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Synthesis and Characterization of Biologically Active Metal Complexes for Tenoxicam

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ABSTRACT

Biologically active [Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II)] complexes of tenoxicam were prepared and characterized using IR, UV-Vis, ESR, magnetic susceptibility, thermal analysis (TGA, DTA and DSC). IR data pointed that all complexes were suggested that tenoxicam coordinates to the metal ions as a bidentate ligand bound to metal through (C=N) nitrogen of pyridine ring, carbonyl oxygen of (C=O) and oxygen atom of OH group with stochiometries 1:2 (M:L). Electronic absorption spectra gathered with the magnetic moment values proved that all tenoxicam complexes have octahedral geometry. The calculated room temperature powdered ESR data of copper tenoxicam complex with the formula [Cu(tenoxicam)$_2$Cl(H$_2$O)], showed isotropic spectra. Thermal analyses (TGA and DTA) of ligands and their metal complexes were carried out to distinguish between the coordinate and hydrate solvents and to estimate the stability ranges, peak temperatures. The thermodynamic parameters, such as activation energy (ΔE), enthalpy of activation (ΔH*), entropy of activation (ΔS*) and Gibbs free energy (ΔG*)are calculated and discussed. Antimicrobial activities were screened for some metal complexes of tenoxicam.*

Keywords: Tenoxicam complexes; Biological activity; Thermal analysis; Molecular modeling

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INTRODUCTION

Antibiotic drug containing beta-lactam ring, i.e., penicillin and cephalosporins, are related to the presence of a four-membered ring containing a nitrogen atom adjacent to a carbonyl group [1-3]. Tenoxicam is a Non-Steroidal Anti-Inflammatory Drug (NSAID) originated by Roche but at (2008), sold by Meda AB under the trade name Mobiflex, Figure 1. It is used to relieve inflammation, swelling, stiffness, and pain associated with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis (a type of arthritis involving the spine), tendinitis (inflammation of atendon), bursitis (inflammation of a bursa, a fluid-filled sac located around joints and near the bones), and periarthritis of

shoulders or hips (inflammation of tissues surrounding these joints) [4]. The aim of the present work is studying the chemical structure, biological activity, and thermal behavior of tenoxicam and its metal complexes.

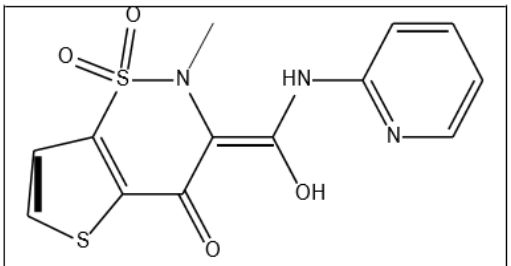
EXPERIMENTAL

Tenoxicam and metal chloride [Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II)] were solvated with distilled water. The molar amount of the metal chloride salt was reacted with the calculated amount of the ligand with molar ratios (M:L) 1:1 and 1:2. The reaction mixture was refluxed for about 50 min then left over-night, where the formed complexes were filtrated, then washed several times with a mixture of EtOH-H_2O and dried in a vaccum desiccator. The analytical results are given in Table 1. All these complexes have melting point >300°C.The metal contents were analyzed based on atomic absorption technique using model 6650 Shimadzu-atomic absorption spectrophotometer and complexometric titration with standard EDTA solution using the appropriate indicator as reported[5,6]. The analysis of chloride contents of the complexes was examined by Volhard method [5] (Figure 1).

$CrCl_3.6H_2O$+Tenoxicam → 2HCl+[Cr(Tenoxicam)$_2$Cl(H_2O)]+5 H_2O

$MCl_2.6H_2O$+2 Tenoxicam → HCl+ [Mn(Tenoxicam)$_2$Cl (H_2O)]+5H_2O (M=Mn, Co, Cu or Ni)

$FeCl_3.6H_2O$+2 Tenoxicam → 2HCl+[Fe(Tenoxicam)$_2$Cl (H2O)]+5H_2O MCl_2+2 Tenoxicam →HCl+[M(Tenoxicam)$_2$Cl(H_2O)](M=Zn, Cd or Hg)



(*E*)-3-(hydroxy(pyridin-2-ylamino)methylene)-2-methyl-2*H*-thieno[2,3-*e*][1,2]thiazin-4(3*H*)-one 1,1-dioxide

Figure 1. The chemical structure of tenoxicam.

MEASUREMENTS

The infrared spectra of the Tenoxicam and their metal complexes were detected by Perkin Elmer spectrophotometer, Model 1430, the instrument was located at central lab of Alexandria University. The electronic spectra for the solid complexes were measured in Nujol mull spectra; the instrument was located at central lab of Alexandria University [°]. Molar magnetic susceptibilities, constants were analyzed using Faraday's method at room temperature 25°C. The electron spin resonance spectra were tested by spectrometer operating at (9.1-9.8) GHz in a cylindrical resonance cavity with 100 KHz modulation, the instrument was located at central lab of Alexandria University. The g values were calculated by comparison with DPPH signal. Differential Thermal Analysis (DTA) and Thermo Gravimetric analysis (TG) of tenoxicam and its complexes were carried out using a Shimadzu DTA/TGA-50 at central Lab., Tanta University. The rate of heating was 20°C/min. The cell used was platinum and the atmospheric nitrogen rate flow was 15 ml/min. The biological screening of Tenoxicam 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}, the biological screening were carried out at faculty of pharmacy, Alexandria University. Computational chemistry programs are applied such as, hyperchem using PM3 semi-empirical and Molecular Mechanics Force Field (MM+) (Table 1).

Table 1. Elemental analysis, m.p, formula, stoichiometries and colour of Tenoxicam complexes.

Complexes	Colour	Calculated/(Found) %	
		M	Cl
[Cr(Tenoxicam)$_2$Cl (H_2O)]	green	6.663 (6.762)	4.549 (4.478)
[Mn(Tenoxicam)$_2$Cl (H_2O)]	yellow	7.013 (7.054)	4.532 (4.506)
[Fe(Tenoxicam)$_2$Cl (H_2O)]	dark brown	7.121 (7.16)	4.527 (4.506)
[Co(Tenoxicam)$_2$Cl(H_2O)]	green	7.486 (7.44)	4.509 (4.406)
[Ni(Tenoxicam)$_2$Cl (H_2O)]	green	7.458 (7.42)	4.511 (4.502)
[Cu(Tenoxicam)$_2$Cl(H_2O)]	green	8.024 (8.007)	4.483 (4.501)
[Zn(Tenoxicam)$_2$Cl(H_2O)]	canary yellow	8.24 (8.235)	4.473 (4.434)
[Cd(Tenoxicam)$_2$Cl(H_2O)]	pale yellow	13.371 (13.396)	4.222 (4.261)
[Hg(Tenoxicam)$_2$Cl(H_2O)]	yellow	21.595 (21.561)	3.822 (3.846)

RESULTS AND DISCUSSION

IR spectra of tenoxicam and its metal complexes

The IR spectral and the characteristic bands were collected in Table 2. The IR spectrum for tenoxicam showed an absorption band at 3395 cm^{-1} due to an O-H stretching vibration; the broadness of this band is indicative of hydrogen bonding. The strong band at 1636 cm^{-1} is attributed to the carbonyl stretching vibration of secondary amide group (CO-NH). The band at 1565 cm^{-1} is due to the stretching vibration of pyridyl nitrogen (C=N).

On complexation, the band at 3395 cm^{-1} disappeared confirming the complex formation and replaced by anew band at (3428-3488 cm^{-1}) in all complexes which suggested that tenoxicam coordinates to metal through oxygen atom of OH group.

The Cr^{3+} and Fe^{3+} complexes assigned that ν (C=O) is shifted to slightly higher frequency (1633-1638 cm^{-1}). The ν (C=N) is abscent, so all the data suggested that tenoxicam ligand acts as a bidentate ligand coordinates to metal through carbonyl oxygen of (C=O) and oxygen atom of OH group.

IR spectra of tenoxicam complexes for Cu^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cd^{2+} and Hg^{2+} report that the ν (C=N) are shifted to slightly higher frequency (1579-1587 cm^{-1}), and also ν (C=O) are shifted to slightly higher frequency, IR spectra of these prepared metal complexes are suggested that From the IR data, all complexes were suggested that tenoxicam coordinates to the metal ions as a bidentate ligand bound to metal through (C=N) nitrogen of pyridine ring, carbonyl oxygen of (C=O) and oxygen atom of OH group with stochiometries 1:2 (M:L).

The (M-N) stretching vibrations in the range 513-584 cm^{-1} in the metal complexes indicated that tenoxicam bonded to the metal ion through nitrogen atom. The new bands at 430 cm^{-1} in the spectra of the metal complexes are tentatively assigned to (M-O) vibrations (Table 2).

Table 2. IR spectral bands of tenoxicam ligand and its metal complexes. Electronic absorption spectra and magnetic susceptibility studies.

Compound	ν_{OH}	$\nu_{(C=O)}$ amide	$\nu_{(C=N)}$	$\nu_{(SOO)}$ asym	$\nu_{(SOO)}$ sym	ν_{C-O} stretch	ν_{M-N}	ν_{M-O}
Tenoxicam	3395	1625	1565	1180	1386	1250	-	-
[Cr(Tenoxicam)$_2$ Cl H_2O] (1: 2)	3425	1636	1566	1180	1387	1063	-	534
[Mn(Tenoxicam)$_2$Cl(H_2O] (1:2)	3465	1633	1580	1179	1386	1261	583	434
[Fe (tenoxicam)$_2$Cl.(H_2O)] (1:2)	3495	1637	1566	1180	1385	1201	-	498
[Co (Tenoxicam)$_2$ ClH_2O] (1:2)	3430	1634	1582	1178	1384	1262	520	426
[Ni(Tenoxicam)$_2$.ClH_2O] (1: 2)	3440	1636	1586	1180	1386	1263	533	434
[Cu (tenoxicam)$_2$Cl(H_2O)] (1: 2)	3428	1632	1579	1481	1384	1234	587	551
[Zn(Tenoxicam)ClH2O] (1:1)	3496	1633	1582	1480	1386	1265	491	437
[Cd(Tenoxicam)ClH_2O] (1:1)	3455	1638	1587	1481	1384	1262	584	426
[Hg (Tenoxicam)H_2OCl] (1:1)	3484	1638	1587	1478	1386	1259	525	422

The green chromium complex,[C(Tenoxicam)$_2$Cl.(H_2O)]showed three bands at 381, 445, 578 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 Oh geometry is further deduced from the μ_{eff} values which equal, 4.5B.M. However, the yellow electronic absorption spectrum of manganese-complex, [Mn (tenoxicam)$_2$.Cl.(H_2O)], Table 3, gave three bands 262, 446, 823 where the first band is assigned to $^6A_{1g}\rightarrow{}^4A_{1g}$, while the second is due to $^6A_{1g}\rightarrow{}^4T_{2g}$ transition and the last band is due to $^6A_{1g}\rightarrow{}^4T_{1g}$ transition [7,8]. Its room temperature μ_{eff} value of 5.75 B.M, typified the existence of O_h configuration. The brown electronic absorption spectra of iron-complex, [Fe(tenoxicam)$_2$Cl.H_2O], Table 3, gave

bands at 359, 453, 896 nm, respectively. These bands are due to CT ($t_{2g} \rightarrow \pi^*$) and CT ($\pi \rightarrow eg$). Its room temperature μ_{eff} value of 5.91B.M, typified the existence of O_h configuration [9-10]. The electronic absorption spectra of [Co(tenoxicam)$_2$Cl.H$_2$O] complex, Table 3, gave bands at 379, 436 nm. Bands are of charge transfer nature and the latter broad bands are assigned to $^4T_{1g}$ (F) $\rightarrow$ $^4T_{2g}$ (P) transition with magnetic moment value equal to 4.15 typified the existence of the complex in O_h geometry. The green electronic absorption spectra for Nickel-complex, [Ni(tenoxicam)$_2$Cl.(H$_2$O)]Table 3, showed three bands at206, 411.2, 887 nm due to $^3T_1(F) \rightarrow {}^3T_1(P)$, $^3T_1(F) \rightarrow {}^3A_2$ transitions, respectively with the μeff values which equals,2.65 B.M. The copper complex, [Cu(tenoxicam)$_2$.Cl.H$_2$O], Table 3, exhibited bands at 371 and 419nm, with μeff=1.77 B.M. The latter broad band is assigned to the $^2E_g \rightarrow {}^2T_{2g}$ (D) transition assignable to octahedral environment [11-12]. Zn (II), Cd (II) and Hg (II) complexes exhibited only a high intensity band at 334-365 and 329 nm, Table 3, which is assigned to ligand →metal charge transfer. Owing to the d10-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 geometry is suggested for these complexes [13]. IR, electronic absorption spectra and magnetic moment values are concluded the proposed structures which are shown in Figure 2 and Table 3.

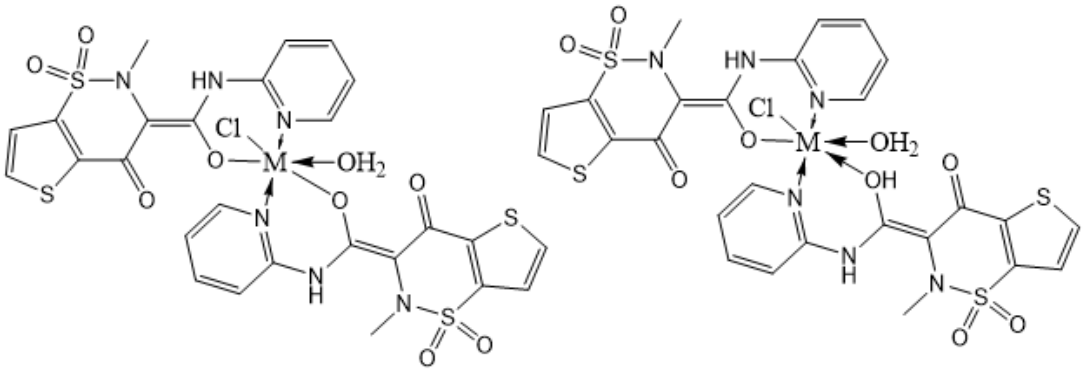


Figure 2. The proposed structure of tenoxicam complexes.

Table 3. Nujol mull electronic absorption spectra λ max (nm), room temperature effective magnetic moment values (μeff 298°K) and geometries of cefazolin metal complexes.

Complex	λ_{max} (nm)	μ_{eff}	Geometry
[Cr (tenoxicam)$_2$Cl.(H$_2$O)]	381, 445, 578	4.5	O_h
[Mn (tenoxicam)$_2$.Cl.(H$_2$O)]	262, 446, 823	5.75	O_h
[Fe(tenoxicam)$_2$Cl. H$_2$O]	359, 453, 896	5.91	O_h
[Co(tenoxicam)$_2$Cl.H$_2$O]	379, 436	4.15	O_h
[Ni (tenoxicam)$_2$Cl.(H$_2$O)]	206, 411, 887	2.65	O_h
[Cu(tenoxicam)$_2$.Cl.H$_2$O]	371, 419	1.77	O_h
[Zn(tenoxicam)$_2$.Cl.H$_2$O]	334	Diamagnetic	O_h
[Cd(tenoxicam)$_2$.Cl.H$_2$O]	365	Diamagnetic	O_h
[Hg(tenoxicam)$_2$.Cl.H$_2$O]	329	Diamagnetic	O_h

Molecular modeling

The charge of oxygen atom is -0.390. So, it is involved on complexation. All C-S bond lengths lie in1.790 (Aº). These values decrease for all C-N bond lengths between the range 1.400-1.500 (Aº). However, for all C-O bond lengths lie within 1.208 (Aº) (i.e. all C-S > C-N > C-O). This is due to electronegativity, whereas it increased the bond length decreased. The angles for atoms of tenoxicam around 120ºC and 109.5ºC, due to sp^2 and sp^3 hybridization of the atoms (Figure 3).

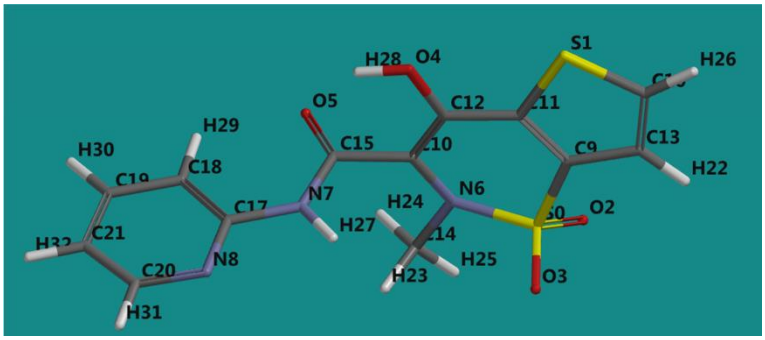


Figure 3. Structure of tenoxicam.

The highest occupied molecular orbital energy (EHOMO), the lowest unoccupied molecular orbital energy (ELUMO), energy gap (ΔE) gave valuable information about the reactive behavior such as electronegativity (χ), chemical potential (μ), global hardness (η) and softness (σ) were calculated for tenoxicam and its cadmium complex, Table 4. The concepts of these parameters are related to each other [14-16]. Where, the energies of the HOMO and LUMO orbitals of the inhibitor molecule are related to ionization potential (I) and the electron affinity (A), softness, (σ) electrophilicity index (ω), respectively, by the following relations[14-17]

$$I=-E_{HOMO} \qquad A=-E_{LUMO}$$

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

$$\mu=-\chi$$

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

$$o=\frac{1}{\eta}$$

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

Global hardness and softness are important properties to measure the molecular stability and reactivity. Evaluating the values of the hardness, Table 4 showed that [Cd(tenoxicam)$_2$ClH$_2$O] is less-harder than ligand, this means that the complex has the larger potential chemical resistance to change the number of electrons among the other molecules. Also, Table 4 showed that [Cd(tenoxicam)$_2$ClH$_2$O] value of global softness which indicated that [Cd(tenoxicam)$_2$ClH$_2$O] complex showed greater reactivity than ligand. The energy gap (ΔE) is directly involved with hardness/softness of a chemical species. A lower value of ΔE makes complex has more reactive or low kinetic stability than ligand. Computed the electrophilicity indexes were measured the stabilization in energy when the system acquires an additional electronic charge from the environment and toxicity of various pollutants. From the ω values, [Cd(tenoxicam)$_2$ClH$_2$O]>tenoxicam. [Cd(cefazolin)ClH$_2$O] have higher value of electrophilicity, which shows their high ability to accept electrons (the most reactive compound) and indicated has higher biological activity.

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

Compound	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (ev)	I (eV)	A (eV)	X (ev)	M (ev)	η (ev)	σ (ev)	ω (ev)
Tenoxicam	-8.24	-1.79	6.45	8.25	1.8	5.02	-5.02	3.22	0.31	3.91
[Cd(tenoxicam)$_2$ClH$_2$O]	-7.17	-3.23	3.94	7.17	3.23	5.2	-5.2	1.97	0.51	6.86

Electron spin resonance of copper complex

The room temperature polycrystalline X-band ESR spectral pattern of [Cu(tenoxicam)$_2$ClH$_2$O] complex is isotropic nature with g_s=1.97 and value of A=170.

Thermal analysis

The thermal behavior of Tenoxicam and some metal complexes were investigated by thermograms (TG, DTA, DSc), the DTA and TG analysis data is presented in Table 5. The DTA curves showed exothermic peaks at temperatures higher than 250°C in all complexes indicating their stabilities up to 250°C and after which they are thermally decomposed. The DTA data of tenoxicam, (Figure 4 and Table 6) showedwelldefinedthreepeaksat115.0and277.5°Cwithactivationenergies30.252 and 154.698 kJ/mole, respectively. The orders of reactions are of the first type. The first peak is endothermic and the second one is exothermic. The TGA data confirmed these results which it gave three peaks, as in the Figure 5. On the other hand, the [Co(tenoxicam)$_2$Cl.H$_2$O] complex, (Figure 6 and Table 6) showed well defined three peaks at 122.85, 191.5, and 580°C with activation energies 35.30, 205.45,and 1.16 kJ/mole, respectively. The orders of reactions were 1.66, 1.50, and 1.16, respectively. All peaks are of exothermic types of the second order type. The TGA data confirmed these results which it gave three peaks (Figure 7).

Based on least square calculations, the lnΔT versus10^3/Tplots, for all complexes gave straight lines from which the activation energies were calculated(Table6) [18].The order of chemical reactions (n) was calculated *via* the peak symmetry method [19].

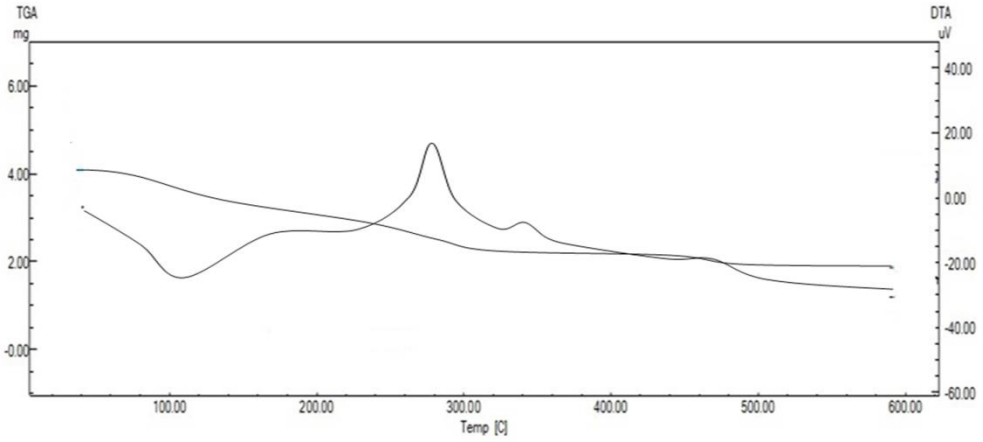


Figure 4. TGA and DTA of Tenoxicam.

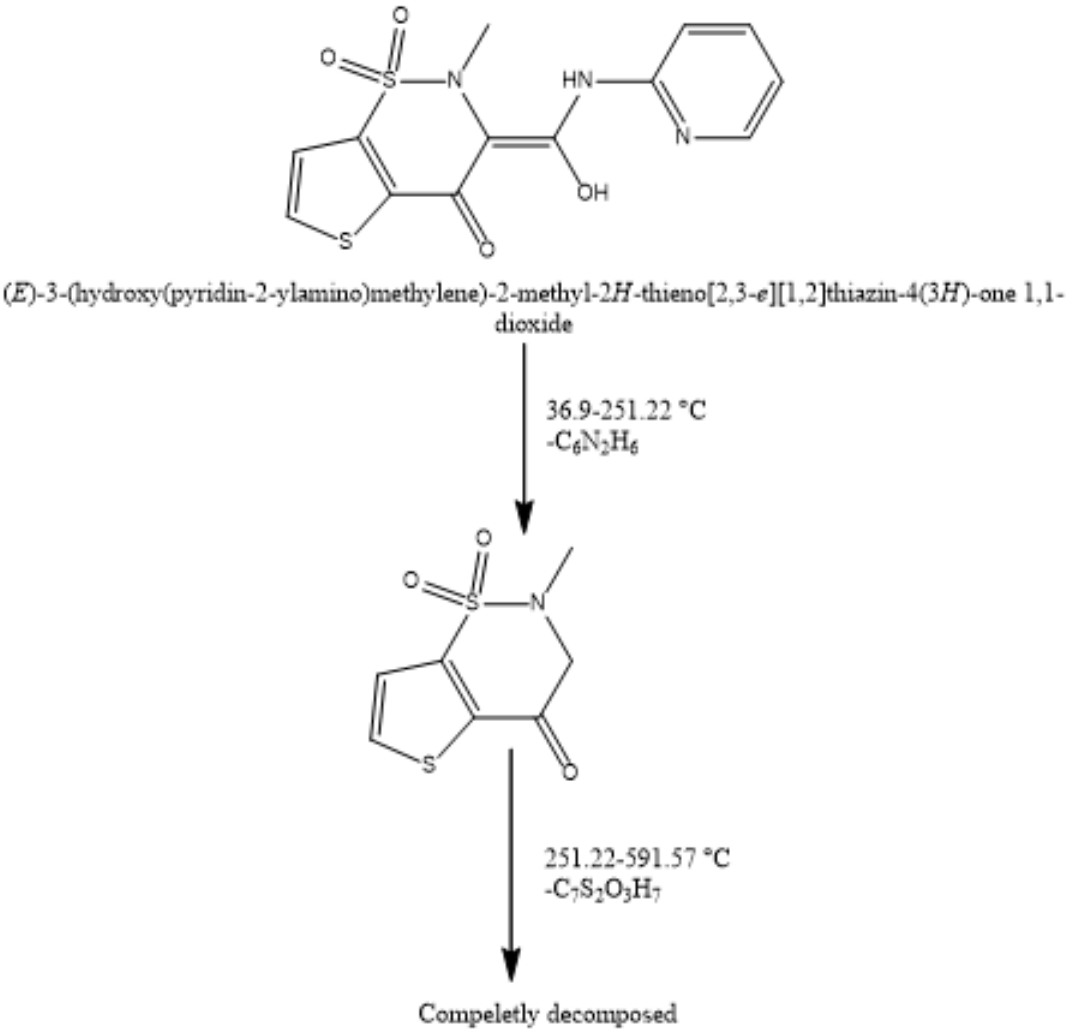


Figure 5. Thermolysis of Tenoxicam.

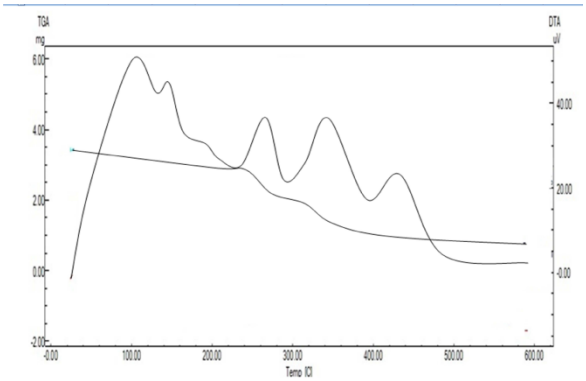


Figure 6. TGA and DTA of [Co(tenoxicam)$_2$ClH$_2$O].

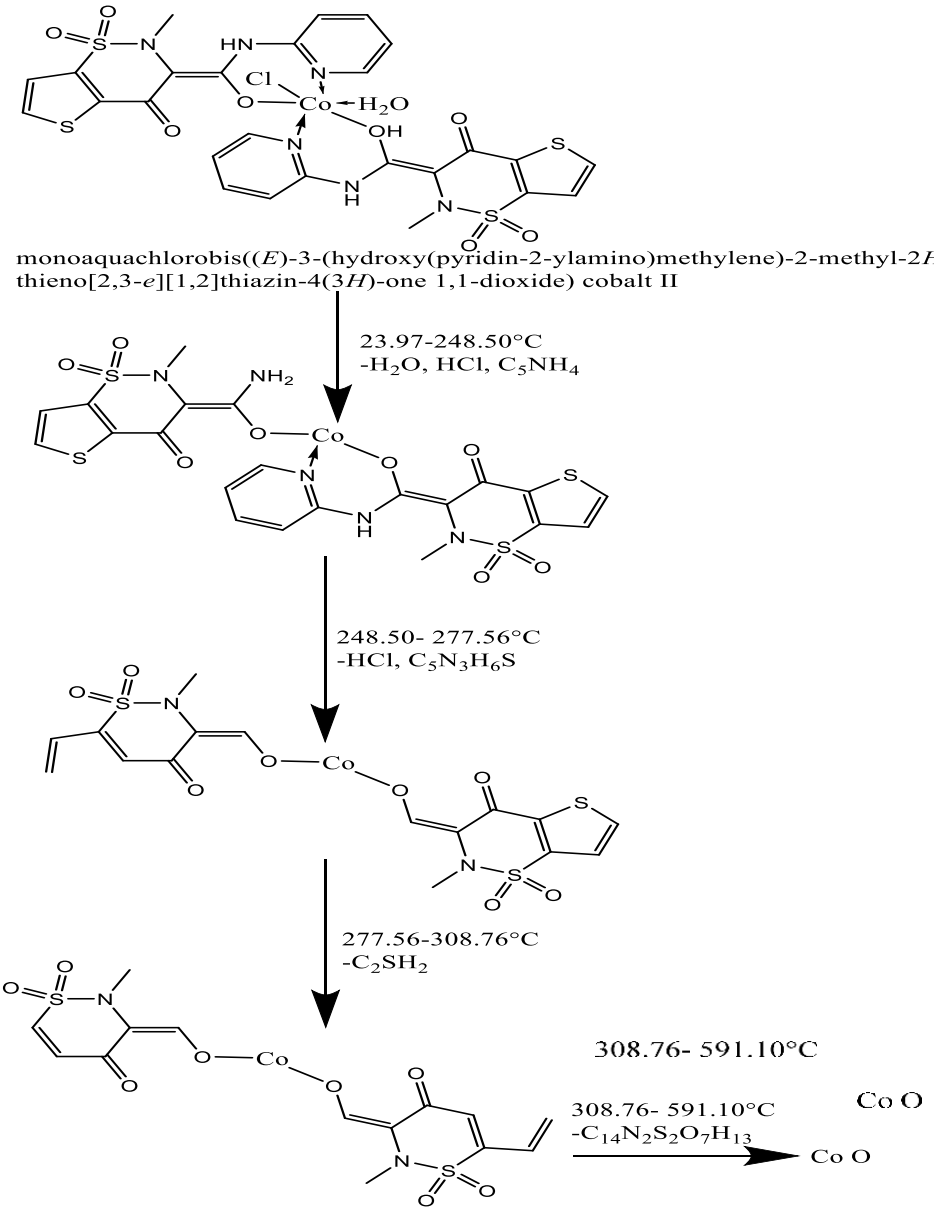


Figure 7. Thermolysis of [Co(tenoxicam)$_2$ClH$_2$O].

The thermal decompositions of cephazolin, Hg(cefazolin)Cl(H_2O), Mn(cefazolin)$_2$Cl (H_2O)complexes of these types were studied by using DSC measurement data.

The glass transition and crystallization temperatures were determined from DSC graph for cephazolin, Hg(cefazolin)Cl(H_2O),Mn(cefazolin)$_2$Cl (H_2O) (Figure 8 and Tables 6 and 7). The glass transition temperature exhibits dehydration process followed by thermal agitation decomposition for the complexes. This is compatible with the explanation of TGA for these complexes. The glass transition temperature for all complexes can be determined from DSC graph since they exhibit dehydration process due to lattice and coordinated water molecules followed by thermal agitation decomposition. This is compatible with the explanation of TGA for these complexes. [Mn(cefazolin)$_2$Cl (H_2O)] has the highest value of Tg and Tc, (Table 6), where this complex forming an octahedral geometry with one water molecules in the inner sphere. DSC plot is used to carefully determine the melting temperature through an exothermic transition. Melting temperature of compounds are ranged between 230 to 340°C. The Cp can be represented in the following empirical forms:

$Cp=aT+b$ $Cp=\alpha T3+\gamma T$

where (a) and (α) are the slopes of the line and (b) and (γ) are the intersection of the line with y-axis and Cp is the specific heat at constant pressure.

Table 5. Thermal transitions of cephazolin, Hg(cefazolin)Cl(H_2O), Mn(cefazolin)$_2$Cl (H_2O).

Compound	Thermal transitions (°C)		
	T_g	T_c	T_m
Cephazolin	100	200	230
[Hg(cefazolin)Cl(H_2O)]	110	180	280
[Mn(cefazolin)$_2$Cl (H_2O)]	150	280	300

Table 6. The slopes and intercepts for DSC curves of cephazolin, Hg(cefazolin)Cl(H_2O) , Mn(cefazolin)$_2$Cl. (H_2O).

Compound	$C_p=a\ T+b$		$C_p/T=\alpha\ T+\gamma$	
	a	b	α	γ
Cephazolin	0.24	35.49	$-7x10^{-6}$	1.742
[Hg(cefazolin)Cl(H_2O)]	0.401	63.42	$-2x10^{-6}$	0.609
[Mn(cefazolin)$_2$Cl (H_2O)]	0.544	144.1	$-9x10^{-7}$	0.425

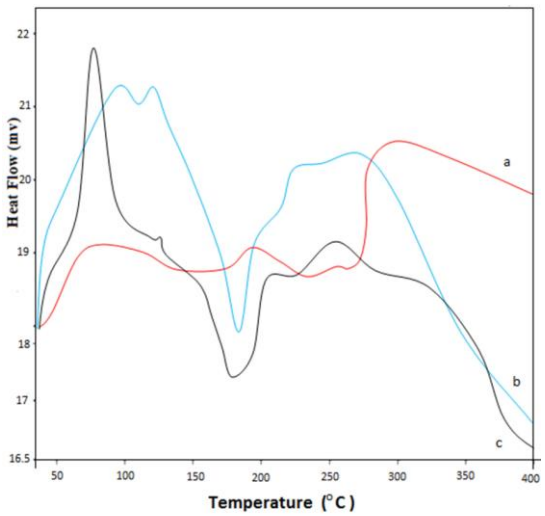


Figure 8. DSC curves for cefazolin and its complexes. a -cephazolin b-[Hg(cefazolin)Cl(H2O)] c-[Mn(cefazolin)2Cl (H2O)].

Table 7. DTA analysis of Tenoxicam and its metal complexes.

Complex	type	Tm (°C)	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 :Found	Assignment	
	endo	115	30.252	0.996	0.633	-0.286	-35.78	0.029	-٦٣.٩ ° 251.22C	36.1	36.1	- $C_6N_2H_6$
Tenoxicam	exo	277.5	154.698	0.996	0.632	-0.276	-34.085	0.148	251.22-591.57°C	97.3	97.2	- $C_7S_2O_3H_7$
[Cr(Tenoxicam)$_2$Cl(H2O)]	endo	112.8	21.886	1.26	0.588	-0.288	-36.116	0.021	56.88-244.22°C	30.8	30.8	- H_2O,HCl, $C_8S_2H_4$
	exo	276.9	90.581	1.313	0.58	-0.277	-34.641	0.087	244.22-284.04°C	40.9	40.9	- C_5NH_4
[Mn(Tenoxicam)$_2$Cl(H_2O)]	exo	89.7	26.717	1.289	0.584	-0.287	-35.909	0.025	23.86-149.93°C	6.9	3.8	- H_2O,HCl
	exo	263.1	230.755	1.195	0.598	-0.269	-33.671	0.221	149.93-261.54°C	33.8	15.3	- C10N4H10
	exo	544.7	956.858	1.5937	0.543	-0.257	-32.203	0.908	261.54-591.80°C	91.1	99.7	- C16N2S4O7H12
[Co(Tenoxicam)$_2$Cl(H_2O)]	exo	119.4	19.848	1.346	0.576	-0.289	-36.217	0.019	23.97-248.50°C	17	17.4	- H_2O,HCl, C_5NH_4

	exo	263.8	264.784	1.0911	0.615	-0.268	-33.529	0.253	248.50-277.56°C	34.7	35.5	-$C_5N_3H_6S$
	exo	330.5	27.167	1.83	0.517	-0.287	-35.891	0.026	277.56-308.76°C	42.2	42.2	-C_2SH_2
	endo	586.1	74.38	0.853	0.66	-0.278	-34.845	0.071	308.76-591.10°C	91.3	77.1	-C14N2S2O7H13
[Ni(Tenoxicam)$_2$Cl(H_2O)]	exo	113.7	20.064	1.324	0.579	-0.289	-36.206	0.019	36.96-142.82°C	6.8	5.5	-H_2O,HCl
	exo	264.7	143.857	1.26	0.588	-0.273	-34.161	0.138	142.82-275.56°C	30.5	31.4	-C10N4H10
	exo	407.8	208.373	1.428	0.564	-0.27	-33.777	0.199	275.56-463.93°C	85.3	81.6	-C16N2S4O7H12
[Zn(Tenoxicam)$_2$Cl(H_2O)]	exo	112.8	13.501	1.21	0.596	-0.292	-36.618	0.012	32.53-159.51 °C	2.2	2.3	-H_2O
	endo	228.2	73.954	1.166	0.603	-0.278	-34.851	0.071	159.51-264.52°C	16.4	15.7	-0.5Cl_2, C_5NH_4
	exo	564.1	799.765	1.543	0.55	-0.259	-32.387	0.761	264.52-591.61°C	28.2	27.5	-$C_2S_2H_4$
[Cd(Tenoxicam)2Cl(H2O)]	exo	116.2	15.538	1.31	0.581	-0.291	-36.472	0.014	22.05-242.99°C	6.4	5.1	-H_2O, 0.5Cl_2
	exo	551.3	145.736	1.626	0.539	-0.273	-34.147	0.139	242.99-590.53°C	17.4	16.71	-$C_2S_2H_4$
[Hg(Tenoxicam)$_2$Cl(H_2O)]	exo	102.7	17.403	1.281	0.585	-0.29	-39.354	0.016	22.85-184.90°C	5.8	6.2	-H_2O, 0.5Cl_2
	endo	222.2	227.637	1.649	0.537	-0.269	-41.685	0.218	184.90-265.66°C	62.4	63.1	-٢C11NS2O3H9
	exo	566.6	53.262	1.224	0.594	-0.281	-38.192	0.051	265.66-591.17°C	99.8	100	-C_4N4OH_{10}
[Fe(Tenoxicam)$_2$Cl(H_2O)]	endo	120	21.1	1.223	0.594	-0.289	-42.154	0.02	22.79-120.19°C	10.4	10.1	-H_2O, HCl, N_2
	exo	314.2	46.534	1.002	0.631	-0.282	-39.332	0.044	120.19-385.68°C	41.1	40.1	-C14N2SH12
	exo	468.5	540.875	2.1	0.49	-0.262	-44.79	0.516	385.68-590.47°C	44.7	44.9	-CO

Biological activity

The data in Table 8, allow the following observations and conclusions.All the investigated compounds have higher positiveantibacterial activity comparedto antifungal activity. [Cu(tenoxicam)$_2$Cl(H_2O)] and [Zn(tenoxicam)Cl(H_2O)] complex showed activity in the same range of tenoxicam for *Escherischia coli*, *Staphyllococcus aureus* and *Bacillus*

subtilis. The [Zn(tenoxicam)$_2$Cl(H$_2$O)] complex showed a relatively good activity higher than cefazolin for *P. aureginosa* although the free ligand showed no activity for this gram negative bacteria type [20-22].

Table 8. 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(tenoxicam)$_2$Cl(H$_2$O)	8	8	8	12	8	8	8	12	8	11
[Zn(tenoxicam)$_2$Cl(H$_2$O)]	8	8	8	12	8	8	8	12	8	11
Tenoxicam	8	8	8	12	8	8	8	12	8	11
Ciprofloxacin	9	30	9	30	9	30	9	30	-	-

CONCLUSION

Most obtained metal complexes showed higher activity than the free ligands which could be explained on the bases of overtones̛ concept and chelation theory, complexation enhances the lipophilicity of the complex.

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