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Antimicrobial Activity of Schiff Base Derived from P-Aminophenol and Benzaldehyde and their Fe (II), Co (II), Ni (II) and Cu (II) Complexes

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Abstract
The Schiff base derived from p-aminophenol and benzaldehyde was found to show significant antimicrobial activity against several strains of bacteria and fungi. The Fe(II), Co(II), Ni(II), and Cu(II) complexes of the Schiff base were also tested and showed enhanced antimicrobial activity compared to the Schiff base alone. This study highlights the potential of these compounds as effective antimicrobial agents.
Keywords: Schiff base, Antimicrobial, Bacteria and Fungi

Introduction
Many metal complexes have powerful antimicrobial activities and are already in common use in medicinal field such as silver bandages for treatment of burns, zinc antiseptic creams, bismuth drugs for the treatment of ulcer etc. (Joseypus *et al,* 2018)**.** The biological activity of metal complex is higher than that of their ligand. The complexes of the Schiff bases are of great consideration due to their stability, electron donating capacity, optical nonlinearity, catalytic, photochromic and biological activity. These, practical activity is all based on the coordination of Schiff bases with the metal ions. (Soroceanu *et al,* 2022)**.** The discovery and development of antibiotics are among the most powerful and successful achievement of modern science and technology for the control of infectious diseases. Metal based drugs represent a novel group of antifungal agents with potential application for the control of fungal infections. (Ceramella *et al,* 2022)

In most cases, higher activity for antibacterial and antifungal have been reported for Schiff bases metal complexes, rather than Schiff base alone. (Kaczmarek *at al,* 2018)
The phenomenon of antibiotic resistance is on the increase in recent years. The overused of antibiotic has led to an increase in bacterial resistance and in turn decreases the efficiency of the available antibiotics. This led to the complexation of Schiff base with metals to enhance its actibactrial and antifugal effect as compare to only Schiff base. (Khalid *et al,*2020)

Statement of the Problem
Nowadays bacteria and fungi infection are becoming more resistant to antibacterial and antifungal drugs and it was found out that Schiff base and metal complexes have powerful antimicrobial activities even though the activities of the metal complexes are higher than that of Schiff base ligand. (Soroceanu *et al,* 2022). Most of the Schiff base metal complexes are not tested hence there is a need to have a good number of research on the antibacterial and antifungal activities of the Schiff base and metal complexes. It is against this background that this study is design to evaluate the antibacterial and antifungal activities of the Schiff base and metal complexes prepared.

Objectives of the Study

The main aim of this research is to study the antimicrobial effect of the prepared Schiff base and their corresponding Co(ii), Fe(ii), Cu(ii) and Ni(ii) complexes.

The objectives of the research work are:

1. To study the antibacterial and antifungal effects of the prepared Schiff base against some selected bacterial and fungal species
2. To study the antibacterial and antifungal effects of the prepared Fe(ii), Co(ii), Cu(ii) and Ni(ii) complexes against some selected bacterial and fungal species

Research Questions

1. What are the effects of bacterial and fungal species on prepared Schiff base?
2. What is the effect of bacterial and fungal species on the prepared Fe(ii), Co(ii), Cu(ii) and Ni(ii) complexes?

Literature Review

The literature reveals that the Schiff base ligands are excellent coordinating ligands. It forms stable complexes with different transition metal ions. In particular, the transition metal complexes have been the subject for thorough investigation because of their extensive application in wide range areas from material science to biological sciences (Usharani, 2012).

Bukhari *et al* (2013) reported the synthesis, characterization and antimicrobial studies of Schiff base transition metal complexes of Cr (II), Mn (II), Co (II), Ni (II), Zn (II) and Cd (II) derived from Cefadroxil. The techniques such as elemental analysis, UV-spectral studies, molar conductivity, AAS and FTIR have been used for the characterization of the Schiff base and their metal complexes. The compositions of the metal complexes were found to be ML_2. The IR study shows that the ligand is bidentate. The conductivity test of the Schiff base and metal complexes show that both have electrolytic nature. Antimicrobial study of both Schiff base and metal complexes were made and they were found to be better than the parent antibiotic.

Choha *et al* (2015) reported the synthesis and characterization of four biologically active triazole derived schiff base ligands prepared by the condensation reaction of 3-amino-5-methylthio-1H-1,2.4-triazole with chloro-, bromo- and nitro substituted 2-hydroxybenzaldehyde in equimolar ratio and their Co(ii), Ni(ii), Cu(ii) and Zn(ii) complexes. The antibacterial and antifungal data showed the metal (ii) complexes to be more effective antibacterial and antifungal than the original Schiff base against some bacterial and fungal species.

Singhal *et al.* (2021) studied 15 novel bis indole-based Schiff bases as antibacterials. Comparative analysis against *S. aureus* and *E. coli* showed a higher inhibition of bis-schiff bases than the reference drug ciprofloxacin and their mono counterparts, the non-schiff base.

Xua *et al* (2020) reported the increase in antibacterial activity of a nobel and green cellulose-based antibacterial complex of a Schiff base with Cu against *Escherichia coli* and *Staphylococcus aureus* in comparison to the Schiff base ligand. This significant increase could be attributed to the incorporation of the Cu(ii) ion.

Materials and Method

Reagents of analytical grade purity and distilled water were used directly without further purification. All glass wares used in this work were washed with detergent, rinsed with distilled water and dried in an oven.

All weighing were carried out on an electric Metler balance model B154, melting point and decomposition temperature were determined using Gallen Kamp melting point apparatus. Molar conductivity were determined using Jen Way 4010 model. IR spectral analysis was determined on a Fourier Transformed Spectrophotometer 8400S model. The antibacterial and antifungal analyses were carried out at Department of Microbiology, Bayero University, Kano.

Other materials used in this experiment includes incubator, petri dish, whatman fiter paper, forcep, cotton swab stick, beakers, refluxing apparatus, measuring cylinder, weighing balance, bacterial species, fungal species, DMSO, Cobalt (ii) chloride, copper (ii) chloride, iron (ii) chloride, nickel (ii) chloride, 4-aminophenol, Benzaldehyde, dessicator, ethanol, ciprofloxin, nystatin, potato dextrox agar etc.

Preparation of Schiff base

4-aminophenol (0.02 mol, 2.183g) were mixed with equimolar amount of benzaldehyde (0.02 mol, 2.122g) in 50cm^3 of ethanol. The resulting mixture was left under reflux for 3 hours and the solid product formed was separated by filtration, purified by recrystallization from ethanol, washed with ethanol and then finally dried in desiccators over P_2O_5 (Ashraf *et al*, 2011).

Preparation of Schiff base metal complexes

The metal complexes were synthesized by mixing an ethanolic solution (50cm^3) of the Schiff base (0.02mol, 4.31g) with an ethanolic solution (50cm^3) of the metal (II) chloride (0.01mol) (where metals are iron, nickel, copper and cobalt). The resulting mixture were refluxed for 4 hours. On cooling, a colored complex that precipitated out was filtered, washed several times with ethanol and finally with ether and dried over P_2O_5 in a desiccators (Aliyu and Al-Hakim, 2012).

Solubility Test

The solubility test of the Schiff base and metal complexes were carried out in water, ethanol, methanol, n-hexane, trichloromethane, benzene, toluene, ethylacetate, dimethylsulphoxide, diethylether etc. The results were shown on table 2.

Melting point of Schiff base and Decomposition temperature of the metal complexes.

The melting points of the Schiff base and decomposition temperature of the metal complexes were determined using Gallenkemp melting point apparatus. The results are shown in table 2.

Determination of water of Hydration in the complexes

0.2g of each of the complexes were taking and placed in an oven at 110^{o}C to dry until a constant weight was obtained. The percentage composition of water in the complex was calculated using the formula below:

$$\frac{\text{Weight loss}}{\text{Weight of the complex taken}} \times \frac{100\%}{1}$$

The results are shown in table 5.

Conductivity Measurement

The electrical conductivity of the complexes were measured using a Zentech electrometer. The results is shown in table 3.

Elemental Analysis

Microanalyses of carbon, hydrogen and nitrogen of the Schiff base and metal complexes were carried out on a Vario EL-III elemental analyser. The results is shown in table 6.

Determination of Metal in the Complex Compounds

0.2g of each of the metal complex was placed in a 100cm^3 beaker containing 25cm^{3}of distilled water to which 5cm^3 of concentrated nitric acid was added and then heated to about dryness. The contents in the beaker were allowed to cool to room temperature and 25cm^3 of distilled water was added and mixture stirred before the filtrate was collected which contains the metal ions (Adamu, 2009).

In vitro antimicrobial activity

The in vitro antibacterial, antifungal were studied at the Department of Microbiology, Bayero University, Kano, Nigeria. Antibacterial activity of the synthesized ligand and their complexes were tested against the bacterial species *Staphylococcus aureus, Escherichia coli, Klebsiella pneumaniae, Proteus vulgaris* and *Pseudomonas aeruginosa* by disc diffusion method. The ligand and complexes were also tested against some fungal species *Aspergillus niger, Rhizopus stolenifer, ASpergillus flavus, Rhizoctonia bataicola* and *Candida albicans,* culture on potato dextrose agar medium which were also be performed by disc diffusion method. Ciprofloxin and Nystatin were used as a standard antibacterial and antifungal agent respectively. The compound was dissolved in DMSO and were soaked in filter paper discs. The discs were placed on an already prepared seed plates which were incubated at 37^{0}c for 24hours for bacteria and 72hours for fungi. The antimicrobial activity was detected by measuring the zone of inhibition that appeared after the incubation period. (Balouiri *et al,* 2016)

Results and Analysis

Table 1: Shows percentage yield, colour, melting point and decomposition temperature of the compounds

Compounds	Colour	% yield	Melting point (^oC)	Decomposition Temperature. (^oC)
Ligand	Brown	72.8	197-198	-
$[NiL_2].2H_2O$	Light green	63.3	-	283
$[CuL_2].2H_2O$	Black	60.6	-	294
$[CoL_2].2H_2O$	Brown	66.4	-	275
$[FeL_2].3H_2O$	Dark brown	51.8	-	277

Compounds	Water H_2O	Methanol CH_3OH	n-hexane	Trichloromethane $CHCl_3$	Diethylether $(CH_3CH_2)_2O$	DMSO $(CH_3)_2SO$	Benzene	Ethanol	Toluene
Ligand	IS	SS	IS	IS	SS	S	IS	SS	IS
$[NiL_2].2H_2O$	IS	SS	IS	IS	SS	S	IS	SS	IS
$[CuL_2].2H_2O$	IS	SS	IS	IS	IS	S	IS	S	IS
$[CoL_2].2H_2O$	IS	SS	IS	SS	SS	S	IS	SS	IS
$[FeL_2].3H_2O$	IS	SS	IS	SS	SS	S	IS	SS	IS

Table 2: Solubility of the Ligand and its metal (II) complexes in some common solvents.
Key: IS = Insoluble, S = Soluble, SS = Slightly Soluble.

Table 3: Molar Conductance of the complexes in 10^{-3}M DMSO Solution

Complexes	Concentration (mol/dm^3)	Electrical Conductivity ($ohm^{-1}\ cm^{-1}$)	Molar Conductivity ($ohm^{-1}\ cm^2\ mol^{-1}$)
$[NiL_2].2H_2O$	1×10^{-3}	37.5×10^{-6}	37.5
$[CuL_2].2H_2O$	1×10^{-3}	38.3×10^{-6}	38.3
$[CoL_2].2H_2O$	1×10^{-3}	16.6×10^{-6}	16.6
$[FeL_2].3H_2O$	1×10^{-3}	43.0×10^{-6}	43.0

Table 4: The IR spectra of the Schiff base and the metal complexes

Compounds	V(C=N) cm^{-1}	V(M-O) cm^{-1}	V(M-N) cm^{-1}	V(H_2O) cm^{-1}
Ligand	1604.83	-	-	-
$[NiL_2]. 2H_2O$	1606.76	511.89	409.89	3387.11
$[CuL_2].2H_2O$	1590.36	482.22	400.24	3422.8
$[CoL_2].2H_2O$	1605.79	516.94	401.21	3029.31
$[FeL_2].3H_2O$	1601.93	561.30	480.00	3316.71

Table 5: Shows Molecular Formula and Percentage Composition of the Complexes

Complex	% Metal	% Water	% Ligand
$[NiL_2] .2H_2O$	11.32	7.5	81.18
$[CoL_2] .2H_2O$	11.68	6.5	81.82
$[CuL_2]. 2H_2O$	13.25	8.0	78.75
$[FeL_2]. 3H_2O$	10.5	10	79.5

Table 6: Elemental analytical data (%) of the Schiff base and complexes

Compounds	% Found (Calculated)		
	C	H	N
Ligand	79.31 (79.17)	5.59 (5.62)	7.23 (7.10)
$[NiL_2] .2H_2O$	64.44 (64.10)	4.96 (4.93)	5.77 (5.75)
$[CoL_2] .2H_2O$	64.30 (64.10)	4.99 (4.93)	5.78 (5.75)
$[CuL_2]. 2H_2O$	63.68 (63.48)	4.91 (4.88)	5.77 (5.70)
$[FeL_2]. 3H_2O$	62.30 (62.20)	5.20 (5.18)	5.58 (5.58)

Table 7: Sensitivity Test of Ligand and metal (ii) complexes against some bacterial isolates

Test organism/ Compounds		**Concentration (µg)/ Zone of inhibition (mm)**			**Control (mm)**
		60	**30**	**15**	
Staphylococcus aureus	Ligand (L)	16	14	12	Amphiclox 26
	$[NiL_2].2H_2O$	18	16	14	
	$[CoL_2].2H_2O$	20	18	17	
	$[CuL_2].2H_2O$	17	13	10	
	$[FeL_2].3H_2O$	17	13	9	
Streptococcus pyogens	Ligand (L)	18	15	14	Amphiclox 28
	$[NiL_2].2H_2O$	19	18	16	
	$[CoL_2].2H_2O$	20	17	15	
	$[CuL_2].2H_2O$	20	16	15	
	$[FeL_2].3H_2O$	20	19	17	
Salmonella typhi	Ligand (L)	16	15	6	Ciprofloxacin 30
	$[NiL_2].2H_2O$	18	16	13	
	$[CoL_2].2H_2O$	19	17	16	
	$[CuL_2].2H_2O$	-	-	-	
	$[FeL_2].3H_2O$	20	18	13	
Klebsiella pneumonia	Ligand (L)	20	18	15	Ciprofloxacin 30
	$[NiL_2].2H_2O$	21	19	17	
	$[CoL_2].2H_2O$	20	18	17	
	$[CuL_2].2H_2O$	18	18	16	
	$[FeL_2].3H_2O$	21	20	18	

Table 8: Sensitivity Test of Ligand and metal (ii) complexes against some fungal isolates

Test organism / Compounds		**Zone of inhibition (mm) /Concentration (µg)**			**Control (mm)**
		60	30	15	
Aspergillus fomigatus	Ligand (L)	15	13	10	Grisofulvin 32
	$[NiL_2].2H_2O$	6	6	6	
	$[CoL_2].2H_2O$	15	13	6	
	$[CuL_2].2H_2O$	17	15	10	
	$[FeL_2].3H_2O$	17	15	13	
Rhizopus spp.	Ligand (L)	6	6	6	31
	$[NiL_2].2H_2O$	15	11	6	
	$[CoL_2].2H_2O$	6	6	6	
	$[CuL_2].2H_2O$	16	14	6	
	$[FeL_2].3H_2O$	17	6	6	
Mucor spp.	Ligand (L)	6	6	6	32
	$[NiL_2].2H_2O$	17	6	6	

$[CoL_2].2H_2O$	6	6	6
$[CuL_2].2H_2O$	6	6	6
$[FeL_2].3H_2O$	6	6	6

Discussion of Findings

The ligand was prepared as reported, it was brown solid crystal and the percentage yield was 72.8%. The Schiff base complexes of Ni (II), Cu (II), Co (II) and Fe (II) prepared are light green, black, brown and dark brown respectively. The colour of the complex may be either due to charge electron transition, where an electron may jump from a predominantly ligand orbital to a predominantly metal orbital given rise to ligand-to-metal charge transfer (LMCT) transition or d-d transition where an electron jumps from one d-orbital to another (Sharma, 2007). The melting point temperature of the ligand was 197-198^{0}C while the decomposition temperatures of Ni (II), Cu (II), Co (II) and Fe (II) Schiff base complexes are 283°C, 294°C, 275°C and 277°C respectively (Table 1). The high decomposition temperatures show that the complexes are very stable (Aliyu and Al-Hakim, 2012). The higher decomposition temperature of the metal complexes may be due to the fact that metal chelate are more stable than the non-chelate compounds (Sharma, 2007).

In Table 2, solubility test shows that the ligand is only soluble in Dimethylsulphoxide (DMSO) but slightly soluble in methanol, ethanol etc and insoluble water, n-hexane etc. However, the Schiff base metal complexes are insoluble and slightly soluble in some solvent but are all soluble in DMSO.

Molar conductance values (Table 3) of metal (II) Schiff base complexes in 10^{-3}M dimethylsulphoxide (DMSO) solution determined were low and in the range of 16.6 -43.0 ohm^{-1} cm^2 mol^{-1}. The lower value suggests the non-electrolytic nature of the complexes (Gufta *et al.,* 2012). The lower value may be due to the fact that the complexes are neutral it does not undergo ionization and hence does not give ions in solution (Sharma, 2007).
The IR spectral data of the ligand showed a band at 1604.83cm^{-1}, which is assigned to v(C=N) stretching vibration, a feature found in Schiff bases (Mehta *et al.*, 1981) has shifted to the regions of 1590.36-1606cm^{-1} are assigned to v(C=N) in the metal complexes. The shifting of values is an indication of coordination of the Schiff base to the metal ion (Mehta *et al.,* 1981). The metal-Schiff base complexes showed some new bands in the region 375-480 cm^{-1} and 482-561 cm^{-1} which are attributed to v(M-N) and v(M-O) stretching vibration respectively (Usharani *et al.,* 2012). These bands confirmed the coordination of the ligand to the respective metal ions. The bands in the region 3029-3445cm^{-1} are attributed to v(O-H_2) stretching frequencies for water of crystallization in the metal-Schiff base complexes (Byeong-Goo *et al.,* 1996). The results are shown in Table 4.

The percent compositions of metal ions and water of crystallization in the complexes were determined. The results are shown in Table 5. The empirical formula of the complexes was determined from known values of percent compositions of metals, Schiff base and water of crystallization. The results revealed that metal-ligand ratio was 1:2 for all the complexes and suggested the formula $[ML_2]$. nH_2O for all complexes. The complexes prepared show a variation in the coordination number of water molecules. Ni (II), Co (II) and Cu (II) complexes has 2 water molecule each, while Fe (II) complex has 3 water molecules.

The elemental analysis for C, N and H in the Ligand and the complexes were determined. The result obtained is in consistent with 1:2 metals to ligand ratio. The result is presented in table 6.

The antibacterial activity of the metal complexes (Table 7) showed more activity than the Schiff base (Ligand). This is due to the fact that metal chelates have more antibacterial activity than free ligand because of the chelation theory, the polarity of the metal ion is reduced to a greater extent due to overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Furthermore, it increases the delocalization of π-electrons over the whole chelate ring and enhances the lipophilicity of the complexes. Thus, inhibiting the growth of bacteria more potent than the parent Schiff base (Usharani *et al.,* 2012). All metal complexes and the Ligand were found to be active against all isolates except for Cu (II) complex which is inactive against *Salmonella Typhi.*

The antifungal activity of the Schiff base (Ligand) showed that it was only active against *Aspergillus formigatus* at all concentration, but no activity on *Rhizopus spp* and *Mucor spp* isolates. Ni (II) complex showed no activity against *Aspergillus formigatus* but active on *Rhizopus spp* at 60μg and 30μg and on *Mucor spp.* at 60μg. Co (II) complex was only active against *Aspergillus formigatus* at 60μg and 30μg. Cu (II) complex showed little activity on *Aspergillus formigatus* at all concentration and on *Rhizopus spp.* at 60μg and 30μg but showed no activity on *Mucor spp*. Fe (II) complex showed activity against *Aspergillus formigatus* at all concentration. The activity on *Rhizopus spp* was only at 60μg with little or no activity on *Mucor spp* (Table 4).

Conclusion

The Fe (II), Co (II), Ni (II), and Cu (II) complexes of the Schiff base were found to show enhanced antimicrobial activity compared to the Schiff base alone. This study highlights the potential of these compounds as effective antimicrobial agents.

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