Synthesis of New Cobalt(II) Captopril as Hypertensive Drug.

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ABSTRACT

This work has reported the synthesis, characterization, and thermogravimetric analysis of binuclear cobalt(II) complex of captopril hypertensive drug. It is verified, by FTIR spectroscopy that, the mercapto and carboxylate group of captopril are employed as the first coordinative site, the carboxylic group is involved in coordination after deprotonated. As a general behavior, it is verified that the coordination compound is thermally stable affected by the metal ion. The microbial test of antibacterial and antifungal were screened.
Keywords: Captopril, cobalt(II) complex, thermal analyses, spectroscopic studies.

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INTRODUCTION

Captopril, 1-[(2S)-3-mercapto-2-methylpropionyl]-1-proline, is an orally active drug for the treatment of high blood pressure [1,2]. Captopril is used therapeutically as an antihypertensive agent. It acts as a potent and specific inhibitor of the zinc-containing angiotensin converting enzyme (ACE) [3]. On the other hand, the side-effects that can arise during captopril treatment [4] may well be caused by the interactions of captopril with other metal ions present in the plasma [5]. The first study on the interactions of captopril with organometallic compounds was performed recently [6]. The main target of the present article is to study the coordination behavior of the captopril ligand (Cap) that incorporate several binding sites towards some metal ions, and also to evaluate the relative thermal stability of the synthesized complexes.
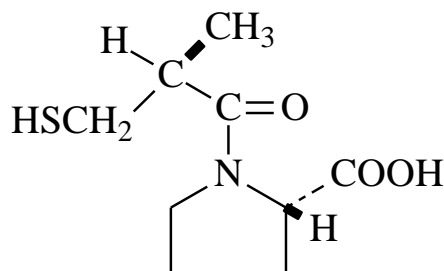

Fig 1: Structure formula of captopril

EXPERIMENTAL

Chemicals

All chemicals used were of the purest laboratory grade (Merck). The $Co(OAC)_2.6H_2O$ was used in a pure grade and received from Aldrich Chemical Company. Captopril was received from Egyptian international pharmaceutical industrial company (EIPICO.).
2-2-Synthesis of metal complexes

The Co(II) complex was prepared upon the reaction mixture of $Co(OAC)_2.6H_2O$ metal cation with (1 mmole) in 20 ml of 99% methanol to dissolved captopril (20 ml of 99% methnol) with molar ratios 1:2. The pH of captopril metal cation mixture was adjusted to 8-9 using 5% alcoholic ammonia solution. The resulting solutions were stirred and refluxed at 60 °C for one hour. The isolated complex was precipitated at once then filtered off and washed several times with methanol. The colored solid complex was dried at 70 °C under vacuum over anhydrous $CaCl_2$.

RESULTS AND DISCUSSION

The selected physical properties and characteristic data of the synthesized cobalt(II) captopril complex was measured and listed in Table (1). This complex show 1:2 ligand-to-metal molar ratios. The analytical data of captopril and its binuclear metal complex with the predicted molar ratio are summarized in Table (1). The colored solid complex is stable in air and soluble in water or methyl alcohol but soluble in DMF, DMSO and concentrated acids. The molar conductance values indicate that the binuclear captopril complex seem to be non-electrolyte. The Co(II) complex undergo decomposing at different temperatures begins at ~ 280 °C, which reflect the high thermal stability of the isolated binuclear metal complex. Elemental analysis in addition to IR and thermogravimetric data are in a good agreement with that required for the proposed formula of the resulted complex. It is clear that the binuclear metal complex behave as non-electrolytic behavior according to conductivity data. Also, the molar conductance values indicate that the counter ions existed inside the coordination sphere. These results were confirmed from the chemical analysis where CH_3COO^- ions are precipitated by addition of $FeCl_3$ solutions to the digested metal complex using concentrated nitric acids.

Table (1): Elemental analysis and physical data of Co(II) complex

Complexes	M.wt (g/mol)	Molar conductance (Ω^{-1} cm^2 mol^{-1})	Elemental analysis			
			%C	%H	%N	%M
$[CO_2(Cap)(OAC)_2(H_2O)_4].6H_2O$	631	32	24.11 (24.72)	6.11 (6.18)	2.13 (2.22)	18.62 (18.70)

Infrared spectra

The most characteristic bands in the infrared spectra of the free ligand and its cobalt(II) binuclear complex are shown in Fig. (2) and listed in Table (2), along with their tentative assignments. The position of these bands provide significant indications confirming the potential sites of complexation of ligand molecules with Co(II) metal ion. The free captopril ligand can exhibit band at 3300 cm^{-1}, which may be assigned to $\gamma(OH)$ of carboxylic group. Infrared spectrum of the free ligand can show strong band within the region 1592 and 1448 cm^{-1}, which may be assigned to $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$, respectively. Also, the band at 2562 cm^{-1} can be assigned to $\nu(SH)$. On comparison of the infrared spectrum of the ligand with its binuclear metal complex revealed the absence of absorption bands associated with the stretching of SH and COOH groups, indicating the loss of two protons of SH and COOH groups on coordination, forming metallo-sulfur and metallo-oxygen bands, at the same time, the $\nu(CO)$ band appears at 1694 cm^{-1}. This band is disappeared in the complex. Also, the $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ bands of captopril complex is formed at 1609 and 1409 cm^{-1}, respectively. The difference $\Delta\nu$ ($\Delta\nu = \nu_{as}(COO^-)$ - $\nu_s(COO^-)$) is as expected for the bidentate bridging mode of carboxylate ligation [7]. The spectra of the binuclear metal complex exhibited broad band at ~3400 cm^{-1} that are attributed to $\nu(OH)$ of coordinated and lattice water molecules. In principle, the multiple medium bands at 555 cm^{-1} and the medium weak bands at 428 cm^{-1} of the binuclear complex are assigned to the $\nu(M-O)$. From IR data, it can be concluded that the capotopril ligand function as multidenatate ligand coordinating through mercapto group and amide (CO) group to the central metal atom from one side and carboxylate group to the central metal atom from the other side in these binuclear complex (Scheme 1).

Table (2): Infrared spectra of Cap ligand and its Co(II) complex

Cap	Co(II)	Assignments
-	3408(br)	$\nu(OH);H_2O$
2562	-	$\nu(SH)$
3300(br)	-	$\nu(OH);COOH$
1694(S)	-	$\nu(OH);Amide$
1592(S)	1609(S)	$\nu_{as}(COO^-)$
1448(S)	1409(S)	$\nu_s(COO^-)$
-	555(w)	ν (M-O)
-	428(w)	ν (M-S)

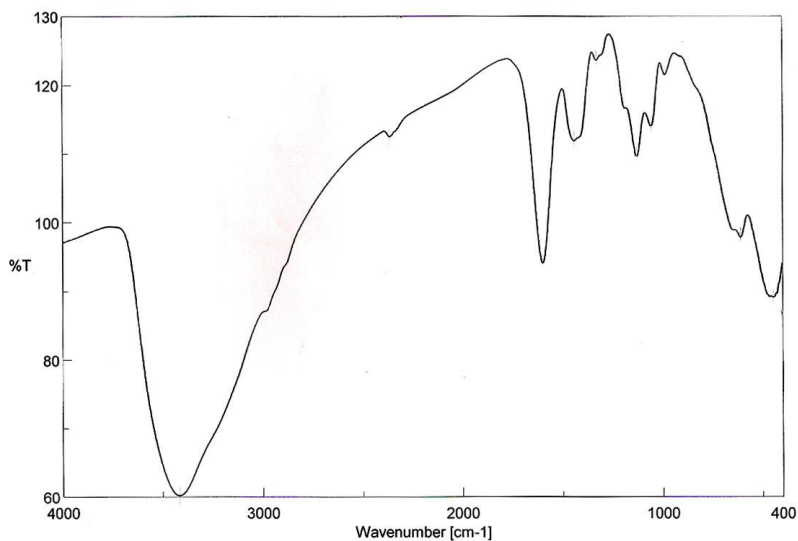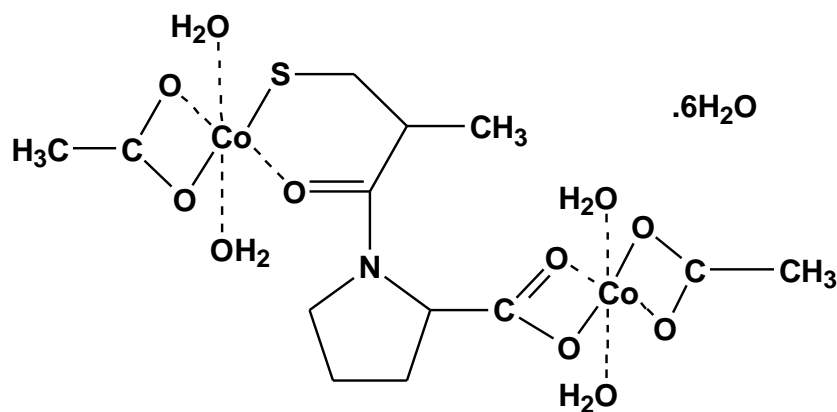br = broad; S = strong; w = weak, m = medium

Fig 2: Infrared spectrum of Co complex

Scheme 1: Mode of chelation of captopril complex

Magnetic and electronic studies

The electronic spectrum of $[Co_2(Cap)(OAC)_2(H_2O)_4].6H_2O$ complex (Fig. 3) has a three transition bands located at 16.447, 20.161 and 28.329 cm^{-1}. These bands are assigned to the $\nu_1 = {}^{14}T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, $\nu_2 = {}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ and $\nu_3 = {}^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$, respectively. These transitions corresponding to the octahedral geometrical structure [8]. The magnetic susceptibility measurements at the room temperature were carried out according to Gauy method and lie at 4.45 B.M. indicating the presence of three unpaired electrons [9].
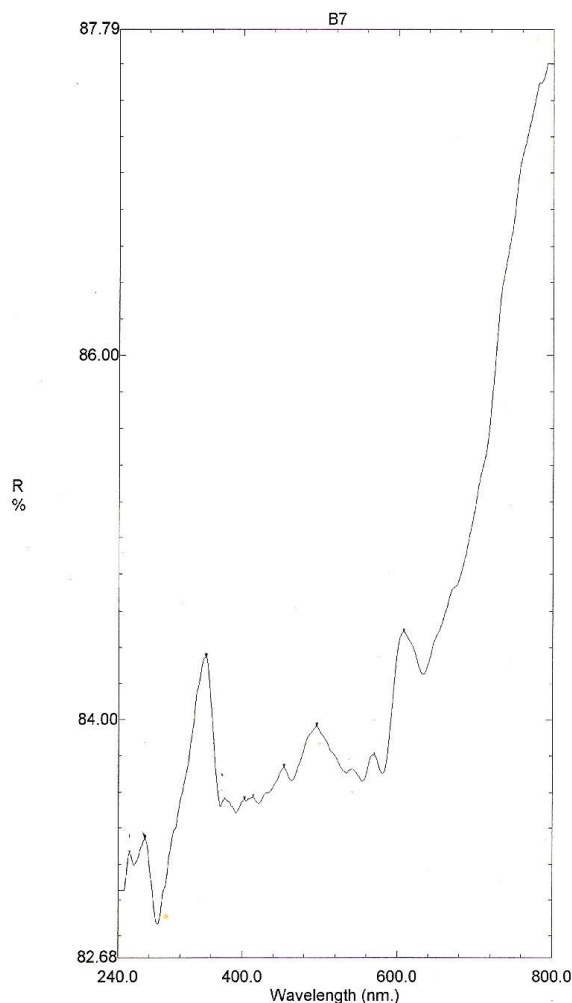
Fig 3: Solid reflectance spectrum of Co(II) complex

Thermal analysis

The heating rates were controlled at (10 °C/min) under nitrogen atmosphere and the weight loss was measured from ambient temperature. The data are listed in Table (3) and shown in Fig. (4). The weight losses were calculated within the corresponding temperature ranges. The $[Co_2(Cap)(OAC)_2(H_2O)_4].6H_2O$ complex was thermally decomposed in four successive decomposition steps within the temperature range 25-745°C. The first decomposition step (obs. = 17.02%, calc. = 17.12%), weight loss within the temperature range 25-145°C, may be attributed to the liberation of six hydrated water molecules. The second decomposition step found within the temperature range 200-420°C (obs. = 42.44%, calc. = 42.79%), which is accounted by the removal of $2OAC^-$, $4H_2O$, CH_4, H_2S and NO molecules. The third decomposition step is occurring with temperature range 420-555°C, which is corresponding to the loss of C_2H_4 and C_2H_2 molecules (obs. = 8.61%, calc. = 8.55%). The last step is occurring at 650-745°C and corresponding to the evolution of $\frac{1}{2}C_2H_2$ molecule and representing a weight loss of 1.95% and its calculated value is 2.06%. The decomposition of the Co(II) complex ended with $2CoO$ polluted with three carbon atoms.

Table (3): Thermal data of Co(II) complex

| Temp. range (°C)	DTG peak (°C)	TG weight loss % Found (calcd.)	Assignments
25-145	65	17.02 (17.12)	$6H_2O$
200-420	285	42.44 (42.79)	$2ACO^-+4H_2O+CH_4+H_2S+NO$
420-555	516	8.61 (8.55)	$C_2H_4+C_2H_2$
650-745	713	1.95 (2.06)	$^1/_2C_2H_2$
745-800		Residual	$2CoO+3C$
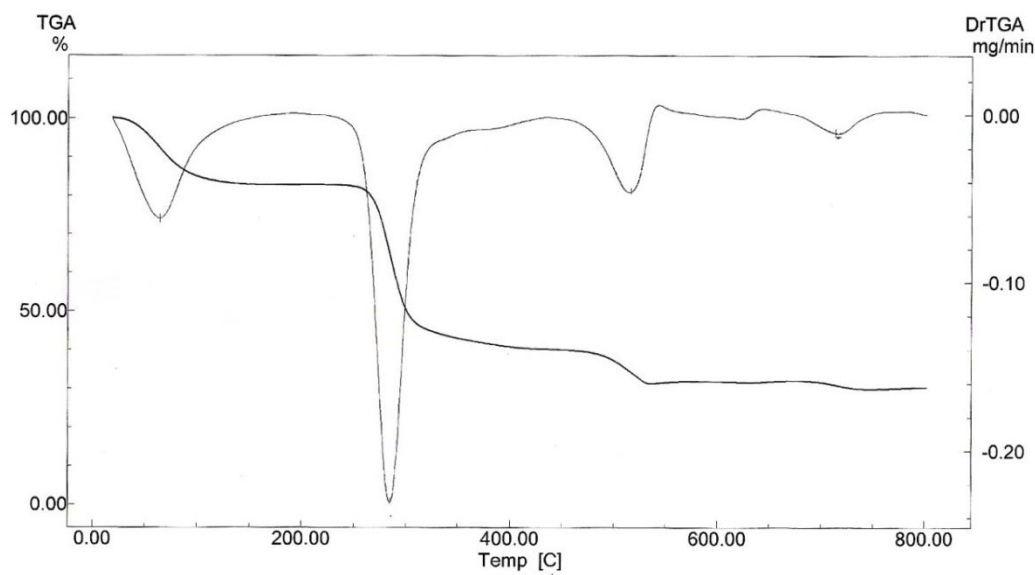
Fig 4: TG-DTG curve of $[Co_2(Cap)(OAC)_2(H_2O)_4].6H_2O$ complex

Antimicrobial assessments

Antibacterial and antifungal activities of the binuclear cobalt(II) complex was carried out against Escherichia coli (Gram –ve), Bacillus subtilis (Gram +ve) and antifungal (Aspergillus niger and Aspergillus flavus). The results of the antimicrobial test are listed in Table (4), and shown in Fig. (5). The antimicrobial assessments were estimated on the basis of size of inhibition zone around dishes. As referred in Table (4), it is clear that,Co(II) complex is active complex against bacteria and fungi, this is due to the role of metal ions which has ability to penetrate cell wall of organized.

Table (4): The inhibition zone diameter (cm.mg^{-1}) sample of captopril cobalt(II) complex against some kinds of bacteria and fungi

Sample	Diameter of inhibition zone (cm.mg^{-1})			
	Escherichia coli	Bacillus subtilis	Aspergillus niger	Aspergillus flavus
Control: DMSO	0	0	0	0
Co(II) complex	1	1.2	1.2	1.5
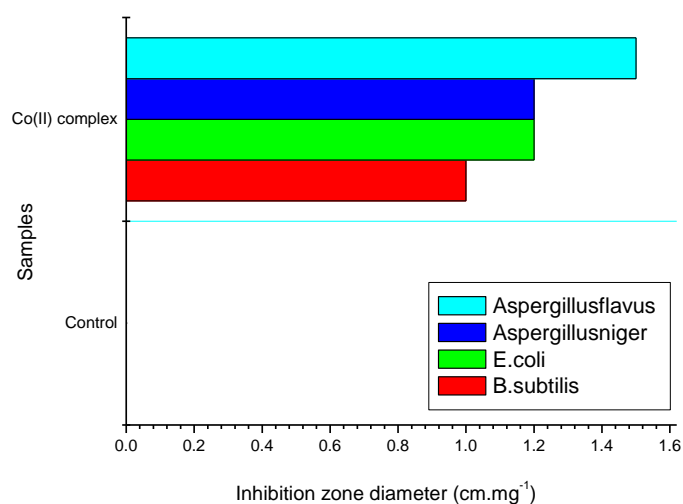
Fig 5: Statistical representation for biological activity of captopril and its cobalt(II) complex

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