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Full Length Research Article

SOLVENT ASSISTED MECHANOCHEMICAL SYNTHESIS, ANTIMICROBIAL AND ANTIOXIDANT STUDIES OF Ni^{2+}, Mn^{2+}, Cr^{2+}, and Cu^{2+} METAL COMPLEXES OF SOME LIGANDS DERIVED FROM L-HISTIDINE AND L-ALANINE

Asiya Usman Musa, *Nura Suleiman Gwaram, Muhammad Saleh Salga, Abubakar Sani

Department of Pure and Industrial Chemistry, Umaru Musa Yar'adua University. P.M.B. 2211, Katsina State, Nigeria

*Corresponding Author Email Address: nura.suleiman@umyu.edu.ng

ABSTRACT
Mechanochemistry enables rapid, quantitative reactions to occur at or close to 27°C. It is a one-step process that allows for reactant homogenization, product nucleation, and particle growth. These processes use little or no solvent, making them less wasteful and more environmentally friendly than solvent-based reactions. Ni^{2+}, Mn^{2+}, $Cr^{2+}$and Cu^{2+} metal ions were synthesized by grinding in an agate mortar with pestle using ligands derived from amino acids (Histidine &Alanine) which were further synthesized to form complexes. The entire experiment was carried out by solvent solvent-assisted mechanochemical process and ethanol was used as liquid liquid-assisted solvent. The complexes were characterized by IR spectroscopy, U-V spectroscopy, X-ray analysis, melting point, solubility test, and conductivity measurement. The Solubility test showed that the complexes are soluble in DMSO, DMF, and ethanol and are insoluble in both hexane and tetrachloromethane. The molar conductivity values are in the range of (6.05-28.56) $\Omega^{-1}cm^2mol^{-1}$) indicating the complexes behave as non-electrolytes. IR analysis showed a vibrational frequency band observed at (1620-1625) cm^{-1} which is assigned to the υ(C=N) of the azomethine, also the new bands M=N, M=O indicate the coordination reaction between the metal and the ligands. The UV visible analysis shows various transitions, the metal complexes showed adsorption bands at λ of 420 and 575nm respectively because of the ligand-to-metal charge transfer (LMCT). The XRD analysis showed that there was a change in phase between the starting material and the product which indicate that a reaction occurred, also the nature of the spectra showed that the compounds are all crystalline. The Antimicrobial activity showed that both the complexes and the ligands have good activity against the bacterial isolates. Antioxidant activity was also tested and the compound appeared to have moderate scavenging activities compared to the reference used. The values indicated that the activities are more pronounced when coordinated with metal ions.

Keywords: Solvent assisted, Mechanochemistry, antimicrobial, antioxidant, complexes

INTRODUCTION

Green Chemistry is now widely spread and progressing and it will gradually gain acceptance in the scientific world. The goal is to embrace chemistry development more sustainably. Hopefully, the current generation and future scientists will embrace this concept for a safer environment. (Ardila-fierro & Hernández, 2021). Mechanochemistry (Green chemistry) refers to reactions of solids induced by the input of mechanical energy, such as grinding or using a ball mill with either no added solvent or only a minimal amount of solvent, It promotes reaction between solids quickly and quantitatively. This makes it become more intensely studied. (Soc *et al*., 2012). Liquid-assisted grinding processes are commonly referred to as liquid-assisted grinding (LAG), Solvent-drop grinding is another name for solvent-assisted grinding. In these reactions, the solvent may be added directly to the vessel or it may be a liquid by-product of the solid-state reaction. LAG is said to facilitate a more intimate mixing of solid reactants. The research aimed at synthesizing Ni^{2+}, Mn^{2+}, $Cr^{2+}$and Cu^{2+} complexes of mixed ligands of L-Alanine, and L-Histidine, using solvent-assisted mechanochemical process, characterization, and study of its antimicrobial and antioxidant activities.

MATERIALS AND METHODS

All the glass wares used for this research were washed thoroughly with detergents and deionized water and dried in a hot oven at 90°C. All weighing was carried out using an electric weighing balance 2003 model U-Clear China. Conductivity measurement was done using the DDS-11 model in DMSO solvent. Melting point and decomposition temperature were measured using an IA9100 melting tester, and FTIR spectra analysis was recorded using the FTIR-IR (Cray630) model. XRD spectra analysis was recorded using the XRD-6000 model. UVspectra analysis was recorded using the 721(Lifecare Medical) model. The antimicrobial and antioxidant screening was carried out in the microbiology and biochemistry laboratory at Umaru Musa Yaradua University Katsina. Nigeria.

Preparation of Histidine and Alanine

Ligand was synthesized by grinding 5mmol of each L-Histidine and L-Alanine in an agate mortar and pestle for 30mins, and a crystalline powder was formed on further grinding and dried at 50°C according to the method of (Muhammad and Kurawa 2019).

Preparation of the Complexes

The metal complexes were synthesized by grinding 10mmol of Ligands and 5mmol of each of the metal salt Ni^{2+}, Mn^{2+}, $Cr^{2+}$and Cu^{2+} and in an agate mortar and pestle. A small amount of ethanol (1.0 drop) was added and grounded for 10-20mins till a crystalline powder was formed and the obtained product was allowed to dry in the air (Sani *et al*., 2021).

Conductivity Measurement

0.05g of the sample was dissolved in DMSO. The molar

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conductance was measured at 27°C using a conductivity meter. The electrode of the meter was rinsed with deionized water and dried. 10cm^3 of 10^{-3}m of each of the complex solutions was transferred into a 50ml beaker. The electrode was dipped into the sample solution. (Yousif *et al*., 2017)

Solubility Test

The following solvents (dimethylsulfoxide (DMSO), dimethylformamide (DMF), H_2O, and Ethanol) were used for the solubility tests at 25 °C. About 0.3g each of the sample was dissolved in 6ml of the solvents in a test tube and shaken. The contents were allowed to settle for 5 minutes and the solubility observed**. Melting/Decomposition Temperature Test**

30mg of the sample was placed on a dry capillary tube and mounted on the Gallenkamp melting apparatus. The temperature at which the sample starts to melt was observed

Antibacterial Activity of Ligands and Complex

0.5g of each of the complexes and ligands were measured and dispersed in a plain container containing 1ml of DMSO to obtain a concentration of 500µg/ml, was transferred to the next tube containing 0.5ml of DMSO to obtain another concentration of 250µg/ml**.** Up to 125µg/ml and 62.5 µg/ml respectively. Which were prepared by dilution method, they were placed on the cultural media, and incubated at 37°C for 24hours.In vitro antimicrobial activity of the ligands and complexes was tested against two bacterial isolates: Gram positive bacteria (*Escherichia coli*)and Gram negative bacteria (*Staphylococcus aureus*) using agar well diffusion method. Standard was used to compare with the diameter of zone of inhibition produced by the ligands and complexes. (Cheesbrough, 2006).

Antioxidant Activity Test

Hydrogen peroxide scavenging assay: The ability of the ligands and complexes to scavenge hydrogen peroxide (H_2O_2) was determined according to the method of (Al-Amiery *et al.,*2015). Aliquot of 0.1 ml of samples (25-400 µg/ mL) were transferred into the Eppendorf tubes and their volume was made up to 0.4 ml with 50 mM phosphate buffer (pH 7.4) followed by the addition of 0.6 ml of H_2O_2 solution (2 mM). The reaction mixture was vortexed and after 10 min of reaction time, its absorbance was measured at 230 nm against a blank solution containing phosphate buffer without hydrogen peroxide. Ascorbic acid was used as the positive control. The ability of the samples to scavenge the H_2O_2 was calculated using the following equation: (Bhatti *et al.,*2020)

Scavenging activity (%) = $\frac{\text{Absorbance}^{control} - \text{Absorbance}^{sample}}{\text{Absorbance}^{control}}$ X 100

Where: A_0 = Absorbance of control, A_1 = Absorbance of the sample**.**

RESULTS AND DISCUSSION

The results obtained from Table 1 show some physicochemical properties of the ligands and their complexes. The ligand derived from reactions of L-Alanine and L-Histidine were synthesized to prepare four metal complexes of Ni2$^+$, Mn^{2+}, Cu^{2+}and Cr^{2+} The complexes were prepared by mechanochemical route and characterized by various analytical methods such as UV Spectroscopy, X-Ray diffraction, Fourier Transmission infrared, Conductivity Test and Melting point Analysis. The results of the analysis showed that the color of both ligands appeared to be white crystals while that of the complexes with L_1 gives Dark blue, light blue, army green, and off-white, for Ni^{2+}, Cu^{2+}, Cr^{2+}, and Mn^{2+} respectively. The melting point of the ligand is 243 °C and the decomposition temperature of the complexes ranges from 331°C-372 °C for all the complexes. The result showed that the rise decomposition temperature compared to melting points observed in the ligands, which indicates high thermal stability of the metal complexes (Jibril *et al*.,2019). The molar conductivity of the complexes in DMSO as shown in Table 1. values shows that CuL_1 has the lowest value of 6.05 $\Omega^{-1}cm^2mol^{-1}$ while MnL_1 gave the highest value of 30.14 $\Omega^{-1}cm^2mol^{-1}$. The low conductivity values of (<50 $\Omega^{-1}cm^2mol^{-1}$) in DMSO are an indication of non electrolytic nature of the complexes. (Ali, I. *et al*, 2013).

Table 1: Physicochemical Properties of Ligands and Complexes

Compounds	M.Wt.Calc	% Yield	Color	M.P°C/ Dec	Molar conduct $\Omega^{-1}cm^2mol^{-1}$
$[C_6H_{13}N_3O]$	195.22		Off-white	243	
$[Ni(C_6H_{13}N_3O)_2]$	626.13	84	Dark blue	265/331	20.22
$[Cu(C_6H_{13}N_3O)_2]$	548.08	90	Light blue	265/324	6.05
$[Cr(C_6H_{13}N_3O)_2]$	513.33	82	Army green	275/370	15.72
$[Mn(C_6H_{13}N_3O)_2]$	557.44	90	Off- white	275/372	30.20

Key L_1=$C_6H_{13}N_3O$

Solubility Test

The free ligands were found to be sparingly soluble in polar solvents such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), H_2O, and Ethanol, but insoluble in nonpolar solvents such as hexane and tetrachloromethane (CCl_4). Some metal complexes showed more solubility in DMSO and DMF than Ethanol. All the complexes were insoluble in both hexane and chloroform as shown in Table.2

Table 2: Solubility Test of the Ligand and Complexes using different solvents.

Compounds	DMSO	CH_3OH	H_2Odistilled	CCl_4	DMF	Hexane
$[C_6H_{13}N_3O]$	S	SS	SS	IS	S	IS
$[Ni(C_6H_{13}N_3O)_2]$	S	SS	S	IS	SS	IS
$[Cu(C_6H_{13}N_3O)_2]$	SS	SS	SS	IS	SS	IS
$[Mn(C_6H_{13}N_3O)_2]$	S	S	SS	IS	S	IS
$[Cr(C_6H_{13}N_3O)_2]$	S	SS	SS	IS	SS	IS

Key L_1=$C_6H_{13}N_3O$, S=Soluble, IS=insoluble, SS= Slightly Soluble

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Fourier Transform Infrared Spectroscopy (FTIR) Analysis

The results of the IR analysis for the ligands and their complexes are given in Table 3. The appearance of azomethine band υ(C=N) at the wavelengths at 1630 cm^{-1} in the ligand's spectra confirmed the formation of the Schiff bases L_1. The shift of those bands to a lower frequency values in all the complexes at the range of (1620-1625) cm^{-1} indicates complexation with the metal ion, similar to the report of Jibril *et al. (*2019). The carbonyl υ(C=O) stretching vibration of the ligand appeared at 1775cm^{-1} and upon complexation. For the complexes, the bands shifted slightly to a lower vibrational frequency at (1670-1700) $cm^{-1}$and this could be attributed to the involvement of carbonyl oxygen that took part in the coordination of the central metal. (Kose *et al.,* 2008). A peak also appeared at 3425cm^{-1} for the ligand indicating υ(O-H) vibration and bands were further shifted to a lower frequency (3211-3244)cm^{-1} in the complexes indicating de-protonation and coordination of the hydroxyl group with a metal ion, this result is similar to that of (Sani *et al*., 2021). The new bands that were absent in the spectra of the ligand, were now formed at (431-466) cm^{-1} and (567-575) cm^{-1} for M-O and M-N vibrational frequency for the complexes. As shown inTable 3. The appearance of these new bands indicates the coordination site and the involvement of N and O atoms in the complexation of metal ions. (Bal *et al.,* 2014).

Table 3: The FTIR Spectra of ligands and complexes in cm^{-1}

Compounds	υ(C=O)	υ(C=N)	υ(N-H)	υ(O-H)	υ(M-N)	υ(M-O)
$[C_6H_{13}N_3O]$	1775	1630	2863	3425		
$[Ni(C_6H_{13}N_3O)_2]$	1697	1620	3221	3211	570	446
$[Cu(C_6H_{13}N_3O)_2]$	1700	1620	3432	3243	567	466
$[Mn(C_6H_{13}N_3O)_2]$	1680	1622	3412	3211	575	445
$[Cr(C_6H_{13}N_3O)_2]$	1670	1625	3400	3244	574	431

UV Analysis

The UV-visible spectra of Ligands and their complexes were recorded in distilled water solutions between 200-800nm at room temperature as shown in Table 4. In the free ligand a band was observed at λ_{max} 283nm which is attributed to $\pi^* \rightarrow \pi$ transition of the aromatic ring and at λ_{max} 364nm is attributed to $n \rightarrow \pi^*$ transition of the azomethine group of the ligands respectively. (Akbari *et al*.,2013) In the metal complexes $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions were shifted to longer wavelength with high intensity at the range of λ_{max} (473-545)nm as a consequence of the Ligand to metal charge transfer (LMCT).As shown in Table 4. A similar observation was made by (Bal *et al*.,2014).

Table 4: UV Spectra Analysis

Compounds	**Λ_{max} (nm)**	**Transitions**
$[C_6H_{13}N_3O]$	283,364	π-π^*, n- π^*
$[Ni(C_6H_{13}N_3O)_2]$	261,383,473	π-π^*, n- π^*, LMCT
$[Cu(C_6H_{13}N_3O)_2]$	261,441,540	π-π^*, n- π^*, LMCT
$[Mn(C_6H_{13}N_3O)_2]$	264,320,485	π-π^*, n- π^*, LMCT
$[Cr(C_6H_{13}N_3O)_2]$	250,322,545	π-π^*, n- π^*, LMCT

X-ray diffraction pattern (XRD) of the solvent-assisted mechanochemical synthesis products revealed the crystalline nature of the synthesized compounds. The XRD pattern of the ligands and complexes was scanned in the range of 0-100º (θ). The result shows that the patterns of the complexes (products) were different from the ligands (starting materials). New peaks were observed corresponding to the mechanochemical product, showing that a new phase was generated due to the coordination. These peaks appeared too sharp indicating that the compounds are crystalline and not amorphores (Khan *et al*., 2013) The major peak in the XRD pattern of complexes observed at 2θ values for L1 appeared at 20.77º However, the major peaks of the complexes L1(Cr, Cu, Mn and Ni) appeared at (20.8º,24.12º,28.53ºand 20.72º). These values did not appear in the reactants which indicates the formation of new phase. A similar observation was reported in the literature. (Sani *et al*., 2021). As shown in Fig(1).

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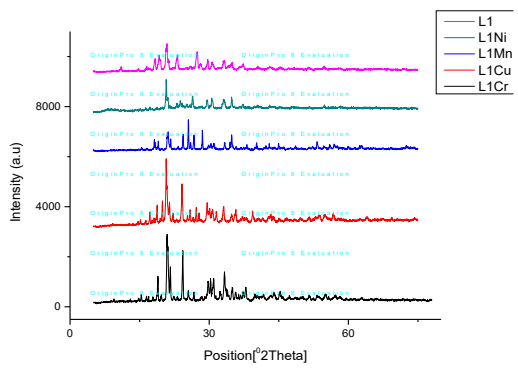


Figure 1. X-ray diffraction pattern of ligand(L1) and complexes (Ni^{2+}, Mn^{2+}, Cr^{2+} and Cu^{2+})

Antimicrobial Activity

The antibacterial activity of all the synthesized compounds was carried out in vitro using the agar dilution method which was done against Escherichia coli (Gram+) and Staphylococcus aureus (Gram-) Ciprofloxacin was used as control. Different concentrations (62µg/g, 125µg/g, 250µg/g, and 500µg/g) were used to determine the activity. The result shows that the ligands and the complexes have moderate activity against the organisms. Table 5 shows that MnL_1 has the highest activity against Escherichia coli at 250µg/g(29mm) and CrL_1 also shows the highest activity against Staphylococcus aureus at 500µg/g(24.5mm) respectively. The activity might be due to their dissociation in DMSO, the dissociation can be a factor increasing the antimicrobial activity (Gurbuz *et.al,* 2015) as presented in Table 6. It also shows that the activity also increases as an increase in concentration (Hadjer *et al*., 2018).

Table 5: Antimicrobial activity of ligands and complexes against *Escherichia Coli*

Complexes /ligands	**500µg/g**	**250 µg/g**	**125 µg/g**	**62.5 µg/g**
$[Ni(C_6H_{13}N_3O)_2]$	15.5	10.5	10	NA
$[Cu(C_6H_{13}N_3O)_2]$	10	9.5	1.0	NA
$[Cr(C_6H_{13}N_3O)_2]$	19	14	13.5	4
$[Mn(C_6H_{13}N_3O)_2]$	24	20.5	18	13
$[C_6H_{13}N_3O]$	13.3	11	10	7
Control	35			

KEY: NA=no activity on the organism
Control= Ciprofloxacin

Table 6: Antibacterial activity of ligands and complexes against *Staphylococcus Aureus*

Complexes/ligands	**500 µg/g**	**250 µg/g**	**125 µg/g**	**62.5 µg/g**
$[Ni(C_6H_{13}N_3O)_2]$	15.5	13	10	8.5
$[Cu(C_6H_{13}N_3O)_2]$	9.5	6	2.5	NA
$[Cr(C_6H_{13}N_3O)_2]$	24.5	15	14	9.5
$[Mn(C_6H_{13}N_3O)_2]$	24	15	19.5	NA
$[C_6H_{13}N_3O]$	10	9	7	7
Control	30			

NA=no activity on the organism
Control= Ciprofloxacin

Antioxidant Activity

The Radical scavenging activity of the free ligands and complexes are represented in Table 7 and these were carried out at different concentrations of H_2O_2 starting from 0.4mg/ml, 0.6mg/ml, and 0.8mg/ml respectively. Ascorbic acid was used as a reference. The Result showed that the ligands and complexes have a moderate scavenging activity. The ligand showed a weak inhibitory activity at 39.12%. The best percentage of scavenging activity was shown by compound MnL_1 (62.14) %. it is said that the ionic nature of metal ions contributes to a greater ability to neutralize free radicals. (Manir *et al*., 2021). From the result, we can observe that the scavenging activity of these compounds increases with increases in concentrations. (Al-Amiery *et al*.,2015).

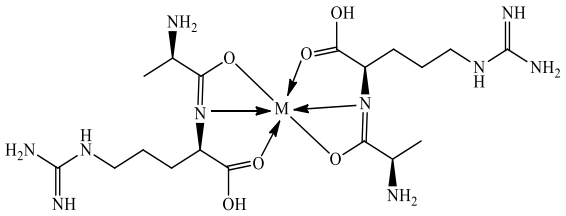
Table 7: Antioxidant Activity

Complexes/Ligands	Hydrogen peroxide Scavenging Activity (Concentration and % Inhibition)		
	0.4mg/ml	0.6mg/ml	0.8mg/ml
$[C_6H_{13}N_3O]$	29.43	32.43	39.12
$[Mn(C_6H_{13}N_3O)_2]$	58.66	60.38	62.14

$[Cr(C_6H_{18}N_4O_2)_2]$	50.67	55.34	61.76
$[Ni(C_6H_{13}N_3O)_2]$	40.01	42.53	42.67

Conclusion

Ni^{2+}, Mn^{2+}, Cu^{2+}, and Cr^{2+}, complexes of ligands derived from L-Histidine and L –Alanine were synthesized and characterized: based on the result, the study shows that all the synthesized complexes are nonelectrolyte in nature. The ligands appeared to be bidentate because they coordinated through the nitrogen atom located in azomethine and oxygen atom as shown in Fig.2 therefore are said to be stable complexes. The decomposition temperature of complexes indicates their stability. The complexes also appeared to be insoluble in most of the organic solvents. The FTIR shows that new bands (M-N and M-O) were formed indicating coordination. The UV analysis indicated that there was a shift to longer wavelengths with high intensity at the range consequences of the ligand-to-metal charge transfer (LMCT). The XRD analysis indicated that all the compounds are crystalline. The ligands and complexes tend to have good antimicrobial activity while the compounds had no antifungal activity against the organisms at different concentrations. Antioxidant activity was also tested, and the compound appeared to have moderated scavenging activities compared to the reference used. The values indicated that the activities are more pronounced when coordinated with metal ions. In conclusion, the research shows that solvent-assisted mechanochemistry is an effective strategy for the synthesis with quantitative yield, safest and fastest way of synthesis.



Where M= Ni^{2+} ,Cu^{2+}, $Cr^{2+}$and Mn^{2+},

Figure 2. Proposed Structure of Ligand1 Complexes

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