Synthesis and Spectroscopic Characterizations of New Mercury(Ⅱ)，Cerium(Ⅲ)，and Thorium(Ⅳ) Captopril Drug Complexes

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Abstract In this article，three types of metal ions with different oxidation state as mercury(Ⅱ)，cerium(Ⅲ) thorium(Ⅳ) have been reacted with captopril drug (CAP). The isolated solid complexes were explained using elemental analysis，conductance measurements，infrared and ^{1}H-NMR spectroscopy as well as the thermo gravimetric (TG/DTG) analysis. The micro analytical and spectroscopic results for all CAP complexes were agreement with the speculated structures. The stoichiometry for divalent Hg^{2+}，trivalent Ce^{3+} and tetravalent Th^{4+} metal ions with CAP ligand was established with 1∶2 (M^{n+}:CAP) molar ratio. The qualitative analysis showed that in case of the mercury(Ⅱ) complex，the chloride ions didn't involved in the complexity，suggesting formula [Hg(CAP)$_2$] in neutral form. However，regarding both Ce(Ⅲ) and Th(Ⅳ) complexes as [Ce(CAP)$_2$(NO$_3$)]·3H$_2$O and [Th(CAP)$_2$(NO$_3$)$_2$(H$_2$O)]·3H$_2$O formulas，the nitrate group is existed inside the coordination sphere. The infrared analysis data proved that CAP drug act as a bidentate ligand with the metal ions of Ce(Ⅲ) and Th(Ⅳ) through oxygen carbonyl group C═O and oxygen of the deprotonated carboxylic COOH group，while for the Hg(Ⅱ) complex，the CAP acts as a bidentate ligand through oxygen of C═O group and sulfur atom of the deprotonated —SH group. Thorium(Ⅵ) complex has a nine-coordinate geometry，while Hg(Ⅱ) and Ce(Ⅲ) have a four and six-coordination behaviors respectively. The ^{1}H-NMR data of the CAP compound has a singlet sharp signal at 1.90 ppm due to the proton of —SH group，this peak absent in the spectrum of the Hg(Ⅱ) CAP complex upon the deprotonated of thiol group.

Keywords Captopril drug；Metal ions；FTIR；^{1}H-NMR
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Introduction

Captopril (CAP) (Fig. 1) therapeutically is used as an antihypertensive agent act as a potent，inhibitor competitive of angiotensin enzyme converting and used for treatment of hypertension[1]. The uses of captopril in treatment of heart failure and hypertension comes from suppression of the renin-angiotensin-aldosterone system (RAAS). Captopril inhibits ACE，which converts angiotensin Ⅰ to angiotensin Ⅱ. Angiotensin Ⅱ binds to AT1 receptors on smooth muscles to produce vasoconstriction and raise in pressure of blood[2]. Captopril used for preventing kidney failure due to diabetes and high pressure of blood. Cerium(Ⅲ) doped nanoparticles of captopril were synthesized by a process called cold welding[3]. The ratio of Ce(NO$_3$)$_3$ added 10% and by using photoluminescence (PL) optical properties have been studied. Prepared compounds were assigned by IR spectroscopy. X-ray diffraction (XRD) used to calculate size of CAP-NP size of CAP-NP which in range of 50 nm. The surface morphology of prepared nanoparticles was studied using scanning electron microscopy. Lactams are main important anti-bacterial，where its activity is inhibited by production of serine and met-

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allo-lactamases (MBLs). The development of useful serine-lactamase inhibitors achieved clinically. L-Captopril that inhibit MBLs[4] by attack active site Zn ions via its SH that used to treat hypertension via angiotensin-converting enzyme inhibition. It is used for hypertension management, following myocardial infraction and in diabetic nephropathy. Angiotensin converting Enzymes (ACE) inhibitors[5] are one of the most important class of drugs for treating hypertension and chronic heart failure. As the ACE-inhibitor type of antihypertensive, captopril, has an importance due to: at first considered as most common drug used, secondly as it has several groups, like carboxylic, carbonyl, thiol and nitrogen of proline[6]. This field is most important due to late publications at 1980 where make reaction between CPA and Cu/Zn[7]. In the presence of more than one ligands, Cu(Ⅱ)/CPA was studied, keeping Cu in (Ⅱ) oxidation number to prevent its reduction. Later in several directions the main data concerning new possible aspects of CPA have spread, to specify mainly the physiological effect of the CPA drug[8]. The living organisms vital functions required metal ions where occur chelation, to control medical substances by forming complexity. Lactic acid/CPA membrane fiber were electro spun for drug delivery[9]. Thermal behavior of the CPA and its cobalt(Ⅱ) complexity was examined by TG/DTG and differental scanning calorimetry in dynamic nitrogen and oxygen atmospheres. Acid-base equilibria of CPA and its complexity formation with Fe(Ⅱ) and Zn(Ⅱ) have been studied[10] in aqueous medium and ionic strength ($I=0.1$ mol·L^{-1} sodium perchlorate) conditions. The complexity of iron(Ⅱ) and Zinc(Ⅱ) with CPA have been synthesized. They were characterized by elemental analysis, infrared and electronic absorption spectra. Binding sites in the complexes with a special regard to the possible role of —SH and —C═O groups in the coordination have been discussed. The thermal behavior of the prepared complexes have been studied by thermogravimetric analysis in nitrogen atmosphere up to 750 ℃.

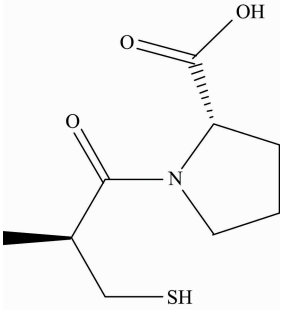


Fig. 1 Structure of captopril drug

1 Experimental

Captopril used was received from the Aldrich Chemical Company. Chemicals used for this study were of analytically reagent grade, commercially available from BDH like $HgCl_2$, $Ce(NO_3)_3 \cdot 6H_2O$ and $Th(NO_3)_4 \cdot 5H_2O$.

1.1 Synthesis

The Hg(Ⅱ), Ce(Ⅲ) and Th(Ⅳ) complexity were prepared by reaction of $HgCl_2$, $Ce(NO_3)_3 \cdot 6H_2O$ and $Th(NO_3)_4 \cdot 5H_2O$ metal ions with (1 mmole) in 25 mL distilled water to dissolved Captopril (25 mL of 99% CH_3OH) with molar ratio 1∶2. The pH of Captopril metal ions mixtures are between ~8.0~9.0 using 5% ammonium hydroxide. The product was stirred and refluxed at 70 ℃ for 3 h. The obtained precipitates were filtered off and washed with distilled water and CH_3OH. The solid product precipitates were dried at 70 ℃ under vacuum over anhydrous calcium chloride.

1.2 Instruments

The C, H and N percentage determined using Vario EL Fab. CHNS. Metal content and water percentage were determined by TG/DTG. IR data for CPA complexity were measured using infrared Bruker spectrophotometer ranged between 400~4 000 cm^{-1}. The conductance measurements with concentration of 10^{-3} mol·L^{-1} for complexity in dimethyl sulfoxide solvent measured using HACH conductivity meter model. ^{1}H-NMR was recorded as dimethyl sulfoxide solutions on a Bruker 600 MHz spectrometer using tetramethyl silane as the internal standard. TGA experiments were conducted using Shimadzu TGA-50H thermal analyzers. All experiments were performed using a single loose top loading platinum sample pan under N_2 atmosphere at a flow rate of 30 mL·min^{-1} and a 10 ℃·min^{-1} heating rate for the temperature range 25~800 ℃.

2 Results and Discussion

C, H and N percentage of the new three complexity were in Table 1. The data of elemental analysis show that (metal∶CAP) molar ratio were of 1∶2 for Ce(Ⅲ), Th(Ⅳ) and Hg(Ⅱ). These complexity didn't completely soluble in hot DMSO and DMF, but insoluble in H_2O and other organic solvents. The suggested formula structures of the complexity were based on the results of the elemental analyses, molar conductivity, (infrared, ^{1}H-NMR) spectra and the thermal analysis. The degradation profile and thermal stability of the CAP complexes were investigated by thermogravimetric (TG) measurements. The Hg-CAP showed good thermal stability compared with other complexes. The TG and DTG indicted that Th/CAP, Ce/CAP and Hg/CAP are thermally stable up to 80, 100 and 235 ℃, respectively. Th(Ⅳ) and Ce(Ⅲ) complexes were thermally decomposed within five and four steps respectively while for Hg(Ⅱ) complexity decomposed within two steps. The thermogram of the Th and Ce/CAP

complxes indicate that the most stable final product of the thermal degradation was metal oxide contaminated with carbon atoms.

Table 1　Analytical and physical data of the CAP complexes

Complexes	Elemental analysis % found (calcd.)			
	C	H	N	M
$[Ce(CAP)_2(NO_3)] \cdot 3H_2O$	31.95 (32.43)	4.43 (5.30)	6.73 (5.97)	20.73 (19.91)
$[Th(CAP)_2(NO_3)_2(H_2O)] \cdot 3H_2O$	31.13 (26.06)	3.63 (4.49)	6.23 (6.40)	28.45 (26.50)
$[Hg(CAP)_2]$	34.15 (34.15)	4.13 (4.46)	4.78 (4.42)	31.33 (31.68)

2.1　Molar conductance

Molar conductance data of the complexity are 43, 45 and 16 $\mu s \cdot cm^{-1}$ for the Ce(Ⅲ), Th(Ⅳ) and Hg(Ⅱ) CAP respectively. Based on electrolytic measurements of the Ce(Ⅲ), and Th(Ⅳ) complexity, NO_3^- anion have coordinated character and exists inside coordination sphere, while in case of Hg(Ⅱ) complex, the Cl^- anions have uncoordinated character and didn't exists inside and outside coordination sphere[11].

2.2　Infrared Spectra

The main bands in the IR of the free captopril ligand and their metal complexes (Fig. 2) which summarized in Table 2. The infrared data refers to involvement of carboxylic and carbonyl groups in chelation, together with water, that presented inner or outer coordination sphere of Ce(Ⅲ) and Th(Ⅳ). The presence of broad band's at 3 408 and 3 426 cm^{-1} which didn't found in the free CPA spectrum, indicates the presence of water molecules that disappears after heating the complexes at 100 ℃. In principle the ligand can exhibit band at 3 300 cm^{-1} which may be assigned to ν(OH) of carboxylic group. IR of the ligand show strong band within the region 1 742 and 1 446 cm^{-1} which may be assigned to asymmetric ν(COO) and symmetric ν(COO), respectively. The band at 2 562 cm^{-1} was assigned to ν(S—H)[12], this peak remains unshifted in the spectrum of Th(Ⅳ) and Ce(Ⅲ) complexes. The presence of (C—S) band at 980 cm^{-1} in the ligand which didn't changed in the Th(Ⅳ) and Ce(Ⅲ) complexes confirm that SH group not participate in coordination process (Fig. 3). The absence of these band at 2 562 cm^{-1} attributed to ν(S—H) and the decrease in vibration of (C—S refers to that SH group participate in coordination in case of Hg(Ⅱ)/CAP complex. The strongest absorption peak at 1 648 cm^{-1} is due to C═O stretching vibration. This peak became weak and shifted to 1 607 and 1 593 cm^{-1} show a bathochromic shift in the spectrum of complexes which suggests bonding of captopril through C═O group. The spectrum of the complexes exhibited broad band's at 3 400 cm^{-1} that are attributed to OH of crystal water molecules. The low intensity bands at 600～400 cm^{-1} are attributed to vibrations of metal—O and metal—S[12]. Other bands observed in case of Ce(Ⅲ) and Th(Ⅳ) complexes at ～1 460, ～1 270, ～1 030, and ～730 cm^{-1} corresponding to ν_1, ν_4, ν_2 and ν_3 vibrations agree with frequencies reported for bidentate nitrate group[12]. Tie separation of highest frequency bands ν_1 and ν_4 (180～140 cm^{-1}) in the complexes favors bidentate character of the nitrate group[12]. These data support a bidentate chelation of CAP with Ce(Ⅲ) and Th(Ⅳ) through C═O and deprotonated COOH group while for Hg(Ⅱ), CAP acts as a bidentate ligand through C═O and deprotonated SH group molecules (Fig. 3).

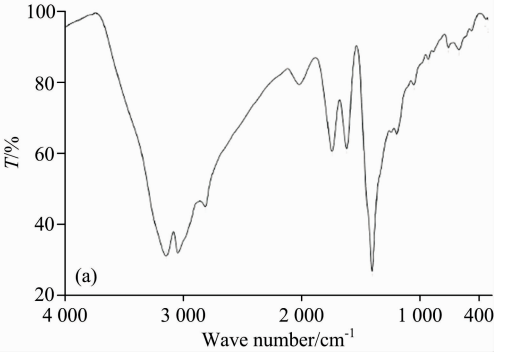


Fig. 2(a)　FTIR spectrum of Hg(Ⅱ) CAP complex

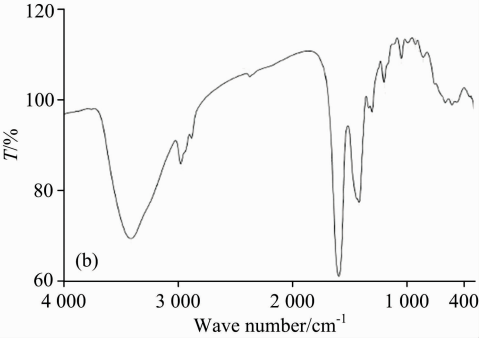


Fig. 2(b)　FTIR spectrum of Ce(Ⅲ) CAP complex

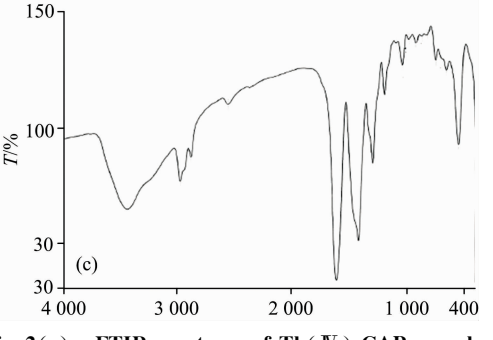
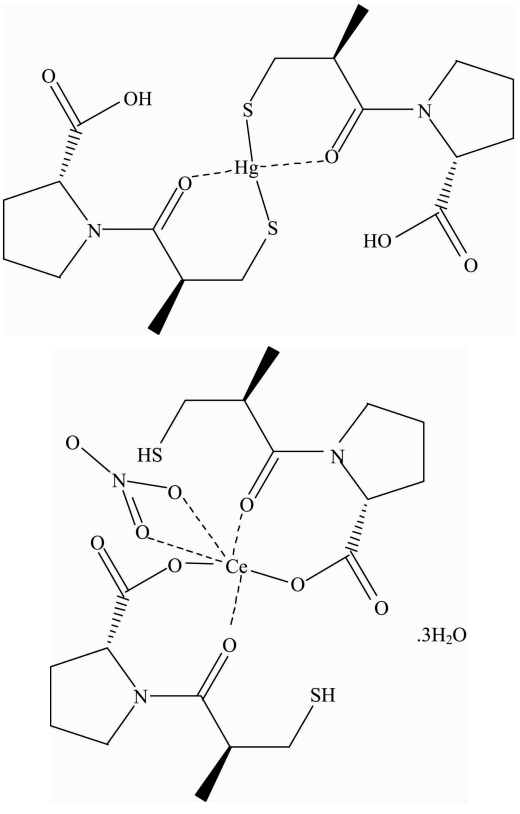


Fig. 2(c)　FTIR spectrum of Th(Ⅳ) CAP complex

Table 2 Infrared spectral bands and assignments of CAP complexes

Compound	ν(O—H) hydrated	ν(SH)	ν(C═O) amide	ν(C═O) acid	ν(M—N)	ν(M—O)	ν(C—S)
CAP	—	2 562	1 648	1 755	—	—	980
Ce(Ⅲ)	3 408	2! 557	1 593	—	450	598	982
Th(Ⅳ)	3 426	2 557	1 607	—	420	546	985
Hg(Ⅱ)	—	—	1 610	1 735	—	547	916



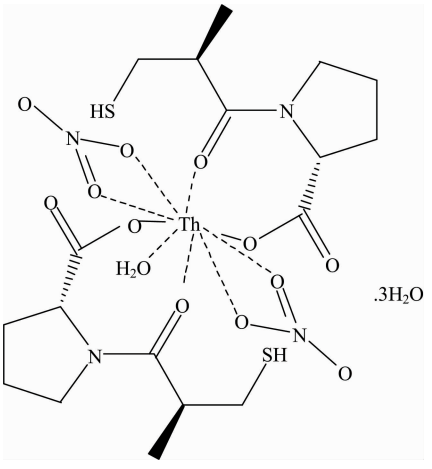


Fig. 3 Speculated structures of Hg(Ⅱ), Ce(Ⅲ) and Th(Ⅳ) captopril complexes

2.3 ^{1}H-NMR spectra

The ^{1}H-NMR spectral analyses for CAP compound in DMSO-d_6 has a singlet sharp signal at 1.90 ppm referred to the proton of —SH, this signal not found in the spectrum of the Hg-CAP complexity due to the deprotonation of the —SH group. The non-equivalent protons of pyrrolidine ring —CH_2 protons, appear as at 2.48～2.51 ppm. The ^{1}H-NMR spectral analyses of the CAP ligand has a singlet sharp signal at 8.53 ppm attributed to the proton of —COOH, this signal not affected in spectrum of the Hg/CAP complexity, supported that carboxylic group not involved in the coordination. These facts confirms the coordination site of captopril which discussed above.

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