



SYNTHESIS, CHARACTERIZATION, AND ANTIBACTERIAL EVALUATION OF DIVALENT METAL COMPLEXES WITH SCHIFF BASES DERIVED FROM 4- ANISALDEHYDE AND ARGININE

*¹Aisha Ibrahim Saulawa, ²Abdullahi Hussaini Dangani and ¹Saudat Muhammad

¹Department of Chemistry, Federal University of Dutsin-Ma, Katsina.

²Department of Industrial Chemistry, Federal University of Dutsin-Ma, Katsina

*Corresponding authors' email: aishaibrahim329@gmail.com

ABSTRACT

In the present study, a new Schiff base, 5-Guanidino-2-[(4-methoxy-benzylidene)-amino]-pentanoic acid, and its metal (II) complexes were synthesized. Structural characterization was done using FTIR, UV-visible spectral analysis, molar conductance, and melting/decomposition temperature determination. Spectral studies revealed the ligand to be bidentate, coordinating with the metal through the carboxylic oxygen and azomethine nitrogen. The antibacterial activity (*in vitro*) against *Escherichia coli* and *Staphylococcus aureus* strains was studied using the agar well diffusion method. The results indicated that the free ligand exhibited no biological activity, whereas the cadmium complex (C₂₈H₃₈CdN₈O₆) proved to be the best antibacterial agent (up to 27 mm diameter inhibition zone against *E. coli*), followed by the Mn (II) complex and the Ni (III) complex having the least activity against both *Escherichia coli* and *Staphylococcus aureus*. This means that metal chelation significantly affected the anti-bacterial behavior of the organic Schiff base. This study contributes to the growing body of knowledge in the field of bioinorganic chemistry and may have potential implications for pharmaceutical and biomedical applications.

Keywords: Antibacterial activity, Schiff base, FTIR, Complexes

INTRODUCTION

The increasing prevalence of antibiotic resistance among pathogenic microorganisms has necessitated the exploration of new antimicrobial agents with novel mechanisms of action. In this context, metal complexes derived from Schiff bases have garnered significant interest due to their potential therapeutic applications, including antimicrobial activities (Singh et al., 2013, Agarwal et al., 2014). Schiff bases, characterized by the presence of the azomethine functional group (-C=N-), are versatile ligands that can form stable complexes with transition metals by donating electrons into the vacant d-orbitals (Worku et al., 2002).

Among the various scaffolds for Schiff base synthesis, arginine, a semi-essential or conditionally essential amino acid, offers unique structural features. Its guanidinium side chain and the presence of amino and carboxyl groups provide potential coordination sites for metal ions, making it an attractive choice for the development of biologically active metal complexes (Saini et al., 2013, Tapiero et al., 2002). Despite the growing interest in Schiff base-derived metal complexes, there is a need to explore new structural modifications and metal combinations to enhance their bioactivities and potential applications. The present study aims to synthesize and characterize a novel Schiff base ligand derived from 4-anisaldehyde and arginine, along with its divalent metal complexes with Co (II), Ni (II), Cd (II), Mn (II), and Zn (II) ions. The objectives are to investigate the structural properties, thermal stability, and antimicrobial activities of these complexes against Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacterial strains.

The exploration of new Schiff base-metal complexes with enhanced antimicrobial properties is crucial in addressing the global threat of antibiotic resistance. The unique structural features of the synthesized complexes may offer insights into structure-activity relationships and pave the way for the

development of novel antimicrobial agents. This study contributes to the growing body of knowledge in the field of bioinorganic chemistry and may have potential implications for pharmaceutical and biomedical applications.

MATERIALS AND METHODS

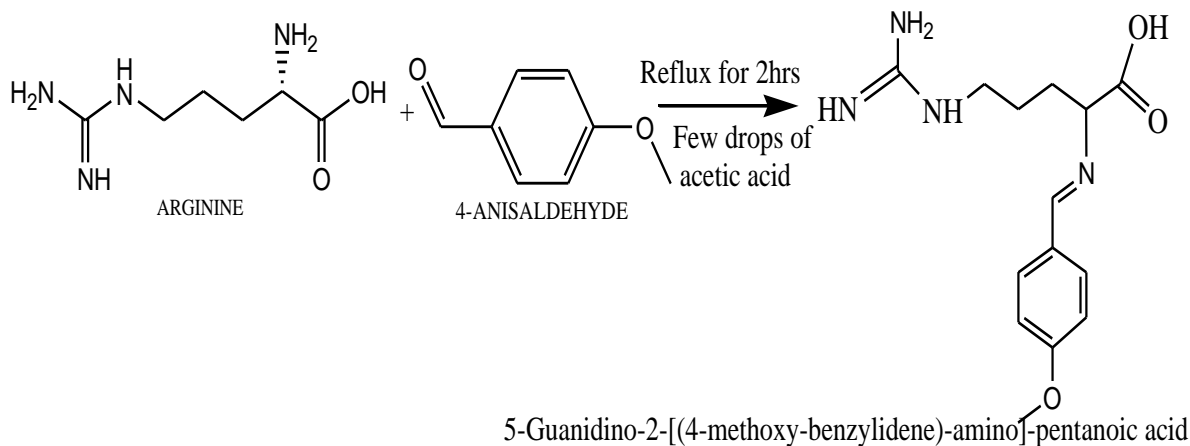
Materials and Instrumentation

All chemicals and reagents used were of analytical grade and were used without further purification. Melting points were determined using a BIBBY-Stuart SMP 10 Scientific melting point apparatus. Molar conductivity measurements were carried out using a HANNA EC215 conductivity meter. Infrared spectra were recorded on a Thermo Nicolet 100 FTIR spectrophotometer in the range of 4000-400 cm⁻¹. UV-visible spectra were measured on a SHIMADZU T60 UV-Vis spectrophotometer. All glassware was washed with water, rinsed with ethanol, and dried in an oven before use.

Synthesis of the Schiff Base Ligand

The Schiff base ligand was synthesized by condensation of 4-anisaldehyde and arginine, following a previously reported method (Agarwal, et al., 2014). A hot ethanolic solution (20 mL) of 4-anisaldehyde (0.13 g, 0.001 mol) and an equimolar amount of arginine (1.74 g, 0.001 mol) in a mixture of distilled water (5 mL) and absolute ethanol (15 mL) were mixed with constant stirring. A few drops of glacial acetic acid were added as a catalyst to facilitate the condensation reaction. The mixture was refluxed at 60°C for 2 hrs. The resulting solution was kept overnight at room temperature to ensure complete precipitation. The precipitate formed was filtered, washed with cold ethanol, and dried in a desiccator over phosphorus pentoxide.

The condensation reaction can be represented by the following scheme:



Scheme 1: Synthetic Route for 5-Guanidino-2-[(4-methoxy-benzylidene)-amino]-pentanoic acid

Synthesis of Metal Complexes

The metal complexes were synthesized by reacting the Schiff base ligand with the corresponding metal salts of Co (II), Ni (II), Cd (II), and Mn (II) in a 1:1 molar ratio (Worku et al., 2002). A hot ethanolic solution (20 mL) of the respective metal salt (0.001 mol) and an ethanolic solution (20 mL) of the ligand (0.001 mol) were mixed with constant stirring. The mixture was then refluxed at 70°C for 2 hours. Upon cooling, a precipitate formed, which was filtered, washed with cold ethanol and dried under a vacuum over phosphorus pentoxide.

RESULTS AND DISCUSSION

The Schiff base was prepared by the condensation of 4-anisaldehyde and arginine with a 72% yield. Regardless of the molar ratio of anisaldehyde to arginine, a 1:1 Schiff base was obtained from all preparations. The solubility test of the complexes shown in Table 1 indicated that the isolated complexes are highly soluble in water and DMSO and insoluble or slightly soluble in other common organic solvents.

Table 1: Solubility Profile of Schiff Base Ligand and Its Metal Complexes

S/N	Compounds	Water	DMSO	Ethanol	Methanol	Chloroform	Diethyl ether	Acetone	Ethylacetate
1.	C ₁₄ H ₂₀ N ₄ O ₃	IS	S	S	S	IS	IS	IS	IS
2.	C ₂₈ H ₃₈ CoN ₈ O ₆	S	S	SS	SS	IS	IS	IS	IS
3.	C ₂₈ H ₃₈ NiN ₈ O ₆	S	S	SS	SS	IS	IS	IS	IS
4.	C ₂₈ H ₃₈ MnN ₈ O ₆	S	S	SS	SS	IS	IS	IS	IS
5.	C ₂₈ H ₃₈ CdN ₈ O ₆	S	S	SS	SS	IS	IS	IS	IS
6.	C ₂₈ H ₃₈ ZnN ₈ O ₆	S	S	SS	SS	SS	SS	SS	SS

Key: S = soluble, SS = sparingly soluble, IS = insoluble

The physicochemical data of the synthesized ligand and its complexes are given in Table 2. The ligand formed has a cream color, while its metal complexes appeared to have pale green, blue, milky, deep brown, and milky colors for Ni (II), Co (II), Zn (II), Mn (II), and Cd (II) complexes, respectively. The color of the ligand was due to the presence of chromophores in their lattice, while that of the complexes was due to charge transfer transitions between the highest occupied ligand molecular orbitals and the lowest unoccupied metal d-orbitals. The change of color in complexes different from that of the free ligand indicates complexation

(Mustapha, 2016). The molar conductance measurement values were quite low, indicating the non-electrolytic nature of the compounds under study.

The results of the melting/decomposition temperature of the ligand and its metal complexes were found to be between 179°C and 311°C. The higher decomposition temperature of the complexes when compared with the melting point of the ligand indicates the high thermal stability of the compounds. The metal-ligand ratio of the compounds was estimated to be 1:2 as obtained from the method of continuous variation.

Table 2: Physicochemical Characterization Data of Schiff Base Ligand and Its Metal Complexes

S/N	MOLECULAR FORMULA	YIELD %	MOL. WT	M.P. (°C)	D.T (°C)	Conductivity (ohm ⁻¹ cm ² mole ⁻¹)	COLOUR
1.	C ₁₄ H ₂₀ N ₄ O ₃	72	193.20	179	-	-	Cream
2.	C ₂₈ H ₃₈ CoN ₈ O ₆	62	530.26	-	302	13.91	Blue
3.	C ₂₈ H ₃₈ NiN ₈ O ₆	68	530.02	-	311	11.25	Pale green
4.	C ₂₈ H ₃₈ MnN ₈ O ₆	79	418.17	-	300	12.10	Brown
5.	C ₂₈ H ₃₈ CdN ₈ O ₆	81	475.65	-	298	14.33	Milky
6.	C ₂₈ H ₃₈ ZnN ₈ O ₆	72	428.62	-	222	8.85	Milky

The infrared data of the ligand and its metal complexes are presented in Table 3. A strong band appeared at 1639 cm^{-1} in the spectra of the ligand, which can be assigned to the $\nu(\text{C}=\text{N})$ stretching vibration. In the complexes, the $\text{C}=\text{N}$ bands are shifted by $12\text{--}16\text{ cm}^{-1}$ to higher wavenumbers, respectively. This indicates the involvement of the azomethine nitrogen in coordination with the metal ions, similar to the observation made by Zahid and Maimoon (2000). The medium intensity peak of absorption in the Schiff base ligand around 3169 cm^{-1} region is due to the $-\text{OH}$ groups of the carboxylic acid, and these peaks of absorption disappear in all the respective complexes upon chelation with the metal ion. This confirms the coordination through the carboxylic $-\text{OH}$ group and the

central metal ion, which is similar to the observation made by Zahid et al. (2009). The broad bands in the range of $3390\text{--}3343\text{ cm}^{-1}$ for the Ni (II), Co (II), Mn (II), Cd (II), and Zn (II) complexes are assigned to the coordinated water molecules. The bands in the spectra of the complexes at $583\text{--}417\text{ cm}^{-1}$ and $420\text{--}402\text{ cm}^{-1}$ are due to the formation of $\nu(\text{M-N})$ and $\nu(\text{M-O})$ bonds, respectively. This observation was supported by a similar observation made by Valamarthy et al. (2013) in similar complexes. These bands were absent in the ligand, and their absence suggests the bidentate nature of the ligand as it coordinated with the metal ions through the carboxylic oxygen and azomethine or imino nitrogen atoms, respectively.

Table 3: Infrared Spectroscopic Data and Assignments for the Schiff Base Ligand and its Metal Complexes

S/N	COMPOUNDS	ASSIGNMENTS					
		$\nu(\text{H}_2\text{O})$	$\nu(\text{O-H})$	$\nu(\text{C}=\text{N})$	$\Delta\nu(\text{C}=\text{N})$	$\nu(\text{M-N})$	$\nu(\text{M-O})$
1.	$\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_3$	-	3169	1639	-	-	-
2.	$\text{C}_{28}\text{H}_{38}\text{CoN}_8\text{O}_6$	-	-	1655	16	583	418
3.	$\text{C}_{28}\text{H}_{38}\text{NiN}_8\text{O}_6$	-	-	1652	13	417	402
4.	$\text{C}_{28}\text{H}_{38}\text{MnN}_8\text{O}_6$	-	-	1654	15	561	416
5.	$\text{C}_{28}\text{H}_{38}\text{CdN}_8\text{O}_6$	-	-	1651	12	550	418
6.	$\text{C}_{28}\text{H}_{38}\text{ZnN}_8\text{O}_6$	-	-	1652	13	548	420

The Schiff base ligand and its metal complexes were tested for their inhibiting effects on the growth of *Staphylococcus aureus* and *Escherichia coli* using the agar well diffusion method because bacteria can achieve resistance to antibiotics through biochemical and morphological modifications. The results of the antibacterial activity of the new compounds are shown in Table 4. The results indicated that the ligand showed insignificant activity for all strains, while the metal complexes were found to inhibit the growth of the same microorganisms under identical experimental conditions. The increased lipophilic character of these metal chelates, with the resultant enhanced ability to permeate through the lipid layers of the cell membrane of the microbes, has been suggested as a reason for their improved activity, as reported similarly by Fahmi et al. (1998). Chelation has been reported to reduce the polarity of the metal ion due to the partial sharing of its

positive charge with the donor groups of ligands and possible π -electron delocalization within the whole chelate ring system formed during coordination (Tumer et al., 2007). However, none of the compounds showed the same or higher activity than the reference drug.

The average antibacterial data for the complexes obtained shows inhibition against *Staphylococcus aureus* and *Escherichia coli* in the following order: Ni < Zn = Co < Mn < Cd and Ni < Co < Zn < Mn < Cd, respectively. In all the cases studied, the cadmium complex ($\text{C}_{28}\text{H}_{38}\text{CdN}_8\text{O}_6$) proved to be the better antimicrobial agent (up to 27 mm diameter inhibition zone against *E. coli*), followed by the Mn (II) complex ($\text{C}_{28}\text{H}_{38}\text{MnN}_8\text{O}_6$) (22 mm diameter against *E. coli*), and the Ni (II) complex ($\text{C}_{28}\text{H}_{38}\text{NiN}_8\text{O}_6$) having the least activity (8 mm diameter against both *E. coli* and *S. aureus*).

TABLE 4: Anti-bacterial Screening Data of the Ligand and its Metal Complexes

COMPOUNDS	ANTIBACTERIAL					
	<i>Staphylococcus aureus</i>			<i>Escherichia coli</i>		
	Concentration ($\mu\text{g/mL}$) and zone(s) of inhibition(mm)			Concentration ($\mu\text{g/mL}$) and zone(s) of inhibition(mm)		
	10^{-1}	10^{-2}	10^{-3}	10^{-1}	10^{-2}	10^{-3}
$\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_3$	6	6	6	6	6	6
$\text{C}_{28}\text{H}_{38}\text{CoN}_8\text{O}_6$	14	12	6	16	14	8
$\text{C}_{28}\text{H}_{38}\text{NiN}_8\text{O}_6$	10	8	6	12	10	6
$\text{C}_{28}\text{H}_{38}\text{MnN}_8\text{O}_6$	18	12	8	22	16	8
$\text{C}_{28}\text{H}_{38}\text{CdN}_8\text{O}_6$	26	19	12	27	18	8
$\text{C}_{28}\text{H}_{38}\text{ZnN}_8\text{O}_6$	14	11	8	18	14	8
Ciprofloxacin	36	-	-	38	-	-
Distilled water	6	6	6	6	6	6

CONCLUSION

The study shows that the complexes were stable to air, non-hygroscopic, and variedly colored. The infrared spectra data of the ligands and their metal complexes showed that the Schiff base ligand acted as a neutral bidentate ligand and coordinated with the central metal ions through the carboxylic oxygen and imino nitrogen atoms. However, the antibacterial studies revealed that the complexes exhibited very good antimicrobial properties, while the parent ligand had insignificant activity against any of the strains. This means

that metal chelation significantly affected the antimicrobial behavior of the organic ligand.

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