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Synthesis, Thermal Analysis and Characterization of Doxycycline Metal Complexes

Alaa E. Ali, Gehan S. Elasala, Rana M. Atta, Sherif A. Kolkaila*

Chemistry Department, Faculty of Science, Damanhour University, Egypt
*email:Sherifkolkaela@yahoo.com, Mobile: +01273769704

Abstract Synthesis, spectral characterization and thermal analysis of doxycycline complexes with transition metals (Mn(II), Fe(III), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II)) were discussed. doxycycline act as bidentate ligand with formation of 1:1 (M : L). measurement of magnetism and spectral data shows tetrahedral structures for all complexes except for Fe^{+3} have octahedral geometry . Hyper chemistry program confirmed the binding sites of doxycycline. Complexes show higher activity than commercial doxycycline for some strains. From TG and DTA curves the thermal decomposition mechanisms of doxycyline and their metal complexes were suggested. The thermal decomposition of the complexes ended with the formation of metal oxides and carbon residue as a final product.

Keywords doxycycline Complexes –biological activity – thermal analysis

Introduction

Doxycycline is a semisynthetic analogue based on the chemical structure
of the metacycline, approved in 1967 by the FDA. These tetracyclines are classified in the second generation (Table S1—Supplementary Materials) [1]. The further development of semisynthetic analogues of the second generation, and, more recently, of the third generation, reveals the evolution of this class. The modern tetracyclines had acquired high potency and an increased efficacy, even against bacteria resistant to tetracyclines [2]. Therefore, biochemical mutants of Streptomycetes strains have been created for a higher production yield and to discover novel tetracyclines [3] At the present work biding of doxycycline towards transition metals were identified by IR, electronic spectra, ESR and magnetic susceptibility. Antimicrobial activities of doxycycline metal complexes were discussed. Applying HyperChem. Program to measure charge density of doxycycline atoms is calculated and confirm the biding sites

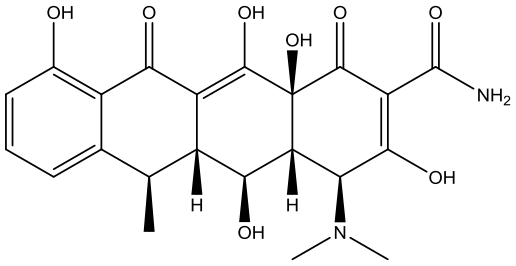


Figure 1: Doxycycline structure

Experimental

A Solution of doxycycline was added to a hot ethanol, an aqueous solution Mn(II) was added with molar ratio (1:1). The mixture was refluxed for 2 h at pH 8.4. The obtained solution was filtered and reduced to half of its volume by evaporation of the solvent. The concentrated solution was left overnight at room temperature, which led to the formation of a solid product. It was filtered, washed with small amount of ethanol and dried. All other complexes were prepared following the same method using the respective metal salts as chloride. Physical measurements, analytical and spectral data of the complexes are given in Tables 1 and 2.

Measurements

Elemental analysis of C, H, S and N for doxycycline and all complexes recorded on CHNS Nr.11042023, at Cairo University .The familiar Volhard method was applied for determination of the analysis of chloride contents of the [4]. The infrared spectra of the doxycycline and their metal complexes were recorded on Perkin Elmer spectrophotometer, Model 1430. The electronic spectra for the solid complexes were measured in Nujol mull spectra [5]. Determination of Molar magnetic susceptibilities, constants were by using Faraday's method at room temperature 25°C. The electron spin resonance spectra were recorded on spectrometer operating at (9.1–9.8) GHZ in a cylindrical resonance cavity with 100 KHZ modulation. The g values were determined by comparison with DPPH signal.The biological screening of doxycycline and their metal complexes were examined against seven microorganisms representing different microbial categories, three of them are Gram-positive (Staphylococcus Aureas , Micrococcus luteus and Bacillus subtilis), three Gram negative (Escherischia coli strain, Proteus mirabilis and Pseudomonas aeruginosa) and candida albicans as a fungi .Hyperchem computer program using PM3 semi-empirical and Molecular Mechanics Force Field (MM+) is applied for ligand.

Table 1: Elemental analysis, m.p. and colour of doxycycline complexes

Complexes	**Colour**	**Calculated/(Found)%**				
		C	**H**	**N**	**M**	**Cl**
[Mn (L_1)(H_2O) Cl]	Yellow	47.88	4.57	5.08	9.96	6.42
		(47.89)	(4.56)	(5.07)	(9.95)	(6.43)
[Fe(L_1)(H_2O)$_2$$Cl_2$]	Brown	43.59	4.49	4.62	9.21	11.70
		(43.57)	(4.47)	(4.61)	(9.23)	(11.71)
[Ni(L_1) (H_2O) Cl]	Green	47.56	4.54	5.04	10.56	6.38
		(47.57)	(4.55)	(5.06)	(10.58)	(6.39)
[Cu(L_1) (H_2O) Cl]	Brown	47.15	4.50	5.00	11.34	6.33
		(47.16)	(4.51)	(5.03)	(11.36)	(6.34)
[Zn(L_1) (H_2O) Cl]	White	46.99	4.48	4.98	11.36	6.31
		(46.95)	(4.47)	(4.97)	(11.35)	(6.32)
[Cd (L_1) (H_2O) Cl]	White	43.37	4.14	4.60	18.45	5.82
		(43.38)	(4.14)	(4.61)	(18.47)	(5.83)
[Hg(L_1) (H_2O) Cl]	White	37.88	3.61	4.02	28.76	5.08
		(37.89)	(3.63)	(4.04)	(28.78)	(5.09)

All the complexes have m.p > 300º C

Results and Discussion

All the prepared complexes contain water. In general, water in inorganic salts may be classified as lattice or coordinated water. There is, however, no definite border line between the two. The former term denotes water molecules trapped in the crystalline lattice, either by weak hydrogen bonds to the anion or by weak ionic bonds to the metal, or by both, whereas the latter denotes water molecules bonded to the metal through partially covalent bonds. Generally, lattice water absorbs at 3652-3352 cm^{-1} (asymmetric and symmetric OH stretching) [6]. From IR spectra of doxycycline metal complexes, one can notice that:

The broad bands at 3297 –3290 cm^{-1} in the systems could be assigned to ν_{O-H} involved in hydrogen bond, due to the presence of coordinated water molecules in all prepared complexes It seems from the elemental analysis of the complexes and thermal analysis that all complexes contain water molecules in their structures. This is evident by ν_{OH}, Figure (7) and Table (5). However, coordinated water in these complexes is indicated by the appearance of metal-oxygen bands attributable to rocking modes at 402 – 421 cm^{-1} region [7].The complexation is confirmed through IR bands of free ligand doxycycline and the metal complexes where the spectra of doxycycline there have two very strong absorption peaks at 1653 cm^{-1} due to ketonic carbonyl groups . The absorption peaks 1251 cm^{-1} is due to amine functions. The CH_2 bending is evident by peaks between 1340 and 1460 cm^{-1} and alkane stretching peaks appeared among 2800-2880 cm^{-1}. Coordinated water appeared as bands between 3353 and 3652 cm^{-1} with peak maxima at 3652 cm^{-1}. In metal complexes of doxycycline, some very prominent peak shifting has been observed along with change in intensities of several important peaks indicating doxycycline has undergone complexation reaction with metals as shown in Table (2). In the far IR spectra, the bonding of oxygen is provided by the presence of bands at 402 cm^{-1} (M-O) [8].

Table 2: Fundamental infrared bands (cm^{-1}) of Doxycycline and its metal complexes

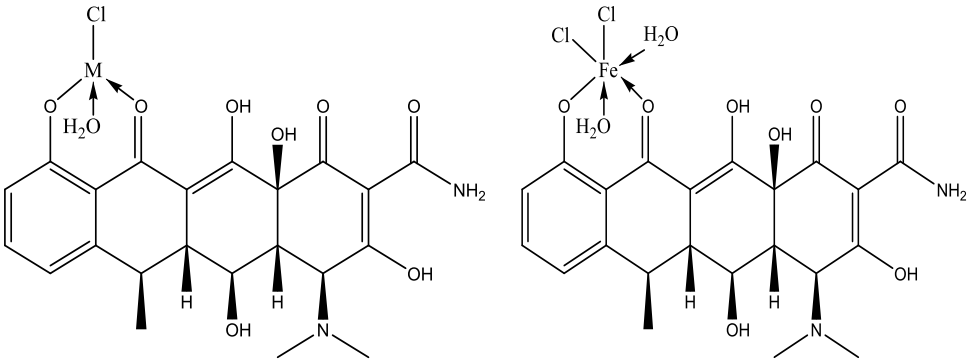
Compound	N_{OH} of H_2O	ν(C=O)	ν (amine)	ν (CH_2)	ν_{M-O}
Doxycycline	-	1653	1251	1460	-
[Mn (L_1)(H_2O) Cl]	3652	1760	1252	1461	402
[Fe(L_1)(H_2O)$_2$$Cl_2$]	3498	1764	1253	1462	405
[Ni(L_1) (H_2O) Cl]	3495	1768	1252	1460	404
[Cu(L_1) (H_2O) Cl]	3592	1752	1251	1463	404
[Zn(L_1) (H_2O) Cl]	3593	1751	1253	1462	405
[Cd (L_1) (H_2O) Cl]	3428	1753	1252	1463	404
[Hg(L_1) (H_2O) Cl]	3496	1752	1250	1464	408

Electronic spectral and magnetic studies

The Yellow electronic absorption spectrum of manganese-complexes, [Mn (L_1)(H_2O) Cl]gave bands at 262, 446, 638 are due to $^6A_{1g} \rightarrow {}^4T_{1g}$ Table (3) Figure (2). Its room temperature μ_{eff} value of 5.7 B.M. The brown electronic absorption spectra of iron-complex [Fe(L_1)(H_2O)$_2$$Cl_2$] , gave bands at 359, 423, 519 nm These bands are due to CT ($t_{2g} \rightarrow \pi^*$) and CT ($\pi \rightarrow e_g$). Its room temperature μ_{eff} value of 5.8, typified the existence of O_h configuration. The green electronic absorption spectra for Nickel-complexes, [Ni(L_1) (H_2O) Cl] Showed band at 620 nm due to $^3T_{1(F)} \rightarrow {}^3T_{1(P)}$ with tetrahedral geometry, further deduced from the μ_{eff} values which equals,(3.1) B.M, while [Cu(L_1) (H_2O) Cl] showed bands at 212,435.5 nm ,which are assigned to the transition $^2T_2 \rightarrow {}^2E_g$, to suggest tetrahedral structure geometry with room temperature μ_{eff} value is 1.8 B.M These complexes exhibited only a high intensity band at 343-426 nm, which are assigned to ligand →metal charge transfer. Owing to the d^{10}- configuration of Zn(II), Cd(II) and Hg(II), no d-d transition could be observed and therefore the strerochemistry around these metals in its complexes cannot be determined from ultraviolet and visible spectra. However, by comparing the spectra of these complexes and those of similar environments.

Table 3: Nujol mull electronic absorption spectra λ_{max} (nm), room temperature effective magnetic moment values (μ_{eff}, 298°K) and geometries of Doxycycline metal complexes

Complex	λ_{max} (nm)	μ_{eff}	Geometry
[Mn (L_1)(H_2O) Cl]	288, 410, 540	4.90	Td
[Fe(L_1)(H_2O)$_2$$Cl_2$]	272.8, 446.8	5.8	O_h
[Ni(L_1) (H_2O) Cl]	359, 423, 519	3.1	Td
[Cu(L_1) (H_2O) Cl]	288, 480, 516	1.8	Td
[Zn(L_1) (H_2O) Cl]	248	diamagnetic	Td
[Cd (L_1) (H_2O) Cl]	290	diamagnetic	Td
[Hg(L_1) (H_2O) Cl]	226	diamagnetic	Td



[Mn (L_1)(H_2O) Cl] [Fe(L_1)(H_2O)$_2$$Cl_2$]

M= Mn, Ni, Cu, Zn, Cd and Hg.

Figure 2: Proposed structures of Doxycycline complexes

By applying hyper chem. Program and measure charge density of doxycycline atoms is calculated, Figure (3) confirmed doxycycline coordination through the Carbonyl group which has highest charge.

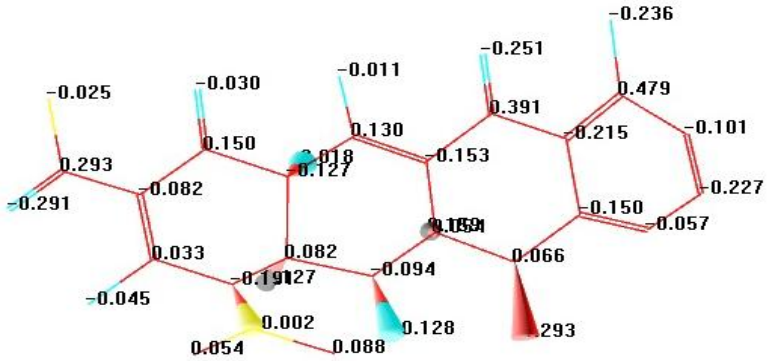


Figure 3: Charge density of doxycycline atoms

Electron spin resonance [Cu(L_1) (H_2O) Cl]

At The room temperature an isotropic nature of The values of α^2 for [Cu(L_1) (H_2O) Cl] complex is 0.985, , assigns that Cu-O bond is more pronounced than the Cu-N. figure(4)

Complex	**G**	**g_{II}**	**$g_{\perp}$**	**<g>**	**$A_{//}$**	**$A_{\perp}$**	**|A|**	α^2	**F^2**
[Cu(L_1) (H_2O) Cl]	4.4	2.66	1.83	2.12	130×10^{-4}	22×10^{-4}	5.2×10^{-3}	0.985	1.230

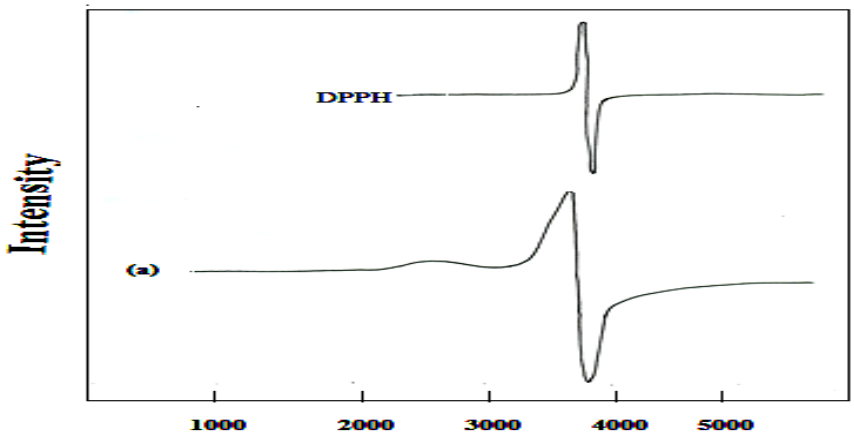


Figure 4: ESR of [Cu(L_1) (H_2O) Cl]

Biological activity

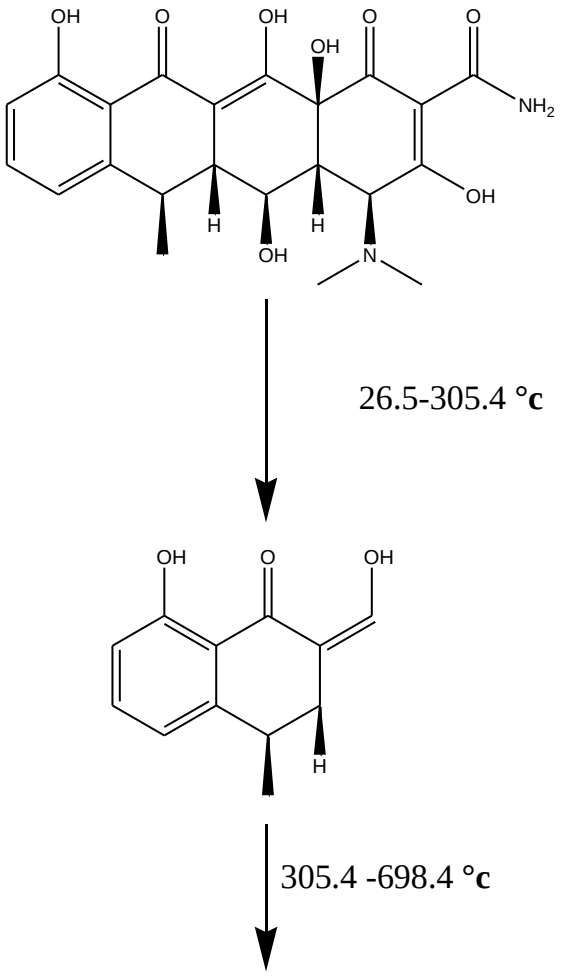
Table (4) shows that some of the investigated compounds have higher antimicrobial activity and antifungal activity than doxycycline as free ligand . All the investigated compounds have higher positive antibacterial activity compaired to antifungal activity. Doxycycline showed similar activities for Pseudomonas aeruginosa [Zn(L_1) (H_2O) Cl]complex higher activity to Candida albicans, Escherischia coli, Staphyllococcus aureus, Pseudomonas aeruginosa *and* Bacillus subtilis. It revealed by the diameter of its inhibition zone.. On the other hand, [Cu(L_1) (H_2O) Cl]complex showed showed higher activity to Candida albicans, Most of the metal complexes have higher activity than the free ligands such increased activity of the metal chelates could be explained on the bases of overtone's concept and chelation theory [9]. The cell permeability the lipid membrane that surrounds the cell favours the passage of only lipid soluble materials on the basis that liposolubility is an important factor that controls antimicrobial activity.

Table 4: Antimicrobial activity of doxycycline metal complexes (20 µg/8 mm disc), as compared to doxycycine

Complexes	***Candida albicans***		***Escherischia coli***		***Pseudomonas aeruginosa***		***Staphyllococcus aureus***		***Bacillus subtilis***	
		Cpd.		**Cpd.**		**Cpd.**		**Cpd.**		**Cpd.**
[Cu(L_1) (H_2O) Cl]	8	14	8	15	8	11	8	12	8	11
[Zn(L_1) (H_2O) Cl]	8	16	8	16	8	17	8	18	8	19
Doxycycline	8	10	8	10	8	11	8	10	8	12
Ciprofloxacin	9	30	9	30	9	30	9	30	-	-
Clotrimazole	-	-	-	-	-	-	-	-	10	17

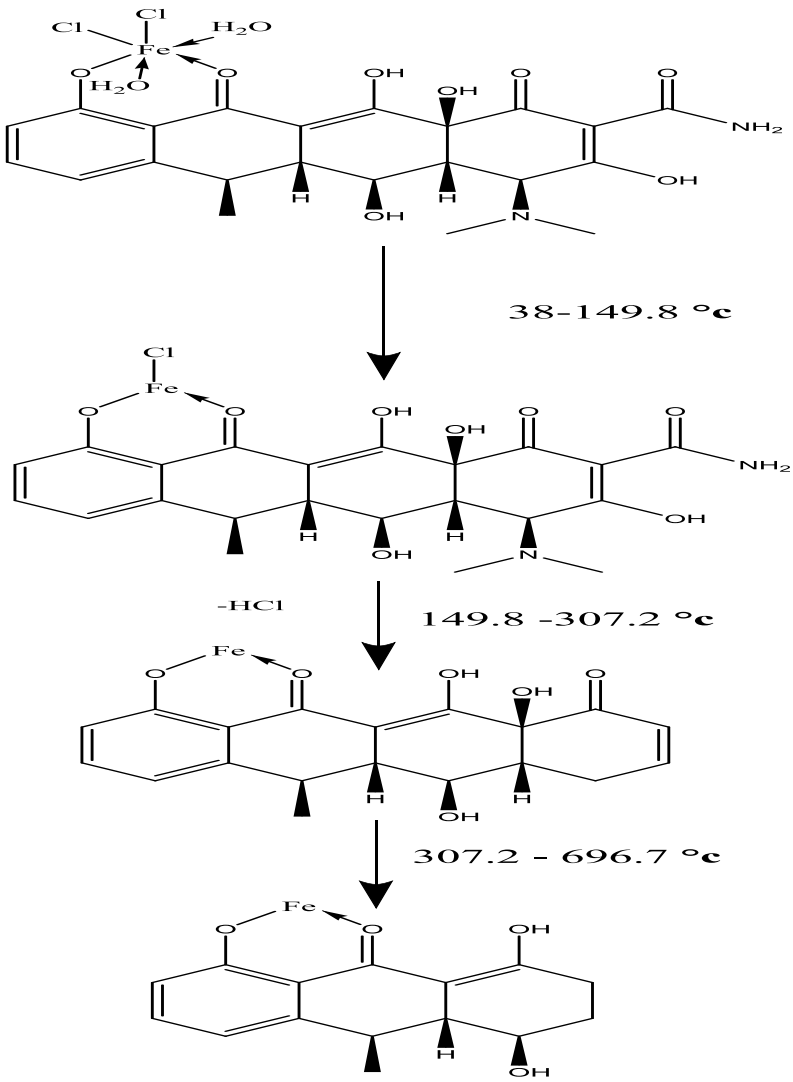
Thermal Analysis

The thermal DTA sheet of **the free ligand "Doxycycline"**, Figures (5-6) and Table (5), showed three peaks at 88.2, 431.5,and 585.7 °C with activation energies 85.96, 95.42, 96.79 and 56.63 kJ/mole, respectively. The orders of reactions were 0.7, 2.03 and 1.07respectively. All peaks are of the first order type except second peak is of second order type. All peaks are endothermic except for last one is exothermic, scheme (1) AlaaE ali et al [9-13]. :



Scheme (1): thermolysis of Doxycycline

The DTA data of $[Fe(L_1)(H_2O)_2Cl_2]$ complex showed well defined three peaks, Figures (7,8) and Table (16), at 87, 23.5 and 480.7°Cwith activation energies 24.04, 31.68 and 66.05 kJ/mole, respectively and the orders of reactions are first order. All peaks are endothermic except last one is exothermic. The TGA data confirmed these results which it gave three peaks, in the following scheme (2):



Scheme (2): thermolysis of $[Fe(L_1)(H_2O)_2Cl_2]$

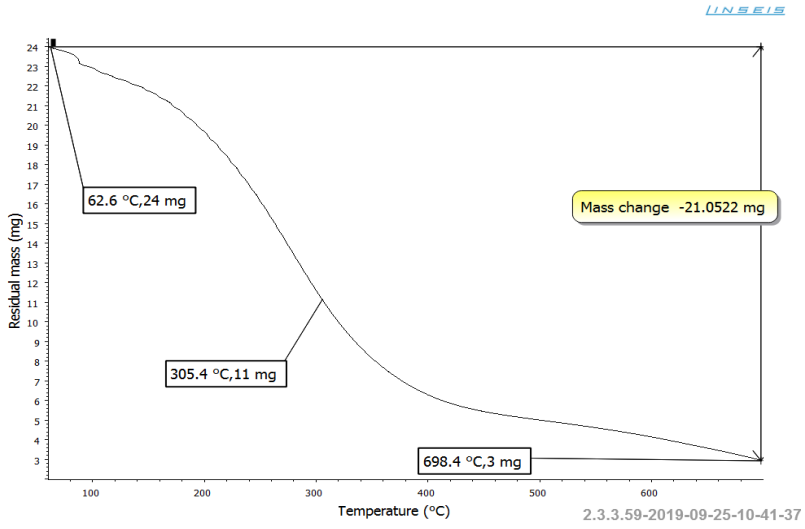


Figure 5: TGA of Doxycycline

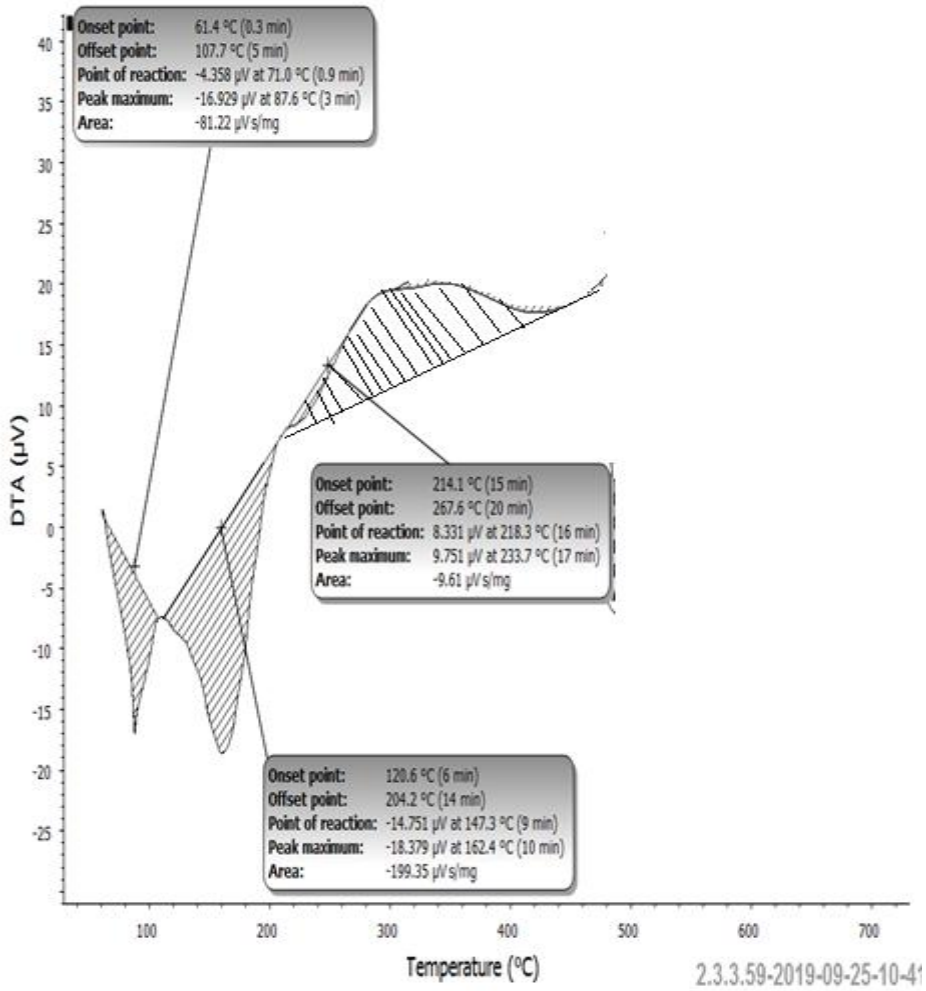


Figure 6: DTA of Doxycycline

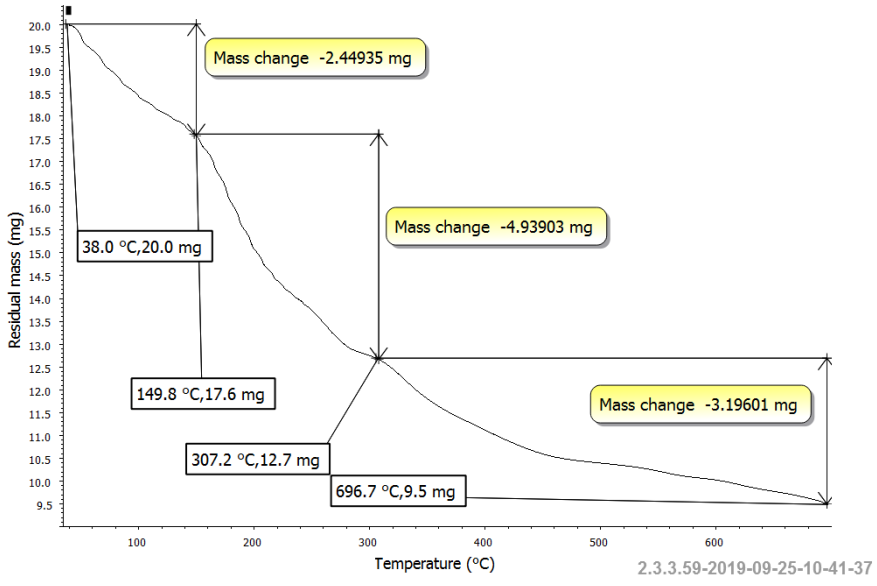


Figure 7: TGA of $[Fe(L_1)(H_2O)_2Cl_2]$

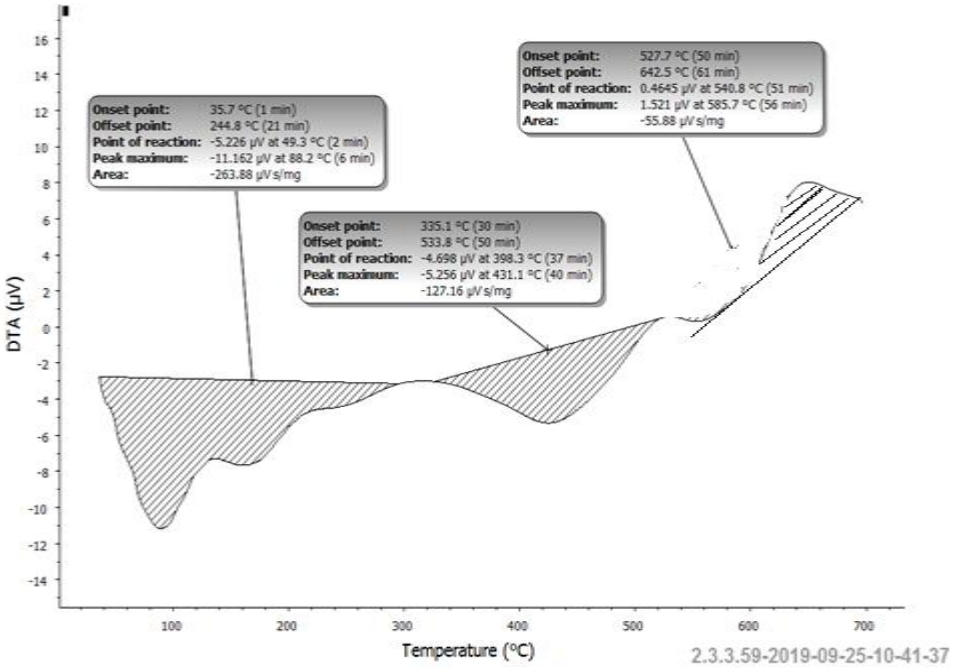


Figure 8: DTA of $[Fe(L_1)(H_2O)_2Cl_2]$

Table 5: DTA analysis of Doxycycline and its metal complexes

Complex	Type	Tm (°K)	E_a kJ mol^{-1}	n	α_m	$\Delta S^{\#}$ kJ K^{-1} mol^{-1}	$\Delta H^{\#}$ kJ mol^{-1}	Z S^{-1}	Temp. (°C) TGA	Wt. Loss % Calc	Wt. Loss % Found	Assignment
Doxycycline	Endo	88.2	6.34	1.17	0.60	-0.29	-32.6	0.006	22 -200	9.24	10.1	loss of 2 NH_3, $CH_3CHCOOH$
	Endo	431.5	294.49	1.16	0.60	-0.27	-57.9	0.168	200 – 288	42.79	43.34	Loss of $CH_3CH_2CH_2OH$, C_2H_5OH, C_6H_6O
	Endo	585.7	158.77	1.74	0.52	-0.29	-109.7	0.050	288 -496	67.15	67.41	Formation of carbon residue
$[Fe(L_1)(H_2O)_2Cl_2]$	Endo	87	24.049	1.38	0.57	-0.28	-35.3	0.023	38- 149.8	12	12.11	Dehydration of $2H_2O$ and loss of HCl
	Endo	232.5	31.685	1.18	0.60	-0.29	-77.4	0.014	149.8-307.2	27.8	27.7	Loss of HCl, NH_3, CH_3COOH
	Endo	480.7	66.501	1.11	0.61	-0.30	-142.2	0.016	307.2-696.7	53.9	54	Loss of C_6H_6OH
$[Cu(L_1)(H_2O)Cl]$	Endo	87	11.700	1.23	0.59	-0.29	-42.3	0.009	36.6-169.6	4.2	4.2	Dehydration of H_2O
	Endo	189.8	81.600	1.36	0.57	-0.28	-74.0	0.038	169.6-477.7	12.6	12.7	loss of CH_3OH andNH_3
	Endo	519.7	82.482	0.77	0.67	-0.29	-116.2	0.025	477.7-697.9	30.25	30.32	Loss of NH_3 and HCl
$[Zn(L_1)(H_2O)Cl]$	Endo	189.8	192.62	1.36	0.57	-0.26	-20.28	0.023	32-205	25.92	25.98	Dehydration of H_2O and Loss of $CH_3CH_2CH_2OH$, NH_3
	Endo	519.7	39.25	1.33	0.57	-0.29	-57.49	0.130	77-199	54.16	54.20	Loss of NH_3
[Cd (L_1) (H_2O) Cl]	Endo	80.9	61.91	1.73	0.52	-0.27	-30.39	0.06	36.6-169.6	28.6	28.6	Dehydration of $2H_2O$ and loss of HCl, NH_3
	Endo	210.7	76.80	1.30	0.58	-0.28	-58.12	0.04	169.6-477.7	53.16	53.18	Loss of $CH_3CH_2CH_2OH$
	Endo	480.4	210.58	1.74	0.52	-0.28	-70.82	0.10	477.7 -697.9			Loss of CH_3CH_2OH

Conclusion

Doxycycline metal complexes are synthesized and characterized by different spectroscopic methods. All of them have tetrahedral geometry except for Fe^{+3} have octahedral geometry and these results confirmed by Nujol and ESR spectra. Doxycycline acts as a bidentate ligand. Also have different sites available for coordination which carries more electronegative charges and the computational study confirms these results. Doxycycline complexes show higher activity than commercial Doxycycline for some strains. The thermal decompositions of the complexes ended with the formation of metal oxides and carbon residue as a final product.

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