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Synthesis and Characterization of Ternary Complexes of certain Hydroxyl Acids and their Biological Applications.

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ABSTRACT

Ternary complexes of Cu(II) and Zn(II) with the amino acid, glycine (gly), as a primary ligand, and hydroxy acids i.e. salicylic acid (HL^1), lactic acid (HL^2) and glycolic acid (HL^3), as a secondary ligand, were synthesized in a slightly acidic medium and isolated in a ratio of (1:1:1). The ternary complexes were characterized using elemental analysis, spectral (UV-vis, IR) studies, thermal techniques, magnetic measurements, ESR and their biological activity were investigated. A square planar geometry for Cu (II) and Zn (II) was proposed. In order to evaluate the biological activity of hydroxy acids and to assess the role of metal ion on biological activity, the hydroxy acids and their metal complexes have been studied in vitro antibacterial against *Staphylococcus Aureus, Escherichia Coli*, and *Pseudomonas Aeruginosa*. In most cases, a higher activity was exhibited upon coordination with metal ions.

Keywords: Ternary complexes; Hydroxy acid; Glycine; elemental analysis; Antibacterial activity

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INTRODUCTION

It is without a doubt that α-hydroxy acids (AHA), β-hydroxy acids (BHA) and their related compounds are therapeutically effective for topical treatment of various dermatological disorders and for cosmetics conditions, [1-4] including dry skin, acne, dandruff, keratoses, age spots, wrinkles and disturbed keratinization [5-10]. The most frequently used classes of these compounds are the α-hydroxy acids (e.g. glycolic acid and lactic acid) and β-hydroxy acids (e.g. salicylic acid) [11-15]. Hydroxy acids have pH values of less than 3.0 and upon repeated topical applications can cause a drastic pH decrease in the stratum corneum of the human skin, and provoke disturbances in intercorneocyte bondings, resulting in adverse skin reactions, especially in individuals with sensitive skin. Moreover, it remains difficult to formulate a lotion, cream, or an ointment emulsion that contains a free acid form of hydroxy acid. When a formulation containing a hydroxy acid is reacted in equimolar or equinormal amounts with alkali, such as sodium hydroxide or potassium hydroxide [16], the composition becomes therapeutically ineffective. For example, a topical preparation containing 5% salicylic acid is therapeutically effective as a keratolytic, but one containing 5% sodium salicylate is not an effective product. The reason for such a difference is that salicylic acid is in its bioavailable form and can penetrate the stratum corneum [17, 19], but sodium salicylate is not, and therefore cannot penetrate the stratum corneum of the skin. The aim of our study is to prepare ternary complexes of Cu(II) and Zn(II) with the amino acid, glycine (gly), as a primary ligand, and the hydroxy acids i.e. salicylic acid (HL^1), lactic acid (HL^2) and glycolic acid (HL^3), as a secondary ligand. The selection of these two ions i.e. Cu(II) and Zn(II) is based on the ability of these ions to form copper hydroxide or zinc hydroxide at physiological pH 7.4, consequently generating amino acids and hydroxyl acids that are in their bioavailable form.

EXPERIMENTAL

Materials and Reagents

All chemicals used in this study are Merck products. Salicylic acid, Glycolic acid, Lactic acid, Glycine, Copper Carbonate basic, Zinc Carbonate basic, Ethanol.

Preparation of Ternary Complexes

All the complexes were obtained with following general procedure. The calculated amounts of metal carbonate, hydroxy acid, and amino acid to give the 1:1:1 complex are mixed together in 100 ml of purified water, and the mixture is heated to 80-90°C for 2 hours. Ethanol is then added until a dense precipitate is obtained. After filtration of the precipitate, it is washed with absolute ethanol and dried in an oven at 80-90°C, then placed in a desiccator over night.

Characterization of the prepared complexes

All measurements are carried out at the Microanalytical Laboratories at Cairo University, Ain Shams University and The National Research Center, Cairo – Egypt. Elemental analysis of carbon, hydrogen, and nitrogen were determined by Vario El Elementar,

Germany. Elemental analysis of Cu, and Zn percentages are determined by atomic absorption spectrometry (AAS), using a Perkin-Elmer AAS 3100, USA. FTIR spectra of the solid complexes were recorded on a JascoFTIR-300 E Fourier, Tokyo, Japan. Transform Infrared Spectrometer, using KBr disks in the range 400–4,000cm^{-1} and CsI technique in the range 200–630 cm^{-1}. Thermogravimetric analysis was carried out using a Perkin-Elmer 7 Series Thermal Analyzer. The measurements were carried out under nitrogen atmosphere at a heating rate 10°C min^{-1}. Magnetic susceptibilities of the paramagnetic metal complexes were measured by using a magnetic susceptibility balance Johnson Mtthy USA, Alfa products; model No MKI at room temperature. The electronic UV–Vis Spectra are measured at room temperature on a Jasco model V-550UV/Vis spectrophotometer. Mass spectra were recorded at350 °C and 70eV on a GL/MS Finnegan mat SSQ 7000 apparatus.

RESULTS AND DISCUSSION

Reaction of Cu and Zn carbonate with the amino acid, glycine (gly), as a primary ligand, and hydroxy acids i.e. salicylic acid (HL^1), lactic acid (HL^2) and glycolic acid (HL^3), as a secondary ligand, afforded solid powders, with analytical data corresponding to the general formula "Metal Amino Acid Hydroxy Acid". The physical and chemical properties of the six ternary complexes are given in Table 1. The elemental analysis and molecular masses of the six complexes suggest the absence of water molecules of crystallization. Glycine has pKa1 and pKa2 at 2.34 and 9.6, respectively. The pH value of the solution at which all the complexes under study that were prepared, range from 5.8 to 6.5. At this pH, there is no formation of the zwitter ion. The glycine coordinates exist as bidentate ligands through N and COO$^-$ and the hydroxy acid coordinates exist as bidentate ligands through OH and COO$^-$. Accordingly, the metal coordinates encompass four sites, two from glycine and two from hydroxyacid

Table 1: Elemental analysis, mass spectrometry data, and physical properties of the complexes

Complexes	Color	Molecular Mass	m/e	Magnetic moment	Conductivity/ µS	Elemental analysis found/calc.			
						C	H	N	M
[Cu (L^1)(Gly)]	Blue	274.72	272	1.94	21.4	39/39.35	3.22/3.3	5.1/5.14	24.0/23.13
[Cu (L^2)(Gly)]	Blue	226.67	225	1.73	19.5	26.1/26.49	3.99/4	6.5/6.18	27.9/28.03
[Cu (L^3)(Gly)]	Blue	212.65	210	1.8	55.7	21.9/22.59	3.31/3.32	6.8/6.58	29.9/29.88
[Zn (L^1)(Gly)]	White	276.56	274	--	21.9	38.94/39.09	3.25/3.3	5.52/5.06	24.01/23.64
[Zn (L^2)(Gly)]	White	228.52	225	--	18.6	26.13/26.28	3.94/3.96	6.55/6.13	29.1/28.61
[Zn (L^3)(Gly)]	White	214.49	212	--	83.5	21.9/22.4	3.32/3.3	6.8/6.53	30.3/30.48

L^1= Salicylate
L^2= Lactate
L^3= Glycolate

All the prepared complexes have common features such as effervescence and evolution of carbon dioxide on reaction with sodium carbonate. This is due to when adding sodium carbonate, the pH increases to 7.4, which leads to the ionization of the Ternary complexes to hydroxyl acid and glycine, which in turn, react with sodium carbonate, releasing carbon dioxide.

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FTIR Spectra

The mode of binding of ligands to the metal ions was elucidated by recording the IR spectra of the complexes as compared with the spectra of free ligands. The important bands were listed in Table 2 and figures 1,2. The IR spectrum of ligands HL^1, HL^2 and HL^3 showed bands at (1748 and 1300 cm^{-1}), (1734 and 1130 cm^{-1}), (1720 and 1230 cm^{-1}) for free carboxylic groups, respectively [20, 21]. In the ternary complexes as shown in Table 2, these bands of carboxylic groups showed a respective shift towards lower frequency for asymmetric carboxylic group and respective shift towards higher frequency for symmetric carboxylic group. The difference between the symmetry and asymmetry stretching vibration for COO^- group (Δυ= 177-206) gives an indication about the manner of coordination of the carboxylic group, this value shows that the hydroxyl acids (HL^{1-3}) coordinate through COO^- group which acts as monodentate. The IR spectra of all the complexes showed two absorption bands in the far infrared region, 328-333 cm^{-1} and 534-580 cm^{-1}, which are assignable to (M-N) and (M-O) vibrations, respectively. The IR spectra of glycine showed bands at 3260 – 3100 cm-1 due to υN-H vibration. In ternary complexes, this band appeared as a broad band at 3155-3452 cm-1 due to coordination of metal with nitrogen[22] and OH of ligands (HL^1, HL^2 and HL^3) without losing its proton, since the solution of the ternary complexes is non-electrolytic (*table 1*). It is not possible to carry out HNMR studies for zinc complexes to test coordination of OH group due to precipitation of the complexes in the deuterium water and insolubility in most of the organic solvents.

Table 2: The important IR frequencies of the ligands and their metal complexes (cm^{-1})

	υOH	υNH2	υ_{asy} COO	υ_{sy}COO	υM-O	υM-N
[Cu (L^1)(Gly)]	3334.07	3266.56	1594	1389	333	561
[Cu (L^2)(Gly)]	3333.1	3265.59	1583	1387	332	560
[Cu (L^3)(Gly)]	3334.07	3266	1593	1387	332	580
[Zn (L^1)(Gly)]	3452.7	3268.49	1592	1395	328	534
[Zn (L^2)(Gly)]	3445.94	3268.49	1597	1393	332	534
[Zn (L^3)(Gly)]	3363	3155.65	1579	1402	357	550
HL^1	3300	--	1748	1300	--	--
HL^2	3401	--	1734	1130	--	--
HL^3	3350	--	1720	1230	--	--
Glycine (Gly)	3300	3100	1703	1400	--	--

L^1= Salicylate
L^2= Lactate
L^3= Glycolate
HL^1= Salicylic acid
HL^2= Lactic acid
HL^3= Glycolic acid

Magnetic Moments and Electronic Spectra

The spectra of the copper (II) complexes show abroad band at 16000 cm-1, ($^2B_{1g}$ $^2A_{1g}$)→d-d transition and is interpreted in terms of a square planar geometry. The absence of any bands below 1000cm^{-1} eliminates the possibility of a tetrahedral or pseudo-tetrahedral environment in this complex. The magnetic moments are 1.94, 1.73, 1.8 BM for

Cu (L^1)(Gly), Cu (L^2)(Gly), and Cu (L^3)(Gly) respectively, indicates square geometry (fig 3). [23, 24].

ESR Spectra

The ESR spectra of the copper (II) complexes provide information of importance in studying the metal ion environment. The EPR spectra for Cu (II) ternary complexes were recorded in polycrystalline solid at room temperature are shown in figures 4, 5, 6. The ESR spectra of the three Cu complexes were similar and showed axial symmetry (g // = 2.09298, g ⊥ = 2.01227, G= 9.1), (g // = 2.09448, g ⊥ = 2.01274, G=8.83), (g// = 2.09589, g⊥ = 2.01305, G=8.71) for [Cu (L^1)(Gly)], [Cu (L^2)(Gly)] and [Cu (L^3)(Gly)], respectively, which is associated with square planar coordination. In square planar complexes, the unpaired electron lies in the dx^2-y^2 orbital giving g // > g ⊥ > 2 while the unpaired electron lies in the dz^2 orbital giving g⊥ > g// >2. This provides evidence that the unpaired electron is localized in the dx^2-y^2 orbital and the ground state is 2B1g [25-28].

The value of the exchange interaction term G, estimated from the expression:

$$G = (g // – 2.0023) / (g \perp – 2.0023)$$

If G> 4, the local tetragonal axes were aligned parallel or only slightly misaligned. If G< 4, significant exchange coupling is present and the misalignment is appreciable. The observed value for the exchange interaction parameter for the Cu complexes (G> 4) suggests that the local tetragonal axes are aligned parallel or slightly misaligned, and the unpaired electron is present in the dx^2–y^2orbital. This result also indicates that the exchange coupling effects are not operative in the present complex [29].

Mass Spectra

The mass spectra of the six complexes were recorded. All the spectra containing molecular ion peaks confirm the molecular mass of the complexes and absence for water molecule. This data is presented in Table 1.

Thermal Analysis

The thermogravimetric analysis was carried out for copper (II) complexes and zinc (II) complexes are shown in figure 7. The decomposition of all the complexes resulted in oxide formation. The determined temperature ranges, percentage mass losses, and thermal effects, accompanying the changes in the coordination compounds on heating, revealed the following findings (table 3).

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Table 3: Temperature values for the decomposition along with the species lost in each step

Complexes	Molar Wt.	TG range/°C	DTG/°C	% Weight loss Found (calcd.)	Total mass loss %	Decomposition Stages & Assignment
[Cu (L^1)(Gly)]	274.72	175-280 280-380 380-700	237 332 Above 332	54.9/56.92 15.1/13.89 29.8/28.95	70.1	Phenol, CO_2, NH_3 Organic moiety CuO
[Cu (L^2)(Gly)]	226.67	185-280 280-395 395-700	271-273 330 Above 330	46.2/47.69 18.4/16.91 35.3/35.1	64.3	Ethanol, CO_2, NH_3 Organic moiety CuO
[Cu (L^3)(Gly)]	212.65	173-270 270-400 400-700	223-229 340 Above 340	43.9/44.19 18.32/18.03 37/37.4	62.22	Methanol, CO_2, NH_3 Organic moiety CuO
[Zn (L^1)(Gly)]	276.56	206-320 320-450 450-700	242-288 335-357 Above 357	57.3/56.54 12.7/13.8 29.1/29.43	70	Phenol, CO_2, NH_3 Organic moiety ZnO
[Zn (L^2)(Gly)]	228.52	186-285 285-380 380-700	197-245 340 Above 340	46.6 /47.31 18.1/16.74 35.1/35.61	64.6	Ethanol, CO_2, NH_3 Organic moiety ZnO
[Zn (L^3)(Gly)]	214.49	178-280 280-380 380-700	206-245 300-327 Above 327	43.9/43.81 18.3/17.87 37.8/37.94	62.1	Methanol, CO_2, NH_3 Organic moiety ZnO

L^1= Salicylate
L^2= Lactate
L^3= Glycolate

In case of complex [Cu (L^1)(Gly)], the first step, in temperature range between 175 – 324˚C, results in a mass loss of 54.9%, (calcd. 56.92%), corresponding to the loss of phenol, carbon dioxide, and ammonia molecules. The second step, in temperature range between 324 – 700˚C, corresponding to the loss of an organic moiety, with mass loss of 15.1% (calcd. 13.89%), and leaving a metal oxide as residue.

In case of complex [Cu (L^2)(Gly)], the first step, in temperature range between 185 – 299˚C, results in a mass loss of 46.2% (calcd. 47.69%), corresponding to the loss of ethanol, carbon dioxide, and ammonia molecules. The second step, in the temperature range between 324 – 700˚C, corresponding to the loss of an organic moiety with mass a loss of 18.4% (calcd. 16.91%), and leaving a metal oxide residue.

In case of complex [Cu (L^3)(Gly)], the first step, in temperature range between 173 – 300 ˚C, results in a mass loss of 43.9% (calcd. 44.19%), corresponding to the loss of methanol, carbon dioxide, and ammonia molecules. The second step, in the temperature range between 300 – 700˚C, corresponding to the loss of an organic moiety with a mass loss of 18.32% (calcd. 18.03%), leaving a metal oxide residue.

In case of complex [Zn (L^1)(Gly)], the first step, in temperature range between 206 – 327 ˚C, results in a mass loss of 57.3% (calcd. 56.54%) corresponding to loss of phenol, carbon dioxide, and ammonia molecules. The second step, in the temperature range between 300 – 700˚C, corresponding to the loss of an organic moiety with mass loss of 12.7% (calcd. 13.8%), leaving a metal oxide residue.

In case of complex [Zn (L^2)(Gly)], the first step, in temperature range of between 186 – 300 ˚C, results in a mass loss of 46.6% (calcd. 47.31%), corresponding to the loss of ethanol, carbon dioxide, and ammonia molecules. The second step, in the temperature range between 300 – 700˚C, corresponding to the loss of an organic moiety, with mass loss of 18.1% (calcd. 16.74%), leaving a metal oxide residue.

In case of complex [Zn (L^3)(Gly)], the first step, in temperature range between 178 – 300 ˚C, results in a mass loss of 43.9% (calcd. 43.81%), corresponding to loss of ethanol, carbon dioxide, and ammonia molecules. The second step, in the temperature range of between 300 – 700 ˚C, corresponding to the loss of an organic moiety, with a mass loss of 18.3% (calcd. 17.87%), leaving a metal oxide residue. The results therefore show a good agreement with the formulae suggested from the analytical data

Pharmacology

Antibacterial activity

The ligands (HA), metal complexes, and standard drugs were screened separately for their antibacterial activity against Staphylococcus Aureus (G+ve) bacteria, Pseudomonas Aeruginosa, and Escherichia Coli (G-ve) bacteria. Qualitative determination of antimicrobial activity was done using the disk diffusion method [30, 31]. Suspensions in sterile peptone water from 24 h cultures of microorganisms were adjusted to 0.5 McFarland. Muller-Hinton Petri dishes of 90 mm were inoculated using these suspensions. Paper disks (6 mm in diameter) containing 10 ml of the substance to be tested at a concentration of (2048 µg /ml in purified water) were placed in a circular pattern in each inoculated plate. Incubation of the plates was done at 37°C for 24 hours. Reading of the results was done by measuring the diameters of the inhibition zones generated by the tested substances using a ruler. The microbial results were summarized in Table 4. The antimicrobial studies suggested that the hydroxy acid are biologically active and their metal complexes show significantly enhanced antibacterial activity against microbial strains in comparison to the free ligands. Positive controls (standard drugs) produced significantly sized inhibition zones against the tested bacteria. Tested compounds show zones of inhibition ranging from 16.9 mm to 33.3mm against the above mentioned bacteria. The ligands (HA) show zones of inhibition ranging from 12.3 mm to 16.5mm against bacteria. It has been observed that the metal complexes show increased zones of inhibition against the bacterial strains, (Table 4), as compared to the free hydroxy acid and the difference is significant $P < 0.05$. The ligand (amino acid) was not effective against any Gram-negative or Gram-positive bacteria. The ligands and their complexes (*Table 4)* showed a moderate activity against the bacterial strains as compared to the standard drug (Tetracycline-HCl). The overtone concept [32] and Tweedy's chelation theory [33] was used to explain the enhanced antimicrobial activity of the metal complexes. According to the Overtone concept of cell permeability, the lipid membrane surrounding the cell favours the passage of only lipid-soluble materials; therefore, liposolubility is an important factor that controls the antimicrobial activity. As for with chelation, polarity of the metal ion is reduced largely, due to the overlapping of the ligand-orbital and partial sharing of the positive charge of the metal ion with donor groups. Moreover, delocalization of the p-electrons over the entire chelate ring is increased and lipophilicity of the complexes is enhanced. The increased lipophilicity enhances the penetration of the complexes into the

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lipid membranes and blocks the metal binding sites in the enzymes of microorganisms. These complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organism. In general, metal complexes are more active than ligands. Also it can be seen from table 4 that the biological activities of Zn (II) complexes are typically higher than those of the corresponding Cu (II) complexes.

Table 4: Antibacterial activity of chemical compounds through agar well diffusion method

	Inhibition zone diameter (mm)		
	Staphylococcus Aureus Mean ± RSD*	Pseudomonas Aeruginosa Mean ± RSD*	Escherichia Coli Mean ± RSD*
1. [Cu (L^1)(Gly)]	16.9 ± 0.23	17.1± 0.1	21.5± 0.08
2. [Cu (L^2)(Gly)]	17.6± 0.04	20.5± 0.03	21.1± 0.04
3. [Cu (L^3)(Gly)]	20.4± 0.05	20.8± 0.04	23.4± 0.05
4. [Zn (L^1)(Gly)]	33.3± 0.05	23.1± 0.1	29.5± 0.04
5. [Zn (L^2)(Gly)]	31.2± 0.06	25.8± 0.03	19.8± 0.04
6. [Zn (L^3)(Gly)]	28.7± 0.16	19.6± 0.05	26± 0.1
7. HL^1	15± 0.16	14.3± 0.09	16.5± 0.11
8. HL^2	12.3± 0.05	13.6± 0.08	14.2± 0.07
9. HL^3	13.6± 0.04	14.1± 0.03	14.7± 0.17
10. Glycine	-----	-----	-----
11. Tetracycline HCl	35.5±0.01	37.2±0.03	36.5±0.02

RSD* : Relative standard deviation

L^1= Salicylate
L^2= Lactate
L^3= Glycolate
HL^1= Salicylic acid
HL^2= Lactic acid
HL^3= Glycolic acid

Determination of minimum inhibitory concentration (MIC)

MIC is the lowest concentration of an antimicrobial compound that will inhibit the visible growth of a microorganism after overnight incubation. MIC of the various compounds against bacterial strains was tested through a modified agar well diffusion method table 5. In this method, The following concentrations of the substances to be tested were obtained in the well plates: 1024; 512; 256; 128; 64; 32; 16; 8; 4; 2 µg /ml. After incubation at 37°C for 24 hours, the MIC for each tested substance was determined by macroscopic observation of microbial growth. It corresponds to the well with the lowest concentration of the tested substance where microbial growth was clearly inhibited. Tetracycline HCl was used as Control drug.

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Table 5: Minimum inhibitory concentration (MIC) (µg /ml) of compounds

	Staphylococcus Aureus	Pseudomonas Aeruginosa	Escherichia Coli
1. Cu (L^1)(Gly)	256	256	256
2. Cu (L^2)(Gly)	512	512	512
3. Cu (L^3)(Gly)	512	512	512
4. Zn (L^1)(Gly)	128	128	128
5. Zn (L^2)(Gly)	128	256	256
6. Zn (L^3)(Gly)	128	265	265
7. HL^1	512	512	512
8. HL^2	1024	1024	1024
9. HL^3	1024	1024	1024
10. Glycine	-----	-----	-----
11. Tetracycline HCl	64	64	64

L^1= Salicylate
L^2= Lactate
L^3= Glycolate
HL^1= Salicylic acid
HL^2= Lactic acid
HL^3= Glycolic acid

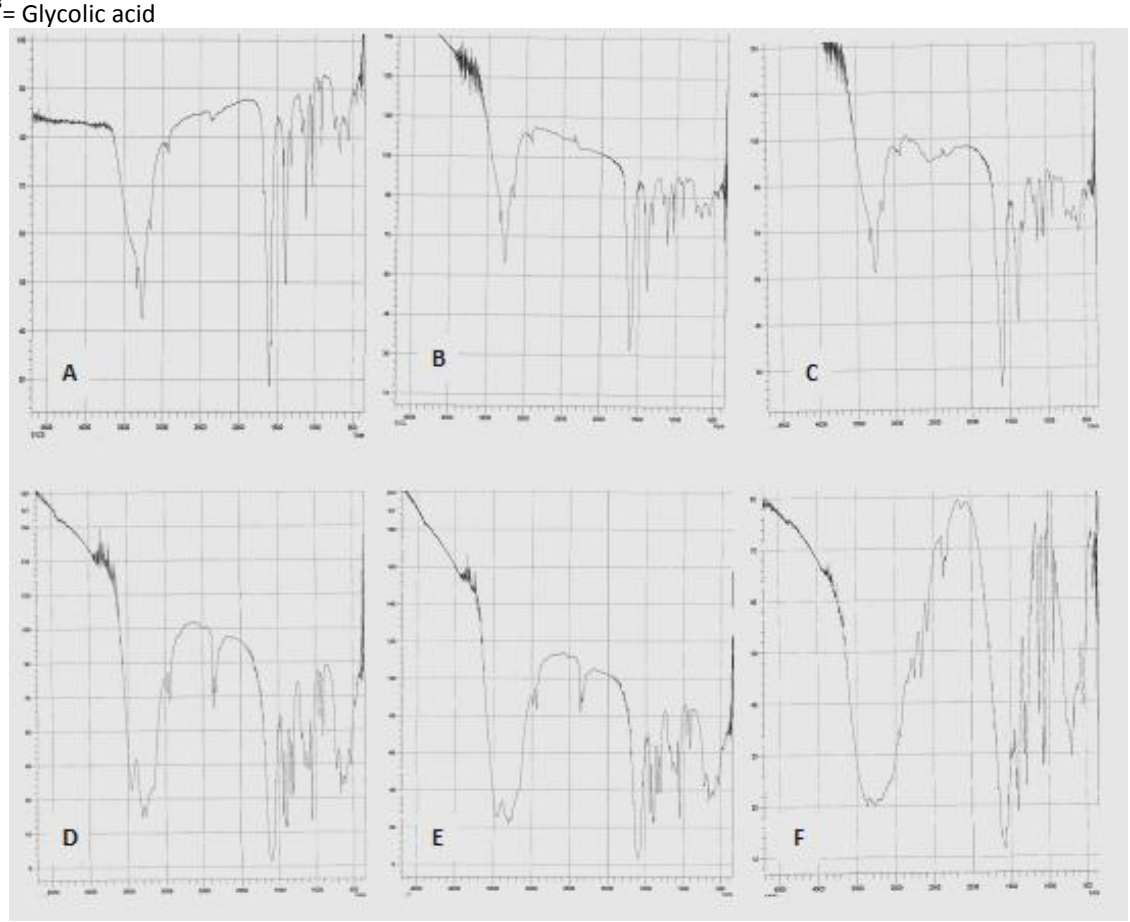

Figure 1: IR spectra of (A) [Cu (L^1)(Gly)], (B) [Cu (L^2)(Gly)], (C) [Cu (L^3)(Gly)], (D) [Zn (L^1)(Gly)], (E) [Zn (L^2)(Gly)], (F) [Zn (L^3)(Gly)]

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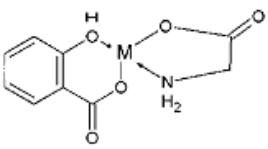
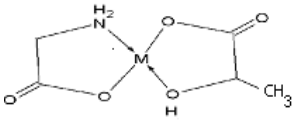
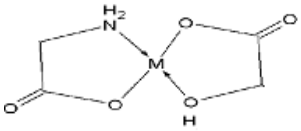


M[(L^1)(Gly)]
M= Cu, Zn



M[(L^2)(Gly)]



M[(L^3)(Gly)]

L^1= Salicylate
L^2= Lactate
L^3= Glycolate

Figure 2: Square planner geometry for the complexes

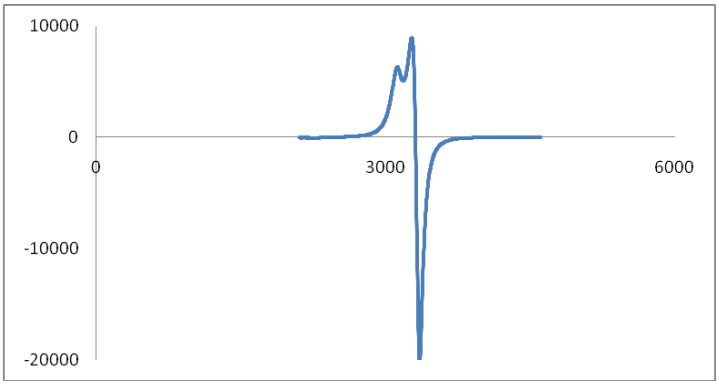


Figure 3: ESR spectra of [Cu (L^1)(Gly)]

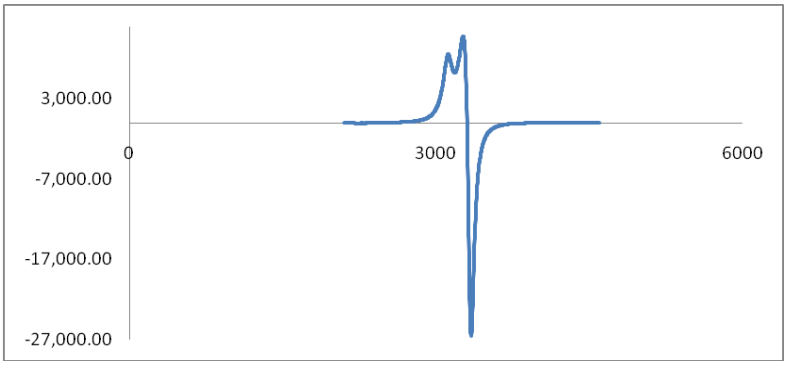


Figure 4: ESR spectra of [Cu (L^2)(Gly)]

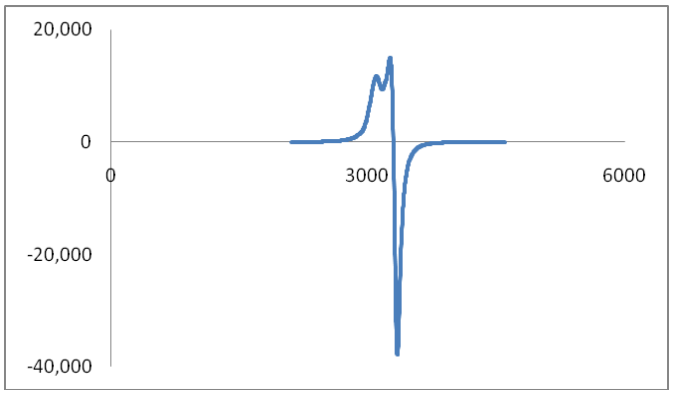


Figure 5: ESR spectra of [Cu (L^3)(Gly)]

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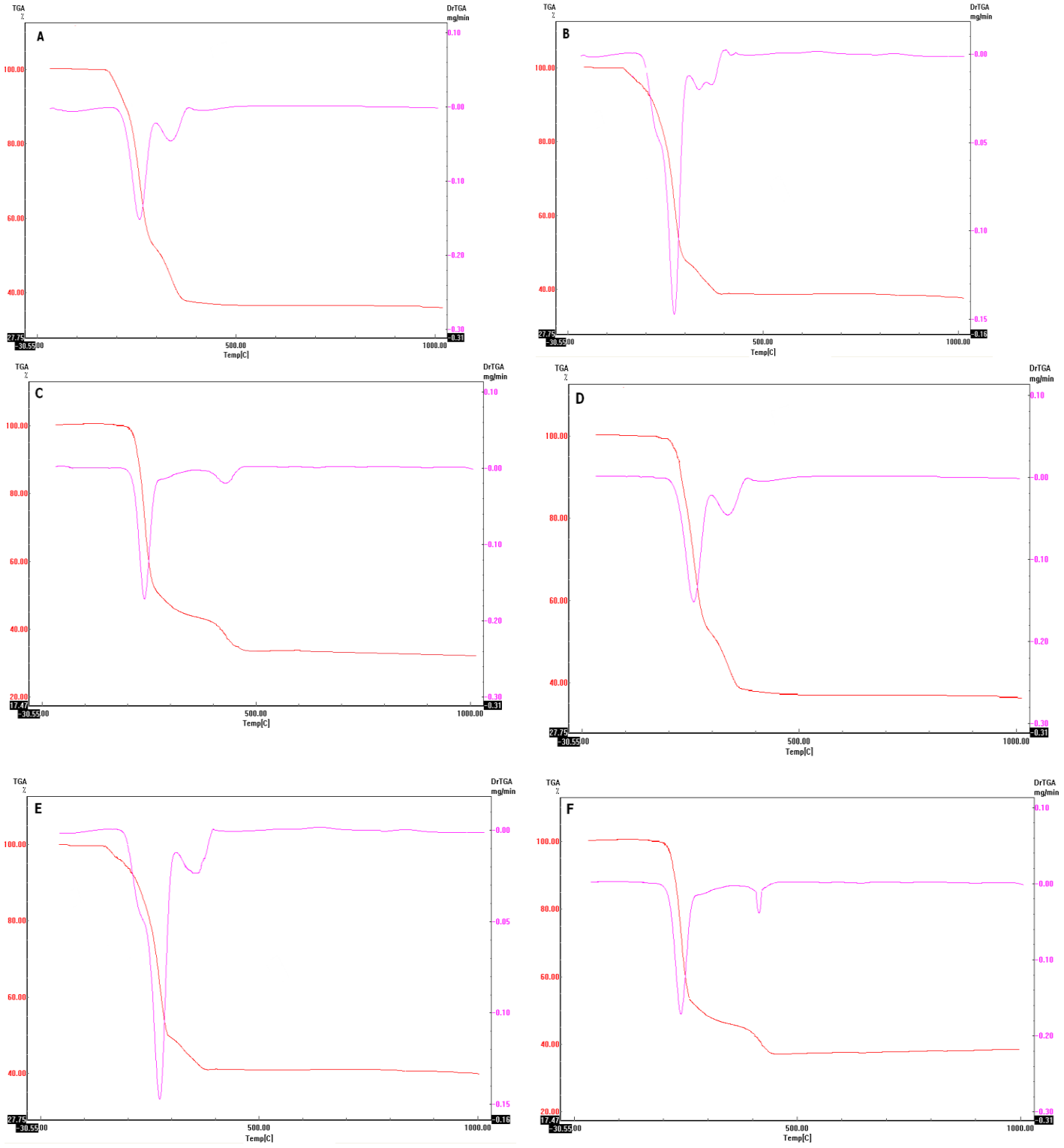

Fig. 6 TG and DTG of ternary complexes: (A) [Cu (L^1)(Gly)], (B) [Cu (L^2)(Gly)], (C) [Cu (L^3)(Gly)], (D) [Zn (L^1)(Gly)], (E) [Zn (L^2)(Gly)], (F) [Zn (L^3)(Gly)]

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CONCLUSION

The synthesis of ternary complexes of Cu(II) and Zn(II) with amino acid glycine (gly), as a primary ligand, and hydroxy acids i.e. salicylic acid (HL^1), lactic acid (HL^2) and glycolic acid (HL^3) and as a secondary ligand, was confirmed by elemental analysis, spectral (UV-vis, IR) studies, thermal techniques, magnetic measurements, ESR and their biological activity were investigated. A square planar geometry for Cu (II) and Zn (II) was proposed. The antimicrobial studies suggested that the hydroxy acids were found to be biologically active and their metal complexes showed significantly enhanced antibacterial activity against microbial strains in comparison to hydroxyl acids.

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