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Physicochemical Studies of Some Biologically Active Metal Complexes of Cefazolin Antibiotics

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ABSTRACT

Several biological active metal complexes of cefazolin were prepared with stochiometries 1:1 and 1:2 (M:L) and characterized using (IR/, UV-Vis, ESR, magnetic susceptibility, thermal (TGA and DTA). Statistical studies gave different correlation coefficients between data. Mode of bonding of the investigated compounds: IR spectra assigned the different modes of vibrations of the fundamental functional groups in the compounds under consideration. On complexation, the shifts of the characteristic IR frequencies serve as a convenient measure of the character of the complex formed. In all complexes, the oxygen atom of (lactam carbonyl, carboxylic or amide carbonyl groups) and the nitrogen atom of amino thiazole ring are involved in chelation. Electronic absorption spectra gathered with the magnetic moment values pointed to that all chromium, manganese, iron, cobalt and complexes are of octahedral geometry and with high spin magnetic moment except nickel and mercury with tetrahedral geometry. The calculated room temperature powdered ESR data of copper cefazolin complex with the formula, [Cu(cefazolin)$_2$Cl(H$_2$O)] is of anisotropic nature.

Keywords: Coordination chemistry; Metal complexes; Cefazolin; Spectral; Thermal analysis

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INTRODUCTION

Beta-lactam antibiotic drug, i.e., penicillin and cephalosporins, are related chemically by the presence of a four-membered ring containing a nitrogen atom adjacent to a carbonyl group [1-3]. Cefazoline or cephazolin antibiotic used for many bacterial infections (Figure 1) [4]. It is a first-generation cephalosporin antibiotic with broad spectrum antibiotic with activity against both gram-negative and gram-positive bacteria [5].

A series of papers are published in our lab about metallo antibiotics of cephalosporins [6-10]. In a sequel of continuation, the aim of the present work is studying the chemical structure, biological activity, and thermal behavior of cefazoline antibiotic and its metal complexes.

EXPERIMENTAL

Cefazolin and metal chloride [Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II)] were dissolved with distilled water. The molar amount of the metal chloride salt was mixed with the calculated amount of the ligand using different mole ratios (M:L) 1:1 and 1:2. The reaction mixture was refluxed for about 50 min then left over-night, where the precipitated complexes were separated by filtration, then washed several times with a mixture of EtOH-H_2O and dried in a vaccum desiccator over anhydrous $CaCl_2$. The analytical results are given in Table 1. The metal contents were determined based on atomic absorption technique using model 6650 Shimadzu-atomic absorption spectrophotometer and complexometrically with standard EDTA solution using the appropriate indicator as reported [11].The analysis of chloride contents of the complexes was determined by applying Volhard method [10].

Measurements

The infrared spectra of the cefazolin 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 [10]. Molar magnetic susceptibilities, constants were determined using Faraday's method at room temperature 25°C in Alexandria University. 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 in Alexandria University. Differential Thermal Analysis (DTA), Thermogravimetric analysis (TG)and Differential Scanning Calorimetry (DSC)of cefazolin and its complexes were carried out using a Shimadzu DTA/TGA-50. The rate of heating was 20°C/min. The cell used was platinum and the atmospheric nitrogen rate flow was 15 ml/min in Tanta University. The biological screening of cefazolin and its metal complexes were examined against 5 microorganisms representing different microbial categories {two Gram-positive (*Staphylococcus aureas* ATCC6538P and *Bacillus subtilis* ATCC19659), two Gram negative (*Escherischia coli* ATCC8739 strain and *Pseudomonas aeruginosa* ATCC9027) and *Candida albicans* as a fungi}in Alexandria University. Hyperchem computer program using PM3 semi-empirical and Molecular Mechanics Force Field (MM+) is applied for ligand.

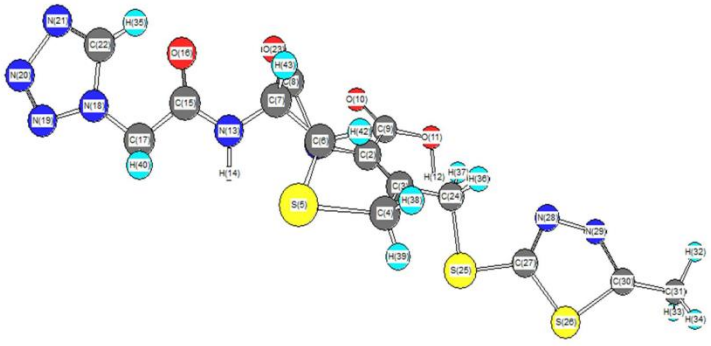

Figure 1. Structure of Cefazolin.

Table 1. Elemental analysis, m.p, formula, stoichiometries and colour of (Cefazolin) complexes.

Complexes	Colour	Calculated/(Found)%	
		M	Cl
[Cr(cefazolin)$_2$(Cl)(H$_2$O)]	Pale Green	5.124 (5.100)	3.49 (3.46)
[Mn(cefazolin)$_2$Cl (H$_2$O)]	White	5.398 (5.379)	3.489 (3.510)
[Fe(cefazolin)Cl$_2$(H$_2$O)$_2$]	Pale Brown	9.045 (9.010)	11.5 (11.540)
[Co(cefazolin) Cl$_2$(H$_2$O)$_2$]	Pale Rose	9.498 (9.458)	11.443 (11.471)
[Ni(cefazolin)Cl(H$_2$O)]	Pale Green	10.356 (10.383)	6.264 (6.291)
[Cu(cefazolin)$_2$Cl(H$_2$O)]	Pale Blue	6.192 (6.161)	3.459 (3.495)
[Zn(cefazolin)Cl(H$_2$O)]	White	11.405 (11.456)	6.191 (6.151)
[Cd(cefazolin)Cl(H$_2$O)]	White	18.118 (18.152)	5.721 (5.701)
[Hg(cefazolin)Cl(H$_2$O)]	White	28.307 (28.332)	5.009 (5.112)

All the complexes have m.p>300ºC

RESULTS AND DISCUSSION

IR spectra of cefazolin and its metal complexes

The IR spectral bands are shown, and the characteristic bands are given in Table 2. The broad band at 3430 cm^{-1} in cefazolin could be assigned to the vibration frequency of hydroxyl group (ν_{O-H}) involved in hydrogen bond in coordinated water molecules or to N-H stretching vibration. The lactam (C=O) band appears at 1762 cm^{-1} while the amide (C=O) band appears at 1669 cm^{-1}. The bands at the region (1545-671) cm^{-1} are attributed to the bending modes of vibrations.

The elemental and thermal analysis of the complexes explained that all complexes contain water molecules in their chemical structures. The band at 1545 cm^{-1}, corresponding to carboxylate symmetrical stretching of shifted to high wave numbers in spectra of all complexes indicating coordination through group.

The carboxylate ligand binds to the metal ion either as a monodentate or a bidentate ligand, so the relative positions of the antisymmetric and symmetric stretching vibrations change [12].The new bands in 430-480 cm^{-1} region observed in the complexes are assigned to M-O (Table 2).

Table 2. IR Spectral bands of Cefazolin free ligand and its metal complexes.

Compound	ν_{OH}	$\nu_{(C=O)}$ lactam	$\nu_{(C=O)}$ amide	$\nu_{(COO)}$asym	$\nu_{(COO)}$sym	$\nu_{(C-N)}$	ν_{C-O} stretch	ν_{M-O}
Cefazolin	3430	1762	1669	1601	1545	1489	1012	433
[[Cr(Cefazolin)$_2$Cl.(H$_2$O] (1:2)	3421	1776	1679	1628	1557	1488	1060	430
[Mn(Cefazolin)$_2$Cl].H$_2$O (1:2)	3286	1770	1678	1621	1567	-	1060	433
[Fe(cefazolin).(H$_2$O)$_2$Cl] (1:1)	3285	1770	1678	1621	1550	-	1060	433
[Co(Cefazolin)Cl(H$_2$O)$_3$] (1:1)	3406	1774	1678	1627	1556	1415	1011	465
[Ni (Cefazolin)Cl.(H$_2$O)] (1:1)	3413	1769	1617	-	1381	-	1005	480
[Cu (Cefazolin)$_2$Cl].H$_2$O (1: 2)	3426	1768	1678	1630	1585	-	1063	433
[Zn (Cefazolin)Cl].H$_2$O] (1:1)	3295	1765	1670	1595	1551	1470	1040	475
[Cd(Cefazolin)Cl].H$_2$O] (1:1)	3447	1767	1684	1594	1561	1400	1012	471
[Hg(Cefazolin)Cl H$_2$O] (1:1)	3439	1759	1673	1681	1542	1481	1042	480

Electronic absorption spectra and magnetic susceptibility studies

The violet chromium complex, [Cr(cefazolin)$_2$(Cl)(H$_2$O)], showed three bands at 278, 428 and 466 nm due to $^4A_{2g}\rightarrow{}^4T_{2g}$ (F), $^4A_{2g}\rightarrow{}^4T_{1g}$(F) and $^4A_{2g}\rightarrow{}^4T_{1g}$(p) transitions, respectively, Table 3, so that, the complex has octahedral geometries. Such O_h geometry is further deduced from the μ_{eff} value equals, 3.9 B.M, The yellow manganese-complex, [Mn(cefazolin)$_2$.Cl.(H$_2$O)], Table 3, gave four bands , 205.4, 435, 546.2, and 693.2 where the first is assigned to $^6A_{1g}\rightarrow{}^4A_{1g}$, while the second is due to $^6A_{1g}\rightarrow{}^4T_{2g}$ transition and the last is due to $^6A_{1g}\rightarrow{}^4T_{1g}$ transition [13,14]. Its room temperature μ_{eff} value of 2.3 B.M, typified the existence of O_h configuration. The brown iron-complex, [Fe (cefazolin) (H$_2$O)$_2$ Cl$_2$.], Table 3, gave bands at 304, 426, and 518 nm. These bands are due to CT ($t_{2g}\rightarrow\pi^*$) and CT ($\pi\rightarrow$eg). Its room temperature μ_{eff} value of5.2 B.M, typified the existence of O_h configuration [15-17].The [Co(cefazolin)Cl(H$_2$O)] complex, Table 3, gave bands at 298, 426, and 460 nm. The first are of charge transfer nature and the latter is of broad nature assigned to $^4T_{1g}(F)\rightarrow{}^4T_{2g}(P)$ transition. Its magnetic moment value equals to 2.8 B.M typified the existence in O_h gesometry. The green nickel-complex, [Ni(cefazolin)Cl H$_2$O],Table 3, showed three bands at 248, 426, and 639 nm due to $^3T_1(F)\rightarrow{}^3T_1(P)$, $^3T_1(F)\rightarrow{}^3A_2$ transitions, respectively with the μ_{eff} value equals, 1.3 B.M. The copper complex, [Cu(cefazolin)$_2$Cl (H$_2$O)], Table 3, exhibited two bands at 216 and 422 nm, with μ_{eff}=3.7 B.M. The latter broadband is assigned to the $^2E_g\rightarrow{}^2T_{2g}$ (D) transition assignable to octahedral environment [18,19]. Zn (II), Cd (II) and Hg (II) complexes exhibited only a high intensity band at 327-335 and 344nm, Table 3, which is 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 stereochemistry 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, an octahedral and tetrahedral is suggested for these complexes [20]. IR, electronic absorption spectra and magnetic moment values concluded the proposed structures which are shown in Figure 2.

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

Complex	λ_{max} (nm)	μ_{eff}	Geometry
[Cr(cefazolin)$_2$(Cl)(H_2O)]	278, 428, 466	3.9	O_h
[Mn (cefazolin)$_2$.Cl.(H_2O)]	205, 435, 546, 693	2.3	O_h
Fe (cefazolin).(H_2O)$_2$ Cl_2.]	304, 426, 518	5.2	O_h
[Co(cefazolin)Cl.(H_2O)$_3$]	298, 426, 460	2.8	O_h
[Ni(cefazolin) ClH_2O]	248, 426, 639	1.3	T_d
[Cu(cefazolin)$_2$Cl(H_2O)]	216, 422	3.7	O_h
[Zn(cefazolin)Cl(H_2O)]	327	Diamagnetic	T_d
[Cd (cefazolin)ClH_2O]	335	Diamagnetic	T_d
[Hg(cefazolin)ClH_2O]	344	Diamagnetic	T_d

Molecular modeling

The charge density of oxygen atoms at carboxylate group are -1.011 and -0.326. So, the carboxylate is involved in complexation as a good lewis base (donor group). All C-S bond lengths lie in the range 1.800-2.000 (Aº). These values decrease for all C-N bond lengths in between the range 1.600-1.300 (Aº). However, for all C-O bond lengths lie within the range 1.200-1.300 (Aº) (i.e., all C-S>C-N>C-O). This is due to electronegativity, whereas it increased the bond length decreased. It was found that the angles between atoms in Cefazolin around are 120ºC and 109.5ºC. These angles were due to sp^2 and sp^3 hybridization of the atoms. The dihedral angles became near to planarity, ± 180, ± n ≈ 0 (n; number).

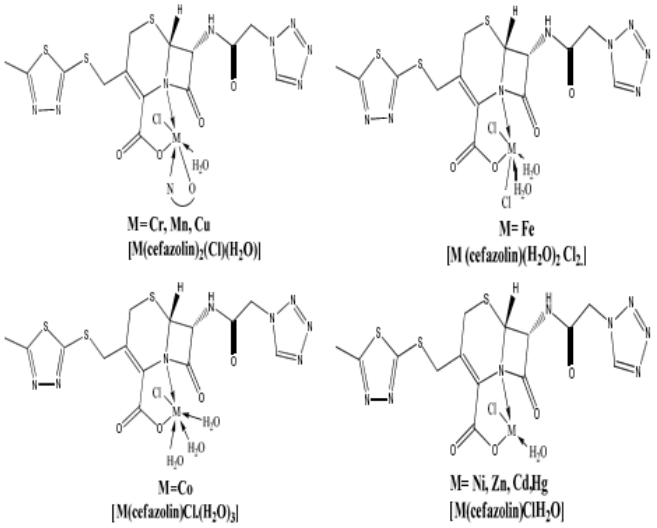

Figure 2. Proposed structures of cefazolincomplexes.

Quantum chemical parameters such as the highest occupied molecular orbital energy (EHOMO), the lowest unoccupied molecular orbital energy (ELUMO), energy gap (ΔE) and those parameters that give valuable information about the reactive behavior such as electronegativity (χ), chemical potential (μ), global hardness (η) and softness (σ) were calculated for cefazolin and its cadmium complex, Table 4.The concepts of these parameters are related to each other [21-23] where, the energies of the HOMO and LUMO orbitals of the inhibitor molecule are related to ionization potential (I) and the electron affinity (A), respectively, by the following relations:

$$I = -E_{HOMO} \quad A = -E_{LUMO} \quad \mu = -\chi \quad \mu = -\frac{(I + A)}{2} = -\frac{E_{HOMO} + E_{LUMO}}{2}$$

The qualitative hardness is closely related to the polarizability because the decrease of the energy gap leads to an easier polarization [22] of the molecule. The inverse of the global hardness is defined as the softness,(σ) as follows.

$$\eta = \frac{I - A}{2} = \frac{(E_{LUMO} - E_{HOMO})}{2} \quad \sigma = \frac{1}{\eta}$$

The electrophilicity index (ω) [24], describes toxicity of various pollutants, in terms of their reactivity and site selectivity and is given from the following equation:

$$\omega = \frac{\mu^2}{2\eta}$$

The reactivity of [Cd(cefazolin)ClH$_2$O] is larger than cefazolin; attributed to the energy values of HOMO, LUMO, σ and ω [23].

Table 4. Quantum chemical parameters (ev) calculated by PM3 method.

Compound	EHOMO (eV)	ELUMO (eV)	ΔE (ev)	I (eV)	A (eV)	χ (ev)	μ (ev)	η (ev)	σ (ev)	ω (ev)
Cefazolin	-9.17	-2.00	7.17	9.17	2.00	5.58	-5.58	3.58	0.28	4.35
[Cd(cefazolin)ClH$_2$O]	-8.33	-4.64	3.70	8.34	4.64	6.49	-6.49	1.85	0.54	11.39

Electron spin resonance of copper complex

The room temperature poly crystalline X-band ESR spectral pattern of [Cu(cefazolin)$_2$Cl (H$_2$O)] complex is axial elongated nature. The spectral analysis of this complex gave two g values g_{11}= 2.25 and g_1= 2.015 and the calculated <g> value=2.17 where < g >= $(g_{11}+2g_1)/3$.

Biological Activity

The data in Table 5, allow higher positive antibacterial activity compared to antifungal activity. Cu(cefazolin)Cl(H$_2$O)]complex higher activity to *Candida albicans, Escherischia coli, Staphyllococcus aureus* and *Bacillus subtilis*. It revealed by the diameter of its inhibition zone. It showed activity in the same range of cefazolin for *Pseudomonas aeruginosa*. On the other hand, [Zn(cefazolin)Cl(H$_2$O)] complex showed higher activity to *Candida albicans*. Most of the metal complexes have higher activity [25,26] than

the free ligands such increased activity of the metal chelates could be explained on the bases of overtones' concept and chelation theory [27].

Table 5. The antifungal activity of the free ligand and its complexes against some reference strains expressed in absolute activity.

Complexes	*Candida albicans*		*Escherischia coli*		*Pseudomonas aeruginosa*		*Staphyllococcus aureus*		*Bacillus subtilis*	
	DMSO	**Cpd**	**DMSO**	**Cpd**	**DMSO**	**Cpd**	**DMSO**	**Cpd**	**DMSO**	**Cpd**
$[Cu(cefazolin)_2Cl(H_2O)]$	8	14	8	12	8	8	8	12	8	11
$[Zn(cefazolin)Cl(H_2O)]$	8	16	8	14	8	8	8	14	8	17
Cefazolin	8	12	8	12	8	8	8	12	8	11
Ciprofloxacin	9	30	9	30	9	30	9	30		

Thermal analysis

In our laboratory, the thermal behavior of some biologically active compounds has been reported [28-31]. The thermal behavior of cefazolin and some metal complexes were investigated by thermograms (TG and DTA), the corresponding thermal analysis data is presented in Table 6.The DTA data of cefazolin, Figure 3 and Table 6, showed well defined two peaks at 113.8 and 525.0°C with activation energies 10.257 and 659.981 kJ/mole, respectively and the orders of reactions are of the first type. All peaks are exothermic. The TGA data confirmed these results which it gave two peaks, as in the Figure 4.On the other hand, the cadmium complex [Cd (cefazolin) ClH_2O], Figure 5 and Table 6, showed three exothermic well defined at 74.3, 180 and 222.85°C with activation energies of 50.14, 59.14, 129.14 kJ/mole, their orders of reactions are 1.3, 1.06 and 1.7, respectively. The TGA data confirmed these results which it gave three peaks, Figure 6.

Based on least square calculations, the ln ΔT versus 103/T plots, for all complexes gave straight lines from which the activation energies were calculated and other thermodynamic parameters, Table 6, are given. The order of chemical reactions(n) was calculated *via* the peak symmetry method [32].

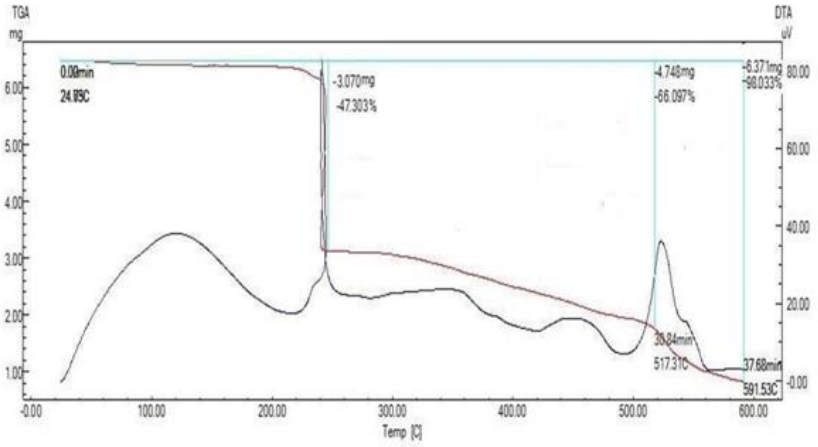

Figure 3. TGA and DTA of cefazolin.

Table 6. DTA analysis of Cefazolin and its metal complexes.

Complex	Type	Tm (°C)	E_a kJ mol-1	n	a_m	$DS^{\#}$ kJ K-1 mol-1	$DH^{\#}$ kJ mol-1	Z S-1	Temp. (°C) TGA	Wt. loss% Calc	Wt. loss% Found	Assignment
	Exo	113.8	10.257	0.996	0.633	-0.295	-36.903	0.009	24.73-250 °C	47.1	47.3	$-C_5N_5S_2H_5$
Cefazolin	Exo	525	659.981	0.996	0.632	-0.261	-32.586	0.629	250-591.53 °C	98	98	-C10N2SO4H12
	Exo	110.8	13.902	0.948	0.641	-0.292	-36.587	0.013	26.80-185.30 °C	5.5	8.1	$-H_2O$, HCl
	Exo	218.9	98.62	1.436	0.563	-0.276	-34.552	0.094	185.3-344.81° C	50.7	50.7	-C14N10S4H22
[Cr(cefazolin)$_2$**(Cl)(H_2O)]**	Exo	462	321.768	0.975	0.636	-0.266	-33.327	0.308	344.81-591.85 °C	90.3	92.4	-C20N4S2H28O4
	Exo	116.2	7.305	1.28	0.585	-0.298	-37.256	0.007	28.73-203.31 °C	5	6.3	$-H_2O$, HCl
	Exo	229.7	124.252	1.642	0.538	-0.274	-34.313	0.119	203.31-246.13 °C	36	36.1	-C10H10N4S4
	Endo	540.5	153.193	1.346	0.576	-0.272	-34.096	0.147	246.13-414.06 °C	65.5	65.6	$-C_7N_8SH_8$
[Mn(cefazolin)$_2$**Cl(H_2O)]**	Exo	586.4	304.358	1.178	0.601	-0.267	-33.384	0.291	414.06-591.10 °C	93	96.9	-C13O5N2SH11
	Exo	119.4	9.2451	1.166	0.603	-0.296	-37.011	0.008	24.55-225.00 °C	5.6	4.8	-HCl, H_2O
	Exo	247.2	174.959	1.505	0.554	-0.271	-33.958	0.167	225.00-255.40 °C	13.3	6	$-CH_3SH$
	Exo	455.5	48.192	1.26	0.588	-0.282	-35.296	0.046	255.40-517.31° C	56.6	72.8	$-C_7N_6S_2H_7$
[Cd(cefazolin)Cl(H_2**O)]**	Exo	525	385.636	1.436	0.563	-0.265	-33.14	0.369	517.31-591.53° C	79.3	87.2	$-C_5O_2N_2H_7$
	Exo	119.4	10.03	1.433	0.564	-0.295	-36.927	0.009	25.88-242.21 °C	25.5	25.5	$-H_2O$, HCl / $-C_4N_2S_2H_5$
	Exo	477.7	214.401	1.49	0.556	-0.269	-33.747	0.205	242.21-368.7°C	43.2	49.3	$-C_3N_5H_4$
[Hg(cefazolin)Cl(H_2**O)]**	Endo	566.6	181.295	0.966	0.638	-0.271	-33.921	0.174	368.7-390.31° C	69.5	96.7	$-C_7O_2NSH_6$

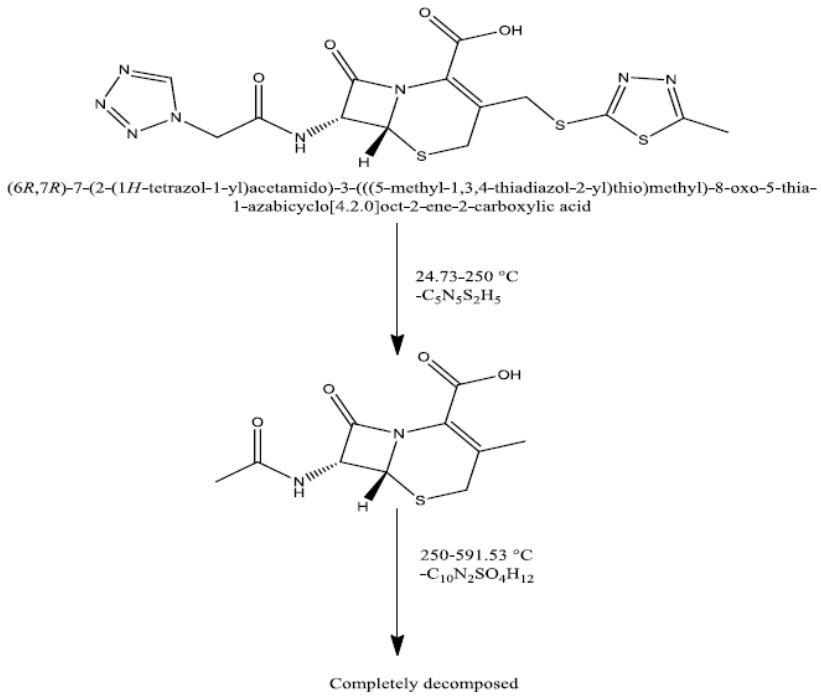

Figure 4. Themolysis of cefazolin.

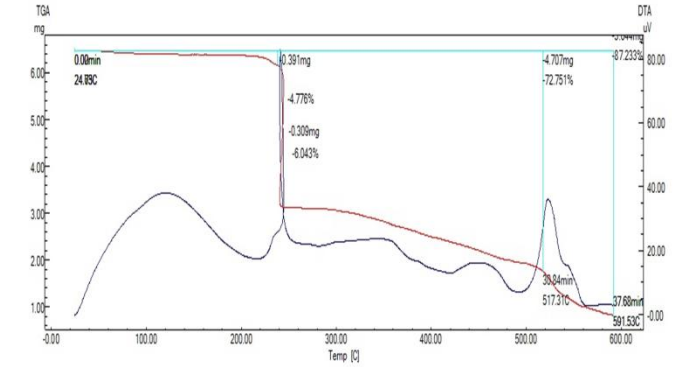

Figure 5. TGA and DTA of [Cd(cefazolin)ClH$_2$O].

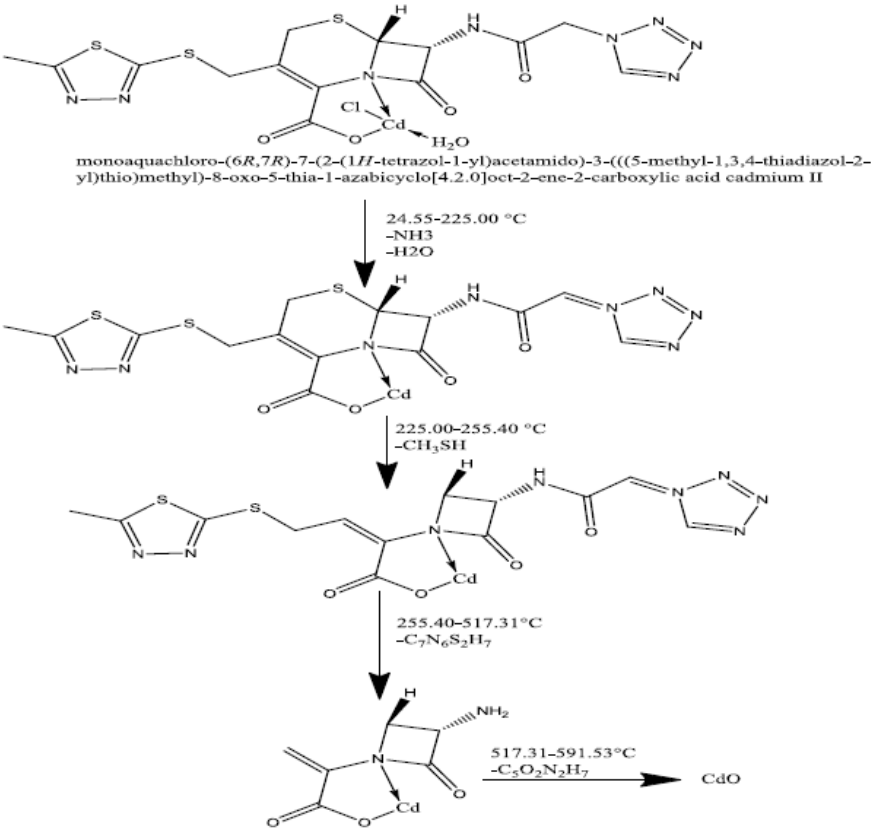

Figure 6. Themolysis of [Cd(cefazolin)ClH$_2$O]

CONCLUSION

Nine cefazolin metal complexes are synthesized and characterized by different spectroscopic methods. The complexes formed in different stoichiometries. All have octahedral geometry except for Ni, Zn, Cd and Hg complexes have tetrahedral geometry. These results are confirmed by Nujol mull and ESR spectra. Also have different sites available for coordination which carries more electronegative charges. The computational study confirms these results. Cefazolin complexes show higher activity than commercial cefazolin for some strains. The thermal decompositions of the complexes ended with the formation of metal oxides as a final product.

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