1382 to (1313–1316) cm^{-1} in the complexes, this observation suggests that S=O group is the another coordination site [54]. The shift of the ν(C=N) and ν(S=O) group by decreased frequencies in the complexes indicates that these groups are involved in the complexation. The presence of water molecules in the above mentioned complexes is assisted by the presence of a broad band of strong intensity at the 3459–3463 cm^{-1} regions which may be

Table 3. ^{1}H NMR spectral data of sulfadoxine and its complexes

Compound	^{13}C NMR spectra, δ ppm (hydrogen)						
	H; $\underline{O}H_2$	H^g; –O$\underline{C}H_3$	H^f; –O$\underline{C}H_3$	H^d; –$\underline{N}H_2$	H^c; –$\underline{C}H$	H^b; –$\underline{C}H$	H^a; –$\underline{N}H$
Sulfadoxine	–	3.802	3.804	6.12	6.62	7.58	11.1
I	3.38	3.65	3.86	5.95	6.53–6.58	7.57–7.61	8.05
III	3.31	3.65	3.86	5.87	6.53–6.55	7.58–7.61	8.04

assigned to the ν(O–H) stretching vibration for the coordinated and uncoordinated water molecules in the complexes. The angular deformation motions of the coordinated water can be classified into four types of vibrations: δ_b(bend), δ_r(rock), δ_t(twist), and δ_w(wag). The assignments of these motions in all isolated complexes are as follows, the bending motion, $\delta_b(H_2O)$ at 1638–1649 cm^{-1}, the rocking motion, $\delta_r(H_2O)$ at 762–772 cm^{-1}, the wagging motion, $\delta_w(H_2O)$ at 590–602 cm^{-1}, the twisting motion, $\delta_t(H_2O)$ at 699–702 cm^{-1} [55]. It should be mentioned here that these assignments for both the bond stretches and angular deformation of the coordinated water molecules fall in the frequencies regions reported for related aquo-complexes. The spectrum of sulfadoxine shows absorption band at 3351 cm^{-1} which assigned to $\nu(NH_2)$ stretching vibration, this peak is also found in the spectra of metal complexes but with slight increase in its value to about 3373–3379 cm^{-1}, this probably is due to the distance of NH_2 group from the coordination sites. This observation suggests that NH_2 group is not involved in the coordination. The ν(V=O) stretching vibration in the vanadyl complex is observed as expected band at 979 cm^{-1}, which is a good agreement with those known for many vanadyl complexes [56]. The coordination of nitrato anion for the Fe(III) ions were also supported by check the IR spectrum of the ferric(III) complex, where the nitrato complex displayed two bands due to $\nu_{as}(NO_2)$ at 1383 cm^{-1} and $\nu_s(NO_2)$ at 1214 cm^{-1} assigned to monodentate group [57]. It is worth mentioned that the test against the presence of sulfato group in the VO(II) and Zn(II) complexes gave a positive result, this conclusion was supported by detected the two infrared frequencies bands at about 1100 and 600 cm^{-1} overlapping with angular deformation motions of the coordinated water molecules. New vibrating absorption bands were observed in the range of 554–555 cm^{-1} and 421–455 cm^{-1} which characterized as the absorption of ν(M–O) and ν(M–N) bands respectively [58]. According to the IR data, sulfadoxine is coordinated to the metal ions as bidentate ligand via C=N and S=O groups.

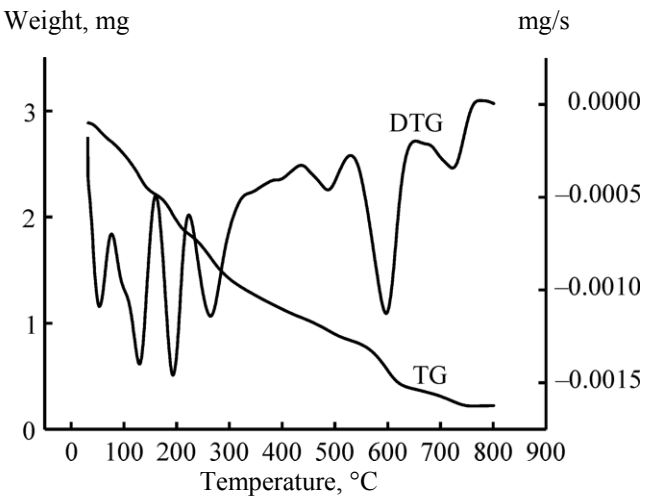


Fig. 2. TG/DTG curves for Mg(II)/Sdx complex **II.**

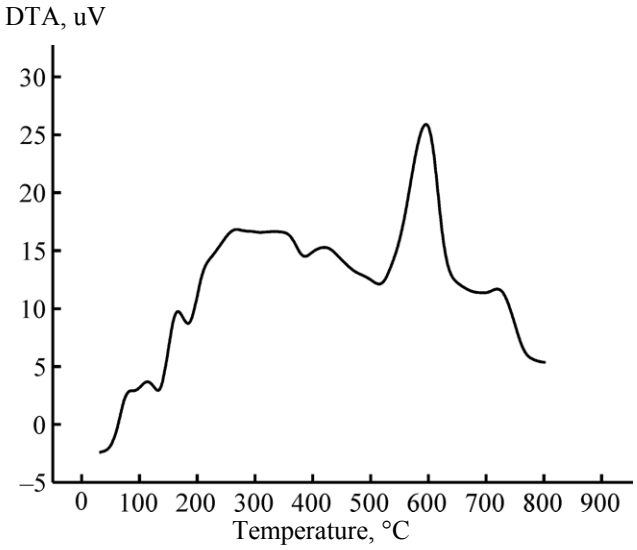


Fig. 3. DTA curve of Mg(II)/Sdx complex **II.**

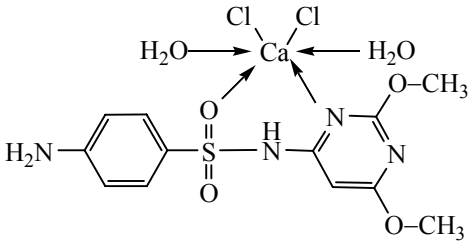


Fig. 4. Suggested structure of Ca(II) complex **I.**

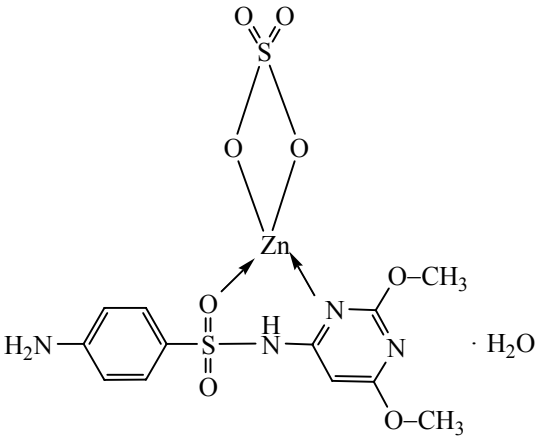


Fig. 5. Suggested structure of Zn(II) complex **III.**

Table 4. Thermal data of sulfadoxine complexes

Comp. no.	Steps	TG, temperature range, °C	DTG_{max}, °C	DTA, °C	TG weight loss, %		Assignments
					calculated	Found	
I	1	34–144	58 and 107	–	15.64	14.66	$2H_2O + 1/2Cl_2$
	2	196–314	257	194 (endo)	39.93	40.51	$1/2Cl_2 + C_4H_9N_3O_3$ (organic moiety)
	3	535–645	580	399 (endo)	11.38	10.63	C_3H_2N (organic moiety)
	4	645–732	680	500 (endo)	15.54	15.98	C_3H_3S (organic moiety)
	Final residue = CaO + 2C (found, %: 18.22, calculated, %: 17.51)						
II	1	32–77	53	–	6.78	6.29	$2H_2O$
	2	77–161	130	132 (endo)	16.95	16.24	$5H_2O$
	3	161–223	193	184 (endo)	13.37	12.36	Cl_2
	4	223–318	264	–	24.48	25.37	$C_4H_6N_2OS$ (organic moiety)
	5	436–649	487 and 597	386 (endo) and 596 (exo)	23.35	24.51	$C_5H_4N_2O_2$ (organic moiety)
	6	649–760	722	719 (exo)	5.27	5.89	C_2H_4
	Final residue = MgO + C (found, %: 9.34, calculated, %: 9.79)						
III	1	43–114	75	79 (endo)	3.68	3.50	H_2O
	2	168–342	258	285 (endo)	39.64	39.15	$H_2SO_4 + C_5H_6NO$ (organic moiety)
	3	342–580	388 and 517	391 (endo) and 513 (exo)	40.05	39.62	$C_7H_6N_3O_2S$ (organic moiety)
	Final residue = ZnO (found, %: 17.73, calculated, %: 16.63)						
IV	1	49–90	67	86 (endo)	1.53	1.32	$1/2H_2O$
	2	138–247	205	210 (exo)	53.74	53.51	$1.5H_2O + 3H_2NO_3 + C_4H_5N_2O$ (organic moiety)
	3	427–601	524	396 (exo)	30.44	30.98	$C_7H_3N_2O_2S$ (organic moiety)
	Final residue = FeO + C (found, %: 14.19, calculated, %: 14.28)						
V	1	150–315	250	193 (endo)	35.61	36.49	$H_2O+3NH_3 + H_2SO_4 + C_2H_2$
	2	315–460	407	452 (exo)	44.28	44.92	$C_8H_8N_4O_3S$ (organic moiety)
	3	495–540	510	–	4.79	4.010	C_2H_2
	Final residue = VO_2 (found, %: 14.13, calculated, %: 14.36)						

Table 5. Kinetic and thermodynamic parameters of the thermal decomposition of sulfadoxine complexes

Comp. no.	Stage	Method	Parameter					r
			E, J/mol	A, s^{-1}	ΔS, J mol^{-1} K^{-1}	ΔH, J/mol	ΔG, J/mol	
I	1	CR	7.66E+04	1.08E+10	–5.37E+01	7.38E+04	9.16E+04	0.98507
		HM	8.07E+04	1.17E+11	–3.39E+01	7.79E+04	8.91E+04	0.97946
	2	CR	9.03E+04	2.60E+10	–4.76E+01	8.72E+04	1.05E+05	0.99511
		HM	9.27E+04	1.06E+11	–3.58E+01	8.96E+04	1.03E+05	0.98964
	3	CR	1.26E+05	1.75E+10	–5.36E+01	1.22E+05	1.50E+05	0.99138
		HM	1.37E+05	4.14E+11	–2.73E+01	1.32E+05	1.47E+05	0.98488
	4	CR	2.12E+05	4.79E+10	–4.92E+01	2.05E+05	2.47E+05	0.99044
		HM	2.21E+05	3.06E+11	–3.38E+01	2.14E+05	2.43E+05	0.9915
II	1	CR	8.99E+04	2.77E+12	–7.45E+00	8.72E+04	8.96E+04	0.98762
		HM	9.66E+04	8.16E+13	2.07E+01	9.39E+04	8.72E+04	0.98766
	2	CR	5.76E+04	3.73E+05	–1.41E+02	5.43E+04	1.11E+05	0.99944
		HM	6.65E+04	5.29E+06	–1.19E+02	6.31E+04	1.11E+05	0.99738
	3	CR	1.19E+05	2.34E+11	–3.10E+01	1.15E+05	1.30E+05	0.99606
		HM	1.31E+05	8.34E+12	–1.27E+00	1.27E+05	1.28E+05	0.99244
	4	CR	1.05E+05	1.01E+08	–9.66E+01	1.01E+05	1.52E+05	0.99449
		HM	1.12E+05	1.00E+09	–7.75E+01	1.08E+05	1.50E+05	0.98824
III	1	CR	8.77E+04	1.97E+11	–3.00E+01	8.48E+04	9.52E+04	0.99391
		HM	9.64E+04	7.72E+12	5.44E-01	9.35E+04	9.33E+04	0.98992
	2	CR	8.00E+04	3.04E+05	–1.45E+02	7.56E+04	1.52E+05	0.98332
		HM	8.95E+04	5.98E+06	–1.20E+02	8.50E+04	1.49E+05	0.97893
	3	CR	1.35E+05	3.13E+08	–8.89E+01	1.30E+05	1.89E+05	0.99408
		HM	1.46E+05	3.50E+09	–6.88E+01	1.40E+05	1.86E+05	0.99322
	4	CR	1.68E+05	7.85E+08	–8.27E+01	1.61E+05	2.26E+05	0.99886
		HM	1.84E+05	1.36E+10	–5.90E+01	1.78E+05	2.24E+05	0.99842
IV	1	CR	1.27E+05	3.62E+17	9.02E+01	1.24E+05	9.36E+04	0.99366
		HM	1.28E+05	1.91E+18	1.04E+02	1.25E+05	9.02E+04	0.99009
	2	CR	1.10E+05	1.10E+10	–5.66E+01	1.06E+05	1.33E+05	0.99448
		HM	1.23E+05	4.19E+11	–2.63E+01	1.19E+05	1.31E+05	0.99022
	3	CR	1.17E+05	2.46E+05	–1.50E+02	1.10E+05	2.30E+05	0.99836
		HM	1.34E+05	3.59E+06	–1.28E+02	1.27E+05	2.29E+05	0.9956
V	1	CR	7.49E+04	6.33E+04	–1.58E+02	7.04E+04	1.56E+05	0.98759
		HM	8.86E+04	3.15E+06	–1.25E+02	8.41E+04	1.52E+05	0.98047
	2	CR	1.09E+05	5.21E+05	–1.43E+02	1.03E+05	2.06E+05	0.99748
		HM	1.30E+05	2.21E+07	–1.12E+02	1.24E+05	2.05E+05	0.9994
	3	CR	3.78E+05	5.43E+22	1.82E+02	3.71E+05	2.26E+05	0.9833
		HM	3.91E+05	6.46E+23	2.03E+02	3.84E+05	2.22E+05	0.9888

^{1}H NMR spectra of sulfadoxine and its complexes. The ^{1}H NMR data of free sulfadoxine and its Mg (II) and Zn(II) complexes, as an examples are listed in Table 3. Upon comparison the free sulfadoxine ligand with its metal complexes Mg(II) and Zn(II), there is no significant change in the ^{1}H NMR spectra, where the characteristic peaks for hydrogen of $–OCH_3$, $–NH_2$, and –CH of aromatic ring in the free

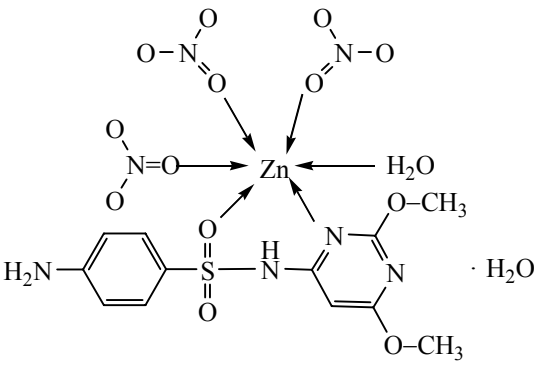


Fig. 6. Suggested structure of Fe(III) complex **IV.**

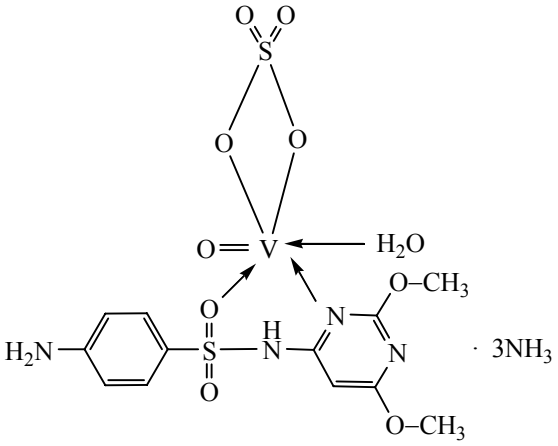


Fig. 7. Suggested structure of VO(II) complex **V.**

sulfadoxine ligand appear at the same ranges of Mg(II) and Zn(II) complexes. The peak of –NH group is shifted from δ 11.1 ppm in the free sulfadoxine ligand to 8.05 and 8.04 ppm in the Mg(II) and Zn(II) complexes respectively, this may be explained due to the flanked of –NH group between the two sites of coordination. This observation means that the coordination occurs without deprotonation of any one of the last groups and this proved that these groups are not involved in the complexation [59]. The appearance of new peaks at 3.38 and 3.31 ppm in the spectra of Mg(II) and Zn(II) complexes which can be assigned to the H_2O molecules and its disappearance in the spectrum of free sulfadoxine ligand supporting the complex formula. The overall observation of the ^1H NMR spectra of the Mg(II) and Zn(II) complexes are indicative of coordination of sulfadoxine ligand to the metal via the S=O and C=N groups. This suggested coordination is in agreement with that obtained by elemental analysis and IR spectra.

Thermal analysis. The obtained sulfadoxine complexes were studied by thermogravimetric (TG), differential thermogravimetric (DTG) and (DTA) analysis from ambient temperature to 800°C under N_2 atmospheres. The TG curves were redrawn as mg mass loss versus temperature and DTG curves were redrawn as rate of loss of mass versus temperature. The thermal decomposition curves (TG/DTG and DTA) for Mg complex **II** as example are given in Figs. 2 and 3, and all thermoanalytical results are summarized in Table 4.

Kinetic studies. The kinetic parameters such as activation energy (Δ*E**), enthalpy (Δ*H**), entropy (Δ*S**), and free energy change of the decomposition (Δ*G**) have been evaluated graphically by employing the Coats–Redfern [60] and Horwitz–Mitzger relations [61]. The calculated values of *E**, *A*, Δ*S**, Δ*H**, and Δ*G** for the decomposition steps of sulfadoxine complexes are given in Table 5. The most significant result is the considerable thermal stability of the Ca(II), Mg(II), Zn(II), Fe(III), and VO(II) complexes reflected from the high values of the activation energy of the decomposition. The second essential result from is that the entropy change Δ*S** for the formation of the activated complexes from the starting reactants is in most cases of negative values. The negative sign of the Δ*S** suggests that the thermodynamic behavior of all sulfadoxine complexes is non-spontaneous (more ordered) reactions and the degree of structural "complexity" (arrangement, "organization") of the activated complexes was lower than that of the starting reactants, also the thermodynamic behavior of all complexes is endothermic ($\Delta H > 0$) and endergonic ($\Delta G > 0$), during the reactions.

The thermodynamic data obtained with the two methods are in harmony with each other. The correlation coefficients of the Arrhenius plots of the thermal decomposition steps were found to lie in the range 0.9789–0.9994, showing a good fit with linear function. The thermograms and the calculated thermal parameters for the complexes show that the stability of these complexes depends on the nature of the central metal ion. The thermal stability of the metal complexes was found to increase periodically with increase in atomic number of the metal and the larger value of charge/radius ratio [62].

Microbiological investigation of sulfadoxine complexes. The free sulfadoxine was found to have the lowest activity against the four types of bacteria

Table 6. Antimicrobial activity of sulfadoxine and its complexes

Compound	Diameter of inhibition zone, cm			
	E. coli	*S. albus*	*Aspergillus niger*	*Aspergillus flavus*
Control	0.0	0.0	0.0	0.0
Sulfadoxine	0.0	0.0	0.0	0.0
Ca(II)/Sdx complex	0.0	0.0	0.2	0.0
Mg(II)/Sdx complex	0.0	0.0	0.1	0.0
Zn(II)/Sdx complex	0.3	0.2	0.3	0.0
Fe(III)/Sdx complex	0.2	0.0	0.0	0.1
VO(II)/Sdx complex	0.0	0.0	0.0	0.0

and fungi, while Zn(II) complex was found to have the highest activity. The biological activities increase in the following order: Zn(II)/Sdx > Fe(III)/Sdx > Ca(II)/Sdx > Mg(II)/Sdx > VO(II)/Sdx. The data are listed in Table 6.

Structure of the sulfadoxine complexes. The structures of the complexes of sulfadoxine with Ca(II), Mg(II), Zn(II), Fe(III), and VO(II) ions have been confirmed from the elemental analysis, IR, ^{1}H NMR spectra, molar conductance, UV-Vis, and thermal analysis data. Thus, from the IR spectra, it is concluded that sulfadoxine behaves as a bidentate feature via (C=N) group and (S=O) group. As a general conclusion, the investigated complexes structures can be given as shown in Figs. 4–7.

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