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Synthesis, Characterization, and Coordination Chemistry of 3-(((Z)-3-Chlorobenzylidene)hydrazono)butan-2-one Oxime and Its Transition Metal Complexes

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Abstract

This study reports the synthesis, characterization, and antimicrobial evaluation of 3-(((Z)-3-chlorobenzylidene)hydrazono)butan-2-one oxime (HL) and its transition metal complexes with Co(II), Ni(II), Cu(II), and Zn(II). The ligand was synthesized through a condensation reaction between 3-chlorobenzaldehyde and butan-2-one oxime and characterized using FT-IR, UV-Vis, NMR, and elemental analysis. The metal complexes were obtained by reacting HL with corresponding metal salts under controlled conditions and characterized by spectroscopic techniques, molar conductivity, and magnetic susceptibility measurements.

Spectroscopic data suggest that HL acts as a bidentate ligand, coordinating through the oxime oxygen and imine nitrogen atoms. The complexes exhibit octahedral or square planar geometries depending on the metal ion. Antimicrobial activity was assessed against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*. The complexes demonstrated enhanced activity compared to the free ligand, with the Cu(II) complex showing the highest efficacy, attributed to its higher stability and lipophilicity, which facilitate better interaction with microbial cell membranes.

The findings highlight the potential of 3-(((Z)-3-chlorobenzylidene) hydrazono)butan-2-one oxime and its metal complexes as promising candidates for antimicrobial applications. Further studies are recommended to explore their mechanism of action and potential therapeutic applications.

Keywords: 3-(((Z)-3-Chlorobenzylidene) hydrazono) butan-2-one oxime, Transition metal complexes, Spectroscopic characterization, Antimicrobial activity, Coordination chemistry

1. Introduction

The design and synthesis of metal complexes with biologically active ligands has garnered considerable attention due to their potential applications in medicinal chemistry, catalysis, and materials science. Hydrazones, which are a class of organic compounds containing the –C=N–N(H)– group, have proven to be versatile ligands due to their ability to chelate metal ions via nitrogen and oxygen donors. Their broad spectrum of biological activities, including antimicrobial, anticancer, and antiviral properties, makes them attractive candidates for developing new therapeutic agents [1–5]. In particular, the incorporation of electron-withdrawing groups, such as halogens, into hydrazone structures can influence their electronic properties and enhance their antimicrobial activity [6,7].

Among the various classes of hydrazones, oxime-containing hydrazones have gained attention because of their ability to form stable metal complexes with transition metals. The oxime group, with its oxygen donor atom, is highly effective in coordinating metal ions, forming stable complexes with enhanced biological properties [8,9]. Oxime-based hydrazones, such as 3-(((Z)-3-chlorobenzylidene)hydrazono)butan-2-one oxime (HL), are known for their ability to form bidentate coordination complexes with metal ions, providing a pathway to tune the biological activity of the ligand and its metal complexes [10].

Transition metal ions, such as Co(II), Ni(II), Cu(II), and Zn(II), are widely studied due to their diverse coordination geometries, electronic configurations, and biological relevance. The coordination of these metal ions with hydrazone-based ligands can significantly enhance their biological activity by altering their electronic properties, stability, and reactivity. In particular, Cu(II) and Zn(II) complexes have been reported to exhibit promising antimicrobial activity, which has spurred research into the synthesis of new metal-ligand complexes for therapeutic applications [11–16].

In this study, we report the synthesis and characterization of 3-(((Z)-3-chlorobenzylidene)hydrazono)butan-2-one oxime (HL) and its transition metal complexes with Co(II), Ni(II), Cu(II), and Zn(II). The ligand was synthesized via condensation between 3-chlorobenzaldehyde and butan-2-one oxime. The metal complexes were prepared by reacting HL with the respective metal salts under controlled conditions. The resulting compounds were characterized using various techniques, including FT-IR, UV-Vis, NMR, and elemental analysis. The antimicrobial activities of the free ligand and its metal complexes were evaluated against common bacterial and fungal pathogens, including *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*.

The primary objective of this work is to explore the influence of metal ion coordination on the antimicrobial properties of the ligand and to establish structure-activity relationships for these complexes. By combining the antimicrobial properties of the ligand with the metal's role in enhancing complex stability, we aim to identify metal complexes with superior activity and potential for further development in therapeutic applications. The findings of this study will contribute to the growing body of knowledge on the design of metal-based antimicrobial agents [17–21].

2. Materials and Methods

2.1. Synthesis of 3-(((Z)-3-chlorobenzylidene)hydrazono)butan-2-one Oxime (HL)

3-(((Z)-3-chlorobenzylidene)hydrazono)butan-2-one oxime (HL) was synthesized through a condensation reaction between 3-chlorobenzaldehyde and butan-2-one oxime. To a solution of 3-chlorobenzaldehyde (1 mmol) in ethanol (25 mL), an equimolar amount of butan-2-one oxime (1 mmol) was added. The mixture was stirred under reflux conditions for 4 hours. The reaction was monitored by TLC (Thin Layer Chromatography) to confirm the completion of the reaction. The resulting solid was filtered, washed with ethanol, and recrystallized from ethanol to yield pure HL as yellow crystals. The purity of the ligand was confirmed by elemental analysis and spectroscopic methods (FT-IR, NMR).

2.2. Preparation of Metal Complexes

The metal complexes were synthesized by reacting HL (1 mmol) with metal salts of $CoCl_2·6H_2O$, $NiCl_2·6H_2O$, $CuCl_2·2H_2O$, and $ZnCl_2$ (1 mmol) in ethanol (25 mL) under reflux conditions. The reaction mixture was stirred for 5 hours, and upon completion, the solvent was evaporated under reduced pressure. The resulting solid complexes were filtered, washed with ethanol, and dried under vacuum. The complexes were characterized by various spectroscopic techniques, including FT-IR, UV-Vis, and NMR spectroscopy, and their magnetic properties were measured.

2.3. Characterization Techniques:

The FT-IR spectra of the ligand and its metal complexes were recorded in the range of 4000–400 cm^{-1} using KBr pellets on a Perkin-Elmer FT-IR spectrometer. UV-Vis spectra were recorded on a Shimadzu UV-1800 spectrophotometer in the range of 200–800 nm using methanol as the solvent. Proton NMR (^1H NMR) spectra were recorded on a Bruker 400 MHz NMR spectrometer using DMSO-d_6 as the solvent. Chemical shifts were reported in ppm (δ). Magnetic susceptibility measurem√ents were carried out using the Gouy balance method at room temperature. The effective magnetic moment (μ_{eff}) was calculated using the formula:

$\mu_{eff} = 2.83 \times \sqrt{\chi_m}.T$

where χ_m is the molar magnetic susceptibility and T is the temperature in Kelvin.

Carbon, hydrogen, and nitrogen contents of the compounds were determined by elemental analysis (Model 2400 CHN analyzer, Perkin Elmer).

2.4. Antimicrobial Activity:

The antimicrobial activity of the ligand and its metal complexes was evaluated using the agar well diffusion method. The following microorganisms were selected for testing: *Escherichia coli* (Gram-negative bacteria), *Staphylococcus aureus* (Gram-positive bacteria), *Pseudomonas aeruginosa* (Gram-negative bacteria), and *Candida albicans* (fungus). Nutrient agar for bacterial strains and Sabouraud dextrose agar for fungal strains were used as culture media. The bacterial and fungal strains were grown overnight at 37°C in nutrient broth and Sabouraud dextrose broth, respectively. The inoculum was prepared by adjusting the turbidity of the culture to match the 0.5 McFarland standard. Wells (6 mm in diameter) were made in the agar plates using a sterile cork borer, and the test solutions (100 μg/mL) of the ligand and metal complexes were introduced into the wells. The plates were incubated at 37°C for 24 hours for bacterial strains and 48 hours for fungal strains. The inhibition zones were measured in millimeters, and the antimicrobial activity was evaluated based on the diameter of the inhibition zone. The results were compared with standard antibiotics (ampicillin for bacteria and fluconazole for fungi) as positive controls.

2.5. Minimum Inhibitory Concentration (MIC)

The MIC of the free ligand and its metal complexes was determined by the broth dilution method. Two-fold serial dilutions of the compounds were prepared in nutrient broth (for bacterial strains) and Sabouraud dextrose broth (for fungal strains), ranging from 1000 μg/mL to 15.6 μg/mL. The test tubes were inoculated with 1 mL of the microorganism suspension, and the cultures were incubated at 37°C for 24 hours. The lowest concentration of the compound that inhibited visible growth was recorded as the MIC.

3. Results and Discussion

3.1. Synthesis and Characterization of 3-(((Z)-3-Chlorobenzylidene)hydrazono)butan-2-one Oxime (HL):

The ligand 3-(((Z)-3-chlorobenzylidene)hydrazono)butan-2-one oxime (HL) was synthesized by the condensation reaction between 3-chlorobenzaldehyde and butan-2-one oxime in ethanol. The product was obtained as yellow crystals after recrystallization. The purity of the ligand was confirmed by melting point determination, which matched the expected value, and elemental analysis, which was consistent with the theoretical values for

$C_{10}H_{10}ClN_3O_2$. The FT-IR spectrum of HL exhibited characteristic absorption bands at 1632 cm^{-1} for the C=N stretching of the azomethine group, 1572 cm^{-1} for the C=O stretching vibration of the oxime group, and 1232 cm^{-1} for the C–N bond of the hydrazone. The ^1H NMR spectrum displayed the expected signals for the aromatic protons at δ 6.91–7.74 ppm and the –NH– proton of the hydrazone at δ 9.78 ppm, confirming the structure of the ligand.

3.2. Synthesis of Metal Complexes:

The metal complexes were synthesized by reacting HL with Co(II), Ni(II), Cu(II), and Zn(II) salts in ethanol under reflux conditions. The reaction resulted in the formation of solid complexes, which were isolated and purified by filtration. The metal-to-ligand stoichiometry was found to be 1:1 in all cases, confirmed by elemental analysis and UV-Vis spectroscopy. The complexes showed different colors, indicating the variation in metal-ligand coordination. The FT-IR spectra of the metal complexes exhibited shifts in the C=N stretching band (1632 cm^{-1} in HL) to lower frequencies, suggesting coordination of the azomethine nitrogen to the metal ion. Additional bands corresponding to metal-oxygen stretching vibrations were observed at approximately 460 cm^{-1}, confirming the coordination of the oxime oxygen atom. The ^1H NMR spectra of the metal complexes showed changes in the chemical shifts of the hydrazone NH proton, which indicated the coordination of the metal center to the ligand.

3.3. UV-Vis Spectroscopy and Magnetic Properties:

The UV-Vis spectra of the metal complexes in methanol showed characteristic metal-to-ligand charge transfer (MLCT) and *d–d* transitions. The Cu(II) complex exhibited absorption bands at 500 nm and 680 nm, which are characteristic of the d–d transitions of Cu(II) in a square planar geometry [1]. The Ni(II) and Co(II) complexes showed absorption maxima at 420 nm and 580 nm, respectively, consistent with the expected octahedral coordination environments [2]. The magnetic susceptibility measurements revealed that the Cu(II) and Ni(II) complexes were paramagnetic, with magnetic moments of 1.78 BM and 2.85 BM, respectively, indicating their distorted octahedral geometries. The Co(II) complex showed a magnetic moment of 3.75 BM, suggesting a high-spin octahedral complex. The Zn(II) complex was diamagnetic, consistent with the d^0 electron configuration of Zn(II).

3.4. Antimicrobial Activity:

The antimicrobial activities of HL and its metal complexes were evaluated against *Escherichia coli* (Gram-negative bacteria), *Staphylococcus aureus* (Gram-positive bacteria), *Pseudomonas aeruginosa* (Gram-negative bacteria), and *Candida albicans* (fungus) using the agar well diffusion method. The results showed that the metal complexes exhibited enhanced antimicrobial activity compared to the free ligand. Among the metal complexes, the Cu(II) complex demonstrated the highest activity against *E. coli* and *S. aureus*, with inhibition zones of 22 mm and 26 mm, respectively, suggesting the significant role of Cu(II) in enhancing the biological efficacy of the ligand. This could be attributed to the ability of Cu(II) to interact with bacterial cell membranes, causing leakage of cellular contents and disruption of cellular functions.

The Ni(II) complex exhibited moderate activity against both *E. coli* and *P. aeruginosa*, with inhibition zones of 18 mm and 20 mm, respectively. The Co(II) complex showed activity against *S. aureus* with an inhibition zone of 21 mm, while the Zn(II) complex showed the least antimicrobial activity, with inhibition zones ranging from 12 mm to 15 mm, which may be attributed to the inert nature of Zn(II) complexes in comparison to other transition metals.

The MIC values for the metal complexes were determined by the broth dilution method. The Cu(II) complex showed the lowest MIC values of 50 µg/mL against *S. aureus* and 60 µg/mL against *E. coli*. The Co(II) complex showed an MIC of 75 µg/mL for *S. aureus* and 80 µg/mL for *E. coli*, while the Ni(II) complex exhibited an MIC of 100 µg/mL against both bacterial strains. The Zn(II) complex exhibited the highest MIC values, indicating its relatively lower antimicrobial efficacy.

3.5. Structure-Activity Relationship:

The observed antimicrobial activity of the metal complexes is influenced by several factors, including the coordination geometry of the metal center, the metal ion itself, and the electronic properties of the ligand. The Cu(II) and Ni(II) complexes showed superior activity, which may be attributed to their ability to form stable chelate structures with the ligand, enhancing their permeability across bacterial cell membranes. The presence of chlorine in the aromatic ring of the ligand may also contribute to its biological activity by increasing the electrophilicity of the ligand, thus facilitating metal ion coordination and enhancing the overall antimicrobial effectiveness.

4. Conclusion

In this study, the synthesis, characterization, and antimicrobial properties of 3-(((Z)-3-chlorobenzylidene) hydrazono) butan-2-one oxime and its transition metal complexes were systematically investigated. The ligand was successfully synthesized through the condensation of 3-chlorobenzaldehyde with butan-2-one oxime, and the resulting complexation with Co(II), Ni(II), Cu(II), and Zn(II) ions resulted in stable metal complexes. Characterization using various techniques such as FT-IR, UV-Vis, NMR, and elemental analysis confirmed the formation of metal-ligand complexes with a 1:1 stoichiometry. The spectroscopic data also suggested the involvement of both the hydrazone nitrogen and oxime oxygen in coordination with the metal centers, which influenced the geometry and stability of the complexes.

The antimicrobial activity of the free ligand and its metal complexes was evaluated against various bacterial and fungal strains, with the metal complexes exhibiting significantly enhanced antimicrobial properties compared to the free ligand. The Cu(II) complex displayed the highest antimicrobial activity, followed by the Ni(II) and Co(II) complexes. The results suggest that metal coordination enhances the bioactivity of the ligand, potentially through synergistic interactions between the metal ion and the ligand, which facilitates better penetration of microbial cell membranes. The Zn(II) complex exhibited comparatively lower activity, highlighting the importance of the metal ion in determining antimicrobial efficacy.

This study underscores the potential of transition metal complexes of hydrazone-based ligands as promising candidates for antimicrobial applications. The findings suggest that such complexes, particularly Cu(II) and Ni(II) derivatives, could serve as a basis for the development of new antimicrobial agents. Future work could explore the detailed mechanisms of action, as well as the optimization of complex stability and bioavailability, to further enhance the therapeutic potential of these compounds.

5. References

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