



Novel Complexes Derived from Some Lanthanons and Some Transition Metals Ions with Carbocysteine as Pharmaceutical Ligand

KEYWORDS

Potentiometry, complexes, thermodynamic, spectrophotometry, elemental analysis, IR, UV-Vis, X-ray, NMR, thermal analysis (TG and DTA), biological activities.

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ABSTRACT

Proton-ligand dissociation constants of carbocysteine ligand and the formation constants of their complexes with some transition metal ions (Cu^{2+} , Ni^{2+} , Co^{2+} , Zn^{2+} , Fe^{3+}) and some trivalent lanthanides (Ce^{+3} , Pr^{+3} , Er^{+3}) ions have been determined potentiometrically in 0.1M KNO_3 in water. The effect of temperature was studied at 20, 30 and 40°C, the thermodynamic parameters (ΔG° , ΔH° , ΔS°) were evaluated and discussed. The stoichiometry of the formed complexes in solution was determined spectrophotometrically. The obtained data reveals the formation of 1:2 (metal : ligand) complexes. The solid complexes derived from the transition metal ions with ligand under investigation were prepared in ammonia solution as 1 : 2 metal : ligand stoichiometry.

The formed complexes were characterized by elemental analysis (C, H, N), IR, UV-Vis, X-ray and $^1\text{H-NMR}$ spectroscopy. The water content of the formed complexes was determined by thermal analysis (TG, DTA). The biological activities of the synthesized complexes were tested on different types of bacteria and fungi. Copper(II) complexes gave the maximum activities while Zn(II) and Ni(II) gave the minimum results.

Aim of the work:

The most accurate and reliable method for the determination of complex stability constants is the potentiometric measurement of hydrogen ion concentration. It could be achieved for any complex soluble in water or in mixed solvents. The dissociation constants of carbocysteine have been calculated at different temperatures and the associated thermodynamic parameters have been determined. The complexing ability of these compounds with some transition elements and lanthanide via, new, fast, simple, sensitive, precise and cheap procedures based on the potentiometric, spectrophotometric and cyclic voltammetric methods was studied. The present investigations, involve the synthesis, characterization and structure determination of the solid complexes of carbocysteine. Different tools as elemental analysis, electronic absorptions IR, UV-Vis, X-ray and $^1\text{H-NMR}$ spectroscopy and thermal analysis (TG and DTA) have been carried out on some complexes. Antimicrobial activity of the synthesized compounds has been screened using non-pathogenic bacteria and fungi. The comparison between the biological activity of free ligand and its complexes were undertaken.

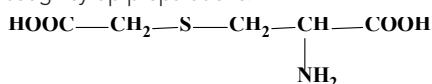
The aim of the present paper is to determine the dissociation constants of carbocysteine as pharmaceutical-ligand and its complexes with some transition elements and some trivalent lanthanides. The thermodynamic parameters of these complexes were evaluated at different temperatures. Our aim was also to characterize the formed complexes by elemental analysis (C, H and N), IR, UV-Vis, X-rays, thermal analysis and $^1\text{H-NMR}$ spectroscopy. The biological effects of the formed complexes compared to the ligand were also investigated on different types of bacteria and fungi and confirmed better activities than cys alone.

1. Introduction

The determination of carbocysteine (Cys) via formation of Pd(II) complex with (Cys) and its metabolites were studied¹. Kinetic-potentiometric method for the determination of Cys

in coloured pharmaceuticals was described². A kinetic-potentiometric method studied the formation of the complex between PdCl_2 and Cys at pH 1.5 – 5 using a stopped-flow technique was carried out³. Spectrophotometric estimation of amoxicillin and Cys in single dosage forms through the complexation with Ni(II) was reported⁴.

Spectrophotometric method was studied⁵ for determination (Cys) in pharmaceutical products. Orlovic et al. (2004)⁶ studied HPLC developed method for the determination of Cys in cough syrup preparations.



Carbocysteine (Cys)

2. Experimental

2.1. Chemicals

All the chemicals used were Analar grade Merck.

2.2. Apparatus

2.2.1. pH meter

pH-measurements were carried out using Fischer Scientific Accrument pH meter model 825 mp fitted with Fischer combined electrode and calibrated by a standard buffer solution at the desired temperature.

2.2.2.

UV/Vis spectrophotometer model spectronic 601 Milton Roy Company with 1 cm quartz cells had been used to obtain the ultraviolet and visible spectra of the investigated compounds at room temperature.

2.2.3.

Pye-Unicam SP2000 instrument (UK) had been used to obtain IR measurements in the rang 4000 to 500 cm^{-1} .

2.2.4.

CHN-Analyser model CHN Rapid, Fa. Heraeus (2400 P.E.) had been used to obtain the elemental analyses (C, H, N) for ligand and its complexes under investigation.

2.2.5.

Shimadzu DTA-TGA50 thermal analyzer, platinum cell, and in atmosphere of nitrogen had been used to obtain the thermal analysis of Cys-complexes.

2.2.6.

PW3710 BASED, tube anode copper Generator tension [KV] 40 Generator current [mA]: 55, Divergence slit : 1.5, and Receiving slit : 0.1 has been used to obtain X-ray analysis of Cys-complexes.

2.2.7

Bank Eelkronic-intelligent controls GmbH Freiburger Strasse ID-38678 Clausthal-Zellerfeld was used to obtain the electroanalysis of ligands and complexes, the used cell consists of a silver-silver chloride (Ag/AgCl) as a reference electrode, an auxiliary electrode of platinum wire and glassy carbon electrode as working electrode.

2.3. Preparation of solid complexes

The solid complexes were prepared by mixing equimolar of ligand and metal salts in ratio of 1 : 2 (metal : ligand), adding 3 ml (30%) NH_4OH . Stirring for 2 h, the separated solid complexes were filtered, washed with diluted NH_4OH and dried at room temperature.

2.4. Antimicrobial activity

The antimicrobial activity of the synthesized complexes has been screened using different strains of nonpathogenic bacteria and fungi. The species were used *Escherichia coli* (gram negative bacteria), *Bacillus subtilis* (gram positive bacteria), *Staphylococcus aureus*, *Candida albicans* (yeast) and *Pseudomonas aeruginosa*. The disc method has been adopted and the diameters of clearing areas around wells (in mm) have been taken as indication to the antimicrobial activity.

2.5. Cyclic voltammetry

A 50 ml of test solution containing (1 : 2) (metal : ligand) ratio, and 3 ml of universal buffer pH = 10.8 were placed into the cell. The voltammogram was recorded by using cyclic voltammetry at different scan rate.

2.6. Methods of calculation**a) pH-metric determination of the dissociation constants**

The pH-meter reading (B), recorded in aqueous medium and in methanol solutions were converted to hydrogen ion concentration $[\text{H}^+]$, by means of the relation of Uiter and Hass⁷.

$$\text{pH} = -\log [\text{H}^+] = B + \log U_H$$

where $\log U_H$ is the correction factor for the effects of solvent composition.

b- Determination of stability constant of metal complexes

$$n/(n-1) [L] = ((2-n) [L]/(n-1) \beta_2 - \beta_1$$

Where

n = the average proton number in ligand

n = an integer that has value 1, 2, 3, N.

β_1 = the formation constant = K_1

$\beta_2 = K_1 K_2$

c- Determination of the thermodynamic functions⁸⁻¹²

Gibb's free energy changes (ΔG), enthalpy changes (ΔH) and entropy (ΔS):

$$\Delta G = -2.303 RT \log K$$

$$\Delta H = -(2.303 RT_2/T_2 - T_1) \times (\log K_{T_1} - \log K_{T_2})$$

$$\Delta S = (\Delta H - \Delta G) / T$$

Where:

R : gas constant = $8.3 \text{ JK}^{-1} \text{ mol}^{-1}$

K : Stability constant for the complex or the ionization constant of the ligand.

T : temperature (K)

K_1 and K_2 are the ionization constants of the ligand or stability constants of the complexes at temperatures T_1 and T_2 .

3- Results and Discussion

3.1. Potentiometric studies of proton-ligand stability constants of carbocysteine (Cys)

The pK_a values were determined using the linear least-square computer program¹³.

3.1.1. Effect of temperature

The effect of temperature on the ionization constants of Cys is shown in Fig. (1).

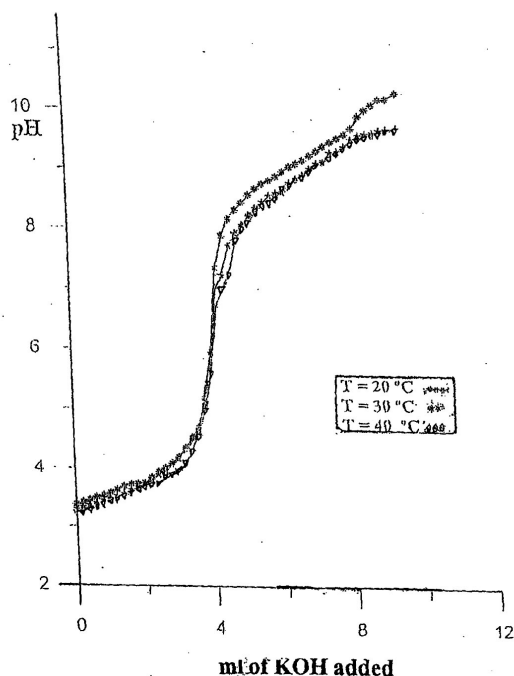


Fig.(1) Effect of temperature on ionization constant of Cys, $C_{\text{KNO}_3} = 0.1\text{M}$, $C_{\text{KOH}} = 0.017\text{M}$ and $C_{\text{Cys}} = 0.003\text{M}$

It is clear that pK_1 and pK_2 values increase with the increase of temperature from 20° to 40°C. This may be due to the fast deprotonation processes at high temperatures.

3.1.3. Ionization constants and thermodynamic functions

The values of ΔH° shown in Table (1) indicate that the endothermic ionization nature process, which is enhanced with the increase of temperature. In addition to the positive values of ΔH° , and the positive values of ΔG° make the ionization process nonspontaneous. At pK_a the values of ΔS° are negative while at pK_{a_2} it is positive, confirming that pK_{a_2} is entropically favorable.

Table (1). Thermodynamic functions for the dissociation constants of Cys in aqueous medium, $C_{KNO_3} = 0.1M$ and at different temperatures.

Temp. K	Dissociation constants		Enthalpy change ΔH°		Free energy change ΔG°		Entropy ΔS°
	pK_{a_1}	pK_{a_2}					
293	4.3635	9.4216	2.12899	9.9380	2.5316	5.48569	-1.3744-5.1955
303	4.3106	9.177	2.1289	9.9380	2.59549	5.52564	-1.5391-14.562
313	4.2056	9.1447	2.12899	9.9380	2.6158	5.6879	-1.555-13.578

ΔG° units are (kcal.mol⁻¹)

ΔH° units are (kcal.mol⁻¹)

ΔS° units are (cal.mol⁻¹.K⁻¹)

3.2. Complexes of transition metals

During the titration of the ligand under investigation there was only one inflection point indicating that the ligand behaves as a diprotonic acid. The ligand-metal mixtures (Zn^{2+} , Ni^{2+} , Co^{2+} , Cu^{2+} and Fe^{3+}), were titrated at 20, 30 and 40°C (ionic strength 0.1M KNO_3 and $C_{KOH} = 0.017M$) in aqueous medium. The formation of a clear homogeneous solution when base is added to a solution of the metal ion and a possible ligand is an indication that a metal chelate compound (or complex) has been formed¹⁴.

Figs. (2a, b, & c) show the effect of temperatures on the titration curves of Cys-complexes. The values of the stability constants $\log K_1$ and $\log K_2$ of the complexes formed at different temperatures are shown in Table (2).

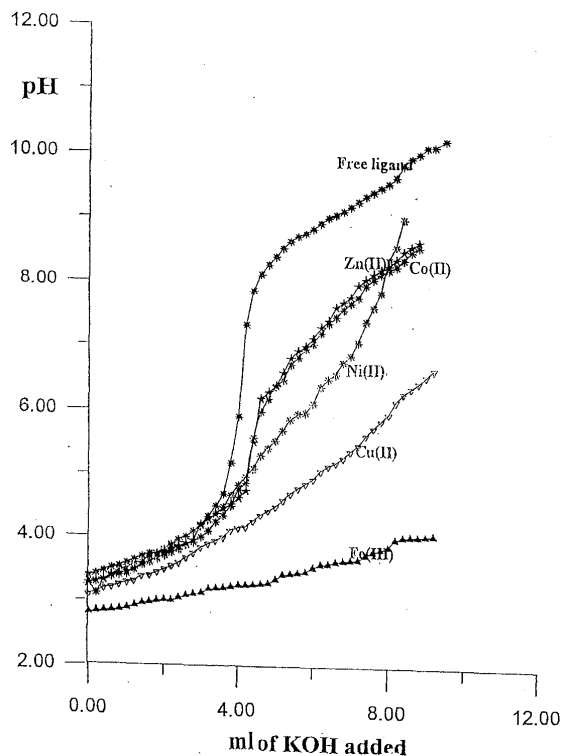


Fig. (2a). pH-titration curves of Cys and its complexes at T= 20°C and ratio of (metal-ligand) = 1:2

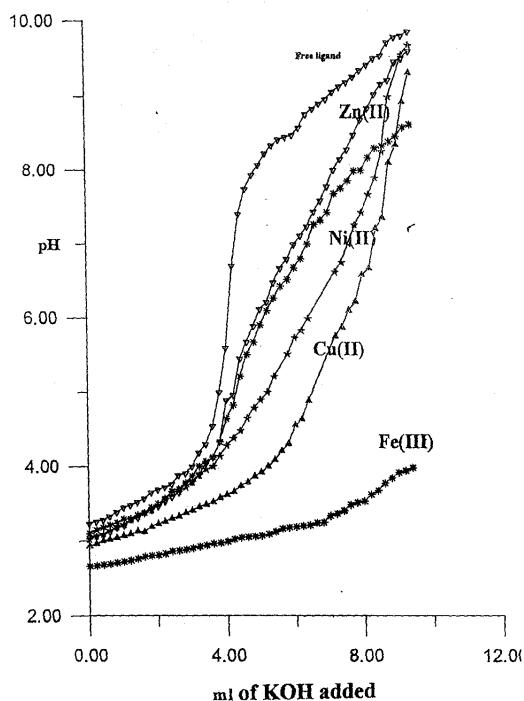


Fig.(2b). pH- titration curves of Cys and its complexes at T= 30°C and ratio of (metal-ligand) = 1:2

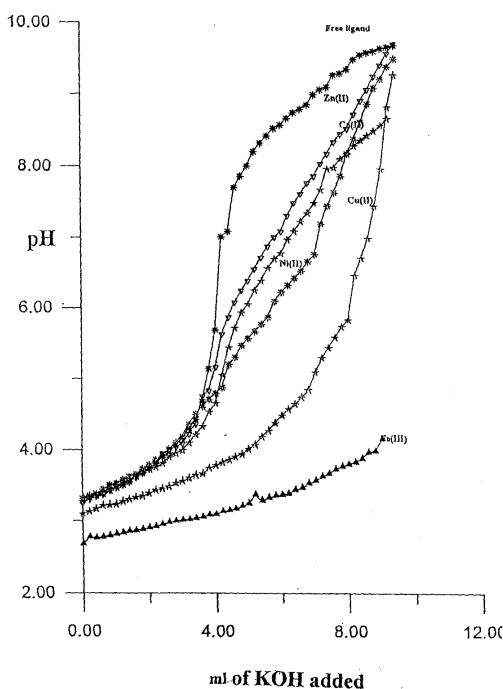
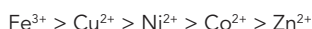


Fig.(2c). pH -titration curves of Cys and its complexes at T= 40°C and ratio of (metal-ligand) = 1:2

Table (2). Stepwise stability constants for the complexation of Cys with Zn^{2+} , Ni^{2+} , Co^{2+} , Cu^{2+} and Fe^{3+} in aqueous medium and 0.1M KNO_3 at different temperatures.

M^{n+}	293 K		303 K		313 K	
	Log K_1	Log K_2	Log K_1	Log K_2	Log K_1	Log K_2
Zn^{2+}	12.46	12.15	12.79	12.41	13.277	12.79
Co^{2+}	12.61	12.27	12.88	12.523	13.39	12.81
Ni^{2+}	12.525	12.39	13.277	12.623	13.44	12.89
Cu^{2+}	12.883	12.07	13.64	12.89	13.87	13.81
Fe^{3+}	14.587	13.354	14.68	13.72	14.75	13.83

The values of the stability constants of Zn^{2+} are relative small compared with those of Cu^{2+} and Fe^{2+} where the d-orbital of Zn^{2+} is completely filled. Therefore these metals form more stable complexes than Zn^{2+} . The stability of the complexes decreases in the following order:



Thermodynamic functions

Thermodynamic parameters ΔG° , ΔH° and ΔS° for the complex compounds were calculated from the stability constants obtained at various temperature (20, 30 and 40°C). The values of the thermodynamic parameters associated with complex formation are indicated in Table 3. The stepwise stability constants of the complexes increase with increasing the temperature. The positive value of ΔG° for complexation process suggests the nonspontaneous nature and the negative value of ΔH° meaning that these processes are exothermic and clearly reflect the increasing metal-ligand strength¹⁵.

Table (3). Thermodynamic functions of Cys with Zn^{2+} , Ni^{2+} , Co^{2+} , Cu^{2+} and Fe^{3+} in aqueous medium and 0.1M KNO_3 .

M^{n+}	ΔG°		ΔH°		ΔS°	
Zn^{2+}	17.1502	16.3028	-13.407	-12.375	-104.2	-103.1
	17.2780	17.1502			-104.7	-103.2
	19.2780	17.2780			-104.4	-103.3
Co^{2+}	16.8955	16.5949	-11.3763	-11.211	-96.4	-95.3
	17.8604	16.8955			-96.4	-95.3
	19.1804	17.8604			-97.6	-96.5
Ni^{2+}	16.7949	16.7949	-30.5535	-29.344	-161.5	-160.4
	18.4109	16.8955			-161.5	-160.4
	19.2520	17.8742			-159.1	-158.1
Cu^{2+}	17.2749	16.1848	-30.7566	33.3163	-163.9	-168.9
	18.2900	17.8742			-161.9	-168.9
	19.7491	18.7378			-161.3	-166.3
Fe^{3+}	19.5598	17.906	-1.625	-15.0736	-72.3	-112.5
	20.2732	19.0321			-72.2	-112.5
	21.0282	19.769			-72.3	-112.5

ΔG° units are (kcal.mol^{-1})

ΔH° units are (kcal.mol^{-1})

ΔS° units are ($\text{cal.mol}^{-1}.\text{K}^{-1}$)

3.3. Complexes of lanthanides with ligand

3.3.1. pH-metric study

The lanthanide ions (Ce^{3+} , Pr^{3+} and Er^{3+}) with $[\text{Cys}] = 0.003\text{M}$ ligand were titrated against KOH, 0.017M at (20, 30 and 40°C) and ionic strength of 0.1M KNO_3 in aqueous medium. The pH-reading decreased comparing with that of the titration curve of the free ligand.

Figs. (3a, b & c) show the effect of temperatures on the titration curves of Cys-complexes. The values of the stability constants log K_1 of the complexes formed at different temperatures are shown in Table (4), the stability of the complexes shows the following order:

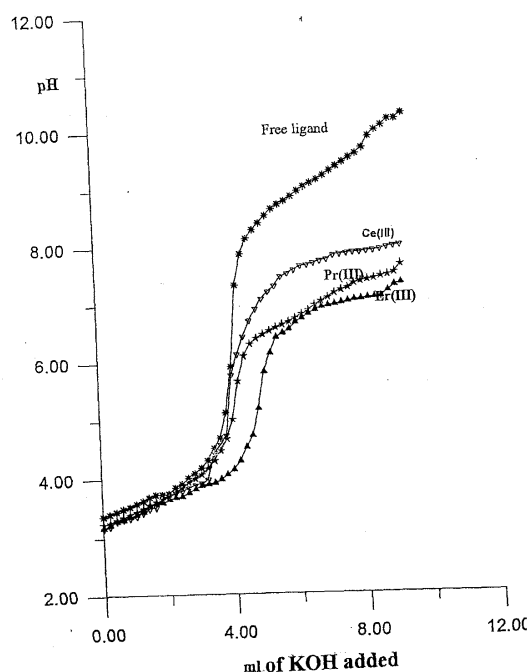
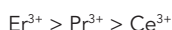


Fig. (3a). pH titration curves of Cys and its complexes at

$T = 20^\circ\text{C}$ and ratio of (metal-ligand) = 1:2

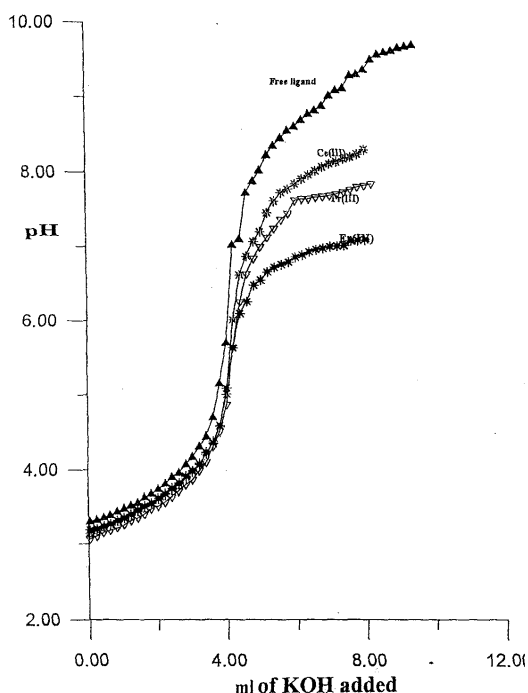


Fig.(3b). pH- titration curves of Cys and its complexes at $T = 30^\circ\text{C}$ and ratio of (metal- ligand) = 1:2

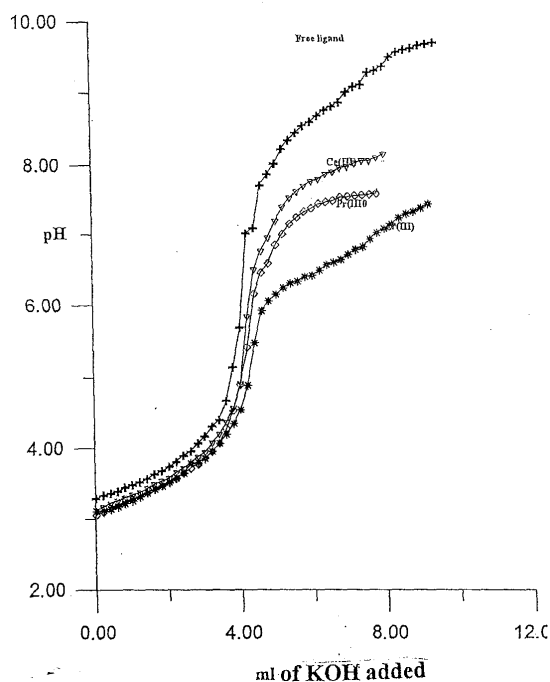


Fig.(3c). pH-titration curves of Cys and its complexes at $T = 40^\circ\text{C}$ and ratio of (metal-ligand) = 1:2

Table (4). Stepwise stability constants for the complexation of Cys with Ce^{3+} , Pr^{3+} and Er^{3+} in aqueous medium and 0.1M KNO_3 at different temperatures.

M^{3+}	293 K		303 K		313 K	
	Log K_1	Log K_2	Log K_1	Log K_2	Log K_1	Log K_2
Ce^{3+}	12.158	--	12.552	--	13.285	--
Pr^{3+}	12.66	--	13.457	--	13.47	--
Er^{3+}	12.693	--	13.491	--	13.50	--

3.3.2. Thermodynamic functions

Thermodynamic parameters ΔG° , ΔH° and ΔS° for the complex compounds were calculated from the stability constants obtained at various temperatures (20, 30 and 40°C). The values of the thermodynamic parameters associated with complex formation are indicated in Table (5).

Table (5). Thermodynamic functions of lanthanide complexes Ce^{3+} , Pr^{3+} and Er^{3+} at ionic strength 0.1M (KNO_3) in aqueous medium.

M^{3+}	ΔG°	ΔH°	ΔS°
Ce^{3+}	16.3028	-16.008	-110.2
	17.4055		-110.2
	19.030		-111.9
Pr^{3+}	16.9759	-32.381	-168.4
	18.660		-168.4
	19.295		-165.0
Er^{3+}	16.003	-40.7515	-196.9
	18.6850		-194.7
	19.339		-191.9

ΔG° units are (kcal.mol^{-1})

ΔH° units are (kcal.mol^{-1})

ΔS° units are ($\text{cal.mol}^{-1}.\text{K}^{-1}$)

3.4. Spectrophotometric studies

Spectrophotometric studies of Cys-complexes

The study on the complexes of Ni^{2+} , Co^{2+} and Cu^{2+} with Cys comprises the following:

- 1) Spectrophotometric studies gave well-defined peaks for the complexes of Ni^{2+} , Co^{2+} and Cu^{2+} with Cys.
- 2) The molar ratio method confirm that Cys formed complexes with Ni^{2+} , Co^{2+} and Cu^{2+} in a molar ratio of (1 : 1) and (1 : 2), (metal : ligand) which agree with potentiometric studies.

3.5. Cyclic voltammetry

Adsorption study of processes for Cys-complexes

3.5.1. Effect of the scan rate

For both Cys- Cu(II) and Cys- Co(II) complexes at different scan rate a well defined peaks were observed on the cathodic branch. This indicates that the oxidation of Cys- Cu(II) and Cys- Co(II) complexes is irreversible (Figs. 4, 5). The peak current increase with the increase of the scan rate that indicating diffusion-controlled nature of Cys- Cu(II) and Cys- Co(II) complexes.

Current/mA

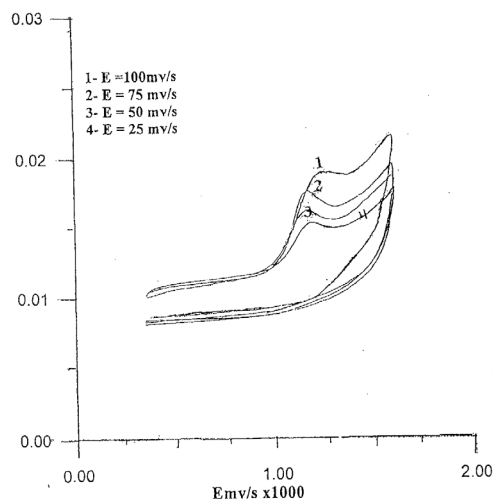


Fig.(4). Cyclic voltammograms for Cys- Cu(II) complex at different scan rate pH = 10.8 (metal:ligand) = 1:2.

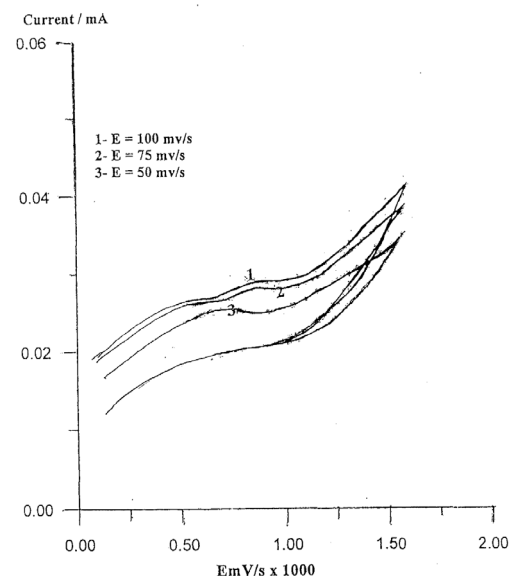


Fig.(5). Cyclic voltammograms for Cys- Co(II) complex at different scan rate, (metal:ligand) = 1:2 and pH = 8.6

3.5.2. Study of reaction mechanisms

One of the most important application of Cyclic voltammetry is for quantitative diagnosis of chemical reactions that proceed or succeed the redox process¹⁶.

3.6. Solid complexes

3.6.1. Infrared spectra

The elemental analysis of the solid complexes shows 1 : 2 metal to ligand stoichiometry. The I.R spectra of solid complexes have been measured in the range, 4000 – 500 cm^{-1} . The interested spectral data of the complexes in different regions are shown in table (6).

Table (6). IR studies of Cys and its metal complexes.

Complexes	$\nu\text{H}_2\text{O}$	$\nu\text{N-H}$	$\nu\text{C}=\text{O}_1$	$\nu\text{C}=\text{O}_2$	$\nu\text{M}-\text{O}_1$	$\nu\text{M}-\text{M}_2$
Cys	---	3426.4 (b)	1687.3	1632.9	---	---
$[\text{Cu.L}_2(\text{H}_2\text{O})_2] \cdot \text{H}_2\text{O}$	3421.4 (b)	3281.6 (s)	---	---	615.5	556.6
$[\text{Co.L}_2] \cdot \text{H}_2\text{O}$	3379.7 to 3150 (broad band)	---	---	---	767.7	715.7
$[\text{Ni.L}_2] \cdot \text{H}_2\text{O}$	3350.4 3323.4 (broad band)	---	---	---	828.8	780.5
$[\text{Zn.L}_2] \cdot \text{H}_2\text{O}$	3565 (b)	3278.7 (s)	1638.3	---	489.1	428
$[\text{Fe.L}_2(\text{H}_2\text{O})_2] \cdot \text{H}_2\text{O}$	3412.1 (b)	3197.2 (b)	---	---	693.3	575.8

3.6.2. Thermal analysis

The thermal gravimetric curves of Cu^{2+} and Fe^{3+} complexes exhibited well-defined endothermic peaks at (6751 – 162.20) and (53.96 – 174.79) as shown by ATG differential curve, the weight loss are 12.56%, 25.321% and 4.66%, 9.62% respectively, indicating that the presence of two molecules of water in the coordination form and one molecule of water of crystallization in the sphere of these complexes²⁰. On the other hand, the other metal complexes studied exhibit one endothermic peak at temperatures around 60 and 100°C for Ni^{2+} -Cys and Co^{2+} -Cys complexes respectively as shown by ATG differential curve, the weight loss are 9.651% and 13.82% respectively, indicating that one molecule of water crystallization in the outer sphere of these complexes. The relevant data is shown in table (7).

Table (8).

Elemental analysis									
$[\text{M.Ln}]_n\text{H}_2\text{O}$	M.W	N%		H%		C%		M.P.	Color
		C	F	C	F	C	F		
Cys	179.2	7.77	7.8	5.05	5.06	33.3	33.5	206	White
$[\text{Zn.L}_2] \cdot \text{H}_2\text{O}$	430.4	5.17	5.22	4.08	4.11	27.4	27.28	260	White
$[\text{Cu.L}_2(\text{H}_2\text{O})_2] \cdot \text{H}_2\text{O}$	473.5	1.38	1.33	5.53	5.51	23.2	23.1	Over-300	Blue
$\text{Fe.L}_2(\text{H}_2\text{O})_2 \cdot \text{H}_2\text{O}$	465.9	3.1	3.5	3.77	3.76	26.06	25.91	Over-300	Brown
$\text{pCo.L}_2 \cdot \text{H}_2\text{O}$	432.9	4.13	4.14	3.73	3.74	27.58	27.98	Over-300	Red-dark
$[\text{Ni.L}_2] \cdot \text{H}_2\text{O}$	432.7	4.12	4.14	4.08	4.11	27.6	27.88	270	Green

3.6.4. X-ray diffraction

X-ray analysis of Cys-complexes

X-ray analysis for Cu(II) -Cys complex, Zn(II) -Cys complex Ni(II) -Cys complex and Co(II) -Cys complex were carried out by using PW 3710 BASED diffractometer type, tube anode copper, and PC-APD, diffraction software indicates that Cu(II) -Cys complex and Zn(II) -Cys complexes formed crystalline structure, but Ni(II) -Cys and Co(II) -Cys complexes formed amorphous structure.

In all the complexes studied a broad band appeared around (3565 – 3323) cm^{-1} attributable to water molecule¹⁷. The values of the stretching vibration frequencies of the two carbonyl groups of Cys are (1687.3, 1632) cm^{-1} and the two bands are disappeared completely in case Cu^{2+} , Co^{2+} , Ni^{2+} and Fe^{3+} complexes, indicating for only oxygen coordination case¹⁸, they play the role of chelation sites and (Zn^{2+} -Cys) complex shows a negative shift of $\nu\text{C}=\text{O}$ at 1638.3 cm^{-1} for the first carbonyl while the second carbonyl group is disappeared. This indicates that the two carbonyl groups play the role of chelation sites on complexation¹⁹. Two new bands appeared in the spectrum of each complex at (780.9 – 489.1) cm^{-1} and (707.5 – 428) cm^{-1} which may be assigned to $\nu\text{M}=\text{O}_1$ and $\nu\text{M}=\text{O}_2$ respectively.

Table (7). The thermo-gravimetric studies of the Cys-complexes.

Metal complexes	Wt% loss	Endo-peaks	Exo-peaks
$[\text{Cu.L}_2(\text{H}_2\text{O})_2] \cdot \text{H}_2\text{O}$	12.565 – 25.321	67.51 – 162.2	--
$[\text{Fe.L}_2(\text{H}_2\text{O})_2] \cdot \text{H}_2\text{O}$	4.66 – 9.62	53.961 – 74.79	--
$[\text{Ni.L}_2] \cdot \text{H}_2\text{O}$	9.651	71.22	--
$[\text{Co.L}_2] \cdot \text{H}_2\text{O}$	13.828	77.05	--

3.6.3. Elemental analysis

Elemental analysis and other physical states of Cys and its metal complexes is shown in table (8).

3.7. Antimicrobial activity

Table (9) shows the metal complexes of the studied (Cys) ligand with the cations; Zn^{2+} , Cu^{2+} and Ni^{2+} enhanced dramatically the antimicrobial properties by comparison with their ligand. This effect is due to the fact that cations, Zn^{2+} , Cu^{2+} and Ni^{2+} form active compounds which have killing effect on two bacterial isolates (*Bacillus subtilis* and *Staph. aureus*) while the other cations (Fe^{3+} and Co^{2+}) had no effect on the tested microorganisms.

Table (9). The antimicrobial activity of the compounds synthesized.

Compounds	Bacterial isolates	Activity	MIC
Zn ²⁺	Staph. aureus	+++	0.000246 0.000492
	Bacillus subtilus	+	
	Candida albicans	-	
	Pseudomonas	-	
Cu ²⁺	Staph.aureus	++	0.000135 0.000135
	Bacillus subtilus	+++	
	Candida albicans	-	
	Pseudonas	-	
Ni ²⁺	Staph.aureus	+++	0.000256 0.000513
	Bacillus subtilus	+	
	Candida albicans	-	
	Pseudonas	-	
Co ²⁺ , Fe ³⁺	Staph.aureus	-	---
	Bacillus subtilus	-	
	Candida albicans	-	
	Pseudonas	-	
Cys	Staph.aureus	-	---
	Bacillus subtilus	-	
	Candida albicans	-	
	Pseudonas	-	

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