



Antibacterial Co (II), Ni (II) and Cu (II) complexes with bidentate NO donor Schiff bases

Seema I Habib*, P. A. Kulkarni

P.G. Department of Chemistry and Organic Research Laboratory, Yeshwant Mahavidyalaya, Nanded., India.

*Corresponding author's E-mail: seemahabib12@gmail.com

Accepted on: 24-03-2013; Finalized on: 31-08-2013.

ABSTRACT

The condensation reactions of 3, 5-dibromo/3, 5-diiodo 2, 4- dihydroxy acetophenone with 2- amino 4-Nitrotoluene to form bidentate NO donor Schiff bases were studied. The prepared Schiff base ligands were further utilized for the formation of metal chelates having the general formula $[ML_2(H_2O)_2]$ where $M = Co(II), Ni(II)$, and ML_2 where $M = Cu(II)$ and $L = HL_1$ and HL_2 . These new compounds were characterized by conductance measurements, magnetic susceptibility measurements, elemental analysis, and IR, 1H NMR, and electronic spectroscopy. Both Schiff base ligands were found to have a mono-anionic bidentate nature and octahedral geometry was assigned to Co (II), Ni (II) and square planar geometry for Cu (II) complex. Co (II), Ni (II) complexes contained coordinated water which was lost at 141–160 °C. These compounds were also screened for their *in vitro* antibacterial activity against four bacterial species, namely: *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi* and *Bacillus subtilis*. The metal complexes were found to have greater antibacterial activity than the uncomplexed Schiff base ligands.

Keywords: Antibacterial activity, Metal complexes, Schiff base.

INTRODUCTION

The promising bacterial resistance to the currently available antibiotics has forced the exploration for new prokaryotic targets as well as novel molecules to inhibit their activity. Among such novel derivatives, metal complexes of biologically active ligands may represent an attractive approach for designing new antimicrobial compounds, due to the dual possibility of both ligands and metal ions interacting with different steps in the life cycle of pathogens. Much work has been realized by bioinorganic as well as medicinal chemists to launch the relationship between the metal ions and their complexes as antitumor and antibacterial agents.^{1,2} Metal Complexes of Schiff bases also used as potential therapeutic reagent³ It is however noteworthy that some biologically active compounds may become more carcinostatic and bacteriostatic upon chelation.⁴ Ketones and amines are versatile reactive organic compounds due to presence of C=O and NH_2 groups, respectively. The nucleophilic addition reactions of these compounds result in an important class of compounds known as Schiff bases, which are considered to be the best candidates for coordination with metal ions. A number of studies have reported the ligational aspects and biological role of Schiff bases and their metal complexes.^{5,6} A comprehensive search through the literature revealed that no work has been realized on the preparation and characterization of metal complexes of Schiff bases derived from 3, 5-dibromo/ 3, 5-diiodo 2, 4-dihydroxy acetophenone and 2-amino 4-nitrotoluene. Consequently, an attempt has been made to synthesize and characterize some novel metal complexes of these Schiff base ligands. The prepared ligands as well as their metal complexes were also investigated for their *in vitro* activity against some bacterial species. The purpose of the work was to

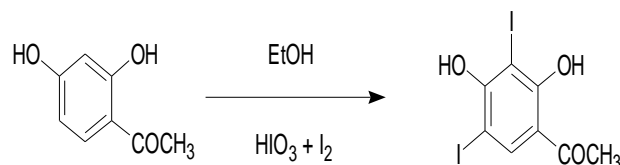
understand the coordination as well as the biological chemistry of these novel synthesized compounds.

MATERIALS AND METHODS

Analytical reagent grade ethanol was used after distillation. All other chemicals and solvents were of reagent grade and procured from Sigma Aldrich or Merck. Metal chlorides were used as the metal (II) salts for synthetic purposes. All the melting points were determined in an open capillary tube and are uncorrected. Completion of the reaction was monitored by thin layer chromatography on pre-coated sheets of silica gel-G.

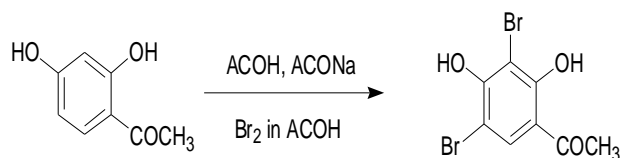
Synthesis of 3, 5-diiodo 2, 4-dihydroxy Acetophenone

Resacetophenone (0.01mole) was dissolved in ethyl alcohol (25ml) iodine (0.02 m) was added and heated at 35-40°C. The iodic acid was dissolved in minimum quantity of water added with in 5 minute and stir the solution for 1 hour. Solid separates out. Separated solid was filtered, washed with water and crystallized from ethyl alcohol. (Scheme-I)



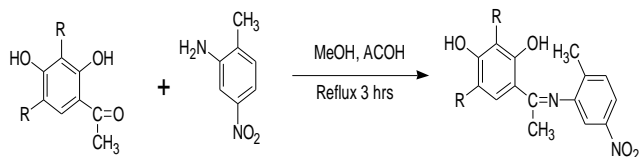
Synthesis of 3, 5-dibromo 2, 4-dihydroxy Acetophenone

Resacetophenone (2gm) was dissolved in acetic acid; sodium acetate (2gm) was added and cooled up to 0-10°C. Bromine in acetic acid (20% 16 ml) was added and reaction kept overnight, solid separates out. Separated solid was filtered, washed with water and recrystallized from ethyl alcohol (Scheme-II).

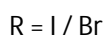


Synthesis of 3, 5-diiodo/ 3, 5-dibromo 2, 4-dihydroxy α -methyl benzylidene 2-amino 4-nitrotoluene

3, 5-diiodo/ 3, 5-dibromo 2, 4-dihydroxy acetophenone and 2-amino 4-nitrotoluene were dissolved in required amount of alcohol, then two drops of acetic acid was added. Reaction mixture was refluxed for 3 hours. The reaction mixture was cooled and poured in water. The separated crystals was filtered, washed with cold water and recrystallized from ethyl alcohol. The purity of the compounds was checked by TLC (Scheme-III)



Where



Synthesis of metal complexes

Take 1:2 metal to ligand ratio. Dissolve both the reactants separately in minimum alcohol than after that mix them and the P^H of the reaction mixture was maintained and then reflux the reaction mixture for 2 hour. The solid mass separated was filtered through a sintered glass crucible (G4) and the residue was washed several times with hot methanol until the washings were free of the excess of ligand. These complexes were finally dried under vacuum desiccator over fused $CaCl_2$. Analytical and physical data is given in Table 1.

UV and visible spectra will be recorded on Shimadzu UV-Vis-1600. 1H NMR spectra of compounds will be recorded (in $DMSO-d_6$) on Avance-300 MHz spectrometer using TMS as an internal standard. IR spectra in KBr ν_{max} in cm^{-1} will be recorded on Shimadzu 8400S FTIR spectrometer. ESR spectra will be recorded on a Varian E-112X-band ESR spectrometer using 100kc modulation and 9 inch electromagnet. Thermo gravimetric analytical studies will be made with Mettler system to study the thermal behavior of the metal complexes. The balance used will be having sensitivity of 0.001mg with the accuracy of ± 0.005 mg.

RESULTS AND DISCUSSION

All the complexes are stable at room temperature insoluble in water and most of the common organic solvents but soluble in DMF and DMSO. The analytical data of the complexes (Table 1) indicates that their stoichiometry may be represented as 1:2 metal to ligand ratio. The molar conductance values of the complexes in DMF solvents suggesting their non-electrolytic nature.

IR Spectra

The IR spectra of ligands show characteristic azomethine ($-C=N-$) peak at $1600-1627\text{ cm}^{-1}$. These same bands show down word shifting in almost all complexes. Shifting of the band itself is the proof of involvement of azomethine 'N' in coordination with metal ion.⁷ The constancy in the band value of 1554 cm^{-1} ($-C=N-$) ring suggests only the involvement of azomethine 'N' in coordination. The band due to Ph-OH in ligands shows significant shifting or it has disappeared on complexation which indicates deprotonation and involvement in coordination with metal ions. The presence of medium intensity band in $3356-3652\text{ cm}^{-1}$ range can be assigned due to $-OH$ stretching due to presence of water of hydration.⁸ This fact is well supported and confirmed by the thermal data analysis and their respective spectral figures. Thermo gravimetric analytical data suggest square planar geometry for Cu (II) complexes.

1H NMR spectra

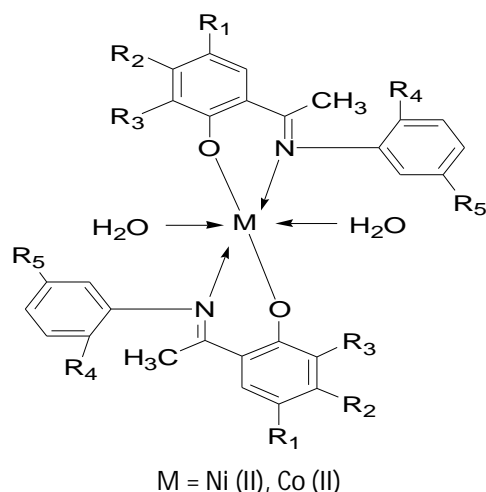
1H NMR spectra of the Cu (II), Ni (II) and Co (II) complexes was recorded. Unfortunately, however due to the presence of a metal ion, proton resonance was not effected and one could observe only broad peaks indicating the formation of the complex.

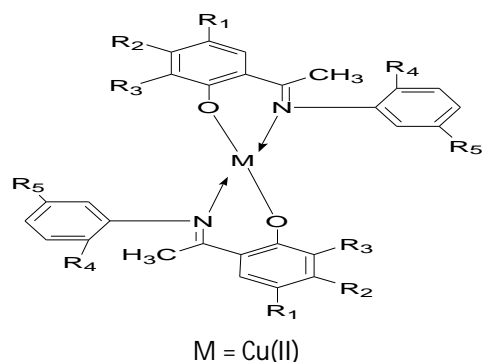
Thermal analysis

The thermogram of Ni (II) and Co (II) complexes shows the coordination of two moles of hydrated water, where as the thermogram of Cu (II) complex shows the absence of hydrated water molecule. Hence from TGA, it is clear that the complexes under study contain two water molecules which are coordinated to central metal ion.

Magnetic moment

The μ_{eff} values at room temperature for Cu (II) complexes are in the range of 1.74-1.86 B.M usually observed for square planar Cu (II) complexes. Ni (II) and Co (II) complexes have magnetic moment values in the range of 2.88-3.46 and 4.48-4.92 B.M respectively. These values are expected for octahedral geometry of Ni (II) and Co (II) complexes at $25^\circ C$.





Where

Complex	R ₁	R ₂	R ₃	R ₄	R ₅
Sa ₁	I	OH	I	CH ₃	NO ₂
Sa ₂	Br	OH	Br	CH ₃	NO ₂
Sa ₃	I	OH	I	CH ₃	NO ₂
Sb ₁	Br	OH	Br	CH ₃	NO ₂
Sb ₂	I	OH	I	CH ₃	NO ₂
Sb ₃	Br	OH	Br	CH ₃	NO ₂

Table 1: Magnetic moment, Conductivity and analytical data of Co (II), Ni (II) and Cu (II) complexes

Complex	Molecular Formula	Colour	M.P/D.P °C	Molar Conductivity Ohm ⁻¹ Cm ² Mol ⁻¹ × 10 ⁻³	μ _{eff} B.M.
Sa ₁	C ₃₀ H ₂₈ N ₄ I ₄ O ₁₀ Ni	yellow	158	26.18	2.88
Sa ₂	C ₃₀ H ₂₈ N ₄ I ₄ O ₁₀ Co	Brown	224	22.84	4.92
Sa ₃	C ₃₀ H ₂₄ N ₄ I ₄ O ₈ Cu	Dark yellow	218	12.38	1.74
Sb ₁	C ₃₀ H ₂₈ N ₄ Br ₄ O ₁₀ Ni	Brown	182	28.34	3.46
Sb ₂	C ₃₀ H ₂₈ N ₄ Br ₄ O ₁₀ Co	Green	234	21.35	4.48
Sb ₃	C ₃₀ H ₂₄ N ₄ Br ₄ O ₈ Cu	Brown	176	16.48	1.86

Electron spin resonance study

The ESR spectra of Cu (II) complexes in the polycrystalline state shows two peaks, one of intense absorption at high field and the other of less intensity at low field. From these spectra the values of g_{\parallel} and g_{\perp} have been calculated by Kneubehls method. The observed g -values point to the presence of the unpaired electron in the dx^2-y^2 orbital with $g_{\parallel} > g_{\perp}$ characteristic of square planar or elongated tetragonal geometry. The g_{\parallel} obtained for the Cu (II) complexes is less than 2.3 indicating covalent character of the metal-ligand bond.⁹ The axial symmetry parameter (G) for the complexes is found to be greater than 4. This shows absence of interaction between copper centers in the solid state.

Antimicrobial activity

The antibacterial activity of the compounds was determined by agar diffusion method against various bacteria like *E.coli*, *S. typhi*, *S. aureus*, and *B. subtilis* at various concentrations such as 20, 50 and 100 μg /ml. The zone of inhibition was measured in mm and DMSO was used as solvent. Sterile nutrient agar was seeded with test organism and layered in sterile petri plate. After solidification, agar cups were bored with cork borer 0.1 ml of the compound solution was added to the cup with the help of micropipettes, one cup in the plates was filled with solvent. Standard penicillin (10v/ml) was used as reference drug. The plates were kept at low temperature (4°C) for 20minute to allow diffusion of the compound. Then the plates were incubated at 37 °C for 24 hr. After proper incubation the plates were observed for zone of no growth (zone of inhibition of growth) around the cup.

Table 2: Antimicrobial activity of synthesized compounds

Product	Bacterial strain			
	Ec	St	Sa	Bs
HL ₁	11	14	13	19
HL ₂	---	---	18	15
Sa ₁	---	16	22	29
Sa ₂	14	21	27	18
Sa ₃	17	19	20	23
Sb ₁	09	22	29	16
Sb ₂	16	18	23	13
Sb ₃	12	15	21	25
Penicillin	18	20	32	28

Ec-*Escherichia coli*, Sa-*Staphylococcus aureus*, St-*Salmonella typhi* and Bs-*Bacillus subtilis*; Zone of inhibition was measured in mm.

The results of antibacterial data are given in Table 2. The data revealed that the metal complexes show enhanced activity than their parent ligand.

CONCLUSION

It is clear from the present results that preliminary studies showed their good inhibitory properties. In general Ni (II), Co (II) and Cu (II) complexes are more active than their parent ligand and hence may serve as vehicles for activation of the ligand as principle cytotoxic species.

Acknowledgement: The authors are thankful to Principal, Yeshwant Mahavidyalaya, Nanded for providing laboratory facilities and also to the Director, IICT, Hyderabad for providing the instrumentation facilities.

REFERENCES

1. Muhammad I, Liviu M, Shoomaila L, Zaid M, Imtiaz N, Sana S, Sumya F, Antibacterial Co(II), Ni(II), Cu(II) and Zn(II) complexes with biacetyl-derived Schiff bases, Journal of Serbian Chemical Society, 72(8), 2010, 1075-1084.
2. Morad FM, EL. Ajaily MM, Ben Gweirif S, Preparation, Physical Characterization and Antibacterial activity of Ni(II) Schiff base complex, Journal of Science and its applications, 1(1), 2007, 72-78.
3. Shazia R, Muhammadl, Anwar N, Haji A, Amin A, Transition Metal Complexes as Therapeutic agents, Biotechnology and Molecular Biology Reviews, 5(2), 2010, 38-45.
4. Mohamed GG, Mohamed MO, Ahmed MH, Metal Complexes of Schiff bases, Preparation Characterization and biological, Turk. J. Chem, 30, 2006, 361-382.
5. Kulkarni AD, Patil SA, Badani PS, Electrochemical properties of some Transition Metal complexes: synthesis Characterization and in vitro antimicrobial studies of Co(II), Ni(II), Cu(II), Mn(II) and Fe(II) Complexes, International Journal of Electrochemical sciences, 4, 2009, 717-729.
6. Chondekar TK, Shelke VA, Jadhav SM, Patharkar VR, Shankarwar SG, Munde AS, Synthesis of Transition Metal Complexes of Bidentate Ligand and their Antimicrobial Studies, Trade Science- An Inorganic Journal, 2(1), 2010.
7. Reddy V, Patil N, Angadi SD, Synthesis Characterization and Antimicrobial activity of Cu(II), Co(II) and Ni(II) complexes with O, N and S donor Ligands, E- Journal of Chemistry, 5(3), 2008, 577-583.
8. Raman N, Dhaveethu Raja J, Sakthivel A, Synthesis, Spectral Characterization of Schiff base Transition Metal Complexes, DNA Cleavage and Antimicrobial activity studies, J. Chem. Sci, 119(4), 2007, 303-310.
9. Chondekar TK, Shelke VA, Jadhav SM, Patharkar VR, Shankarwar SG, Munde AS, Synthesis of Transition Metal Complexes of Bidentate Ligand and their Antimicrobial Studies, Trade Science- An Inorganic Journal, 2(1), 2010.

Source of Support: Nil, **Conflict of Interest:** None.

Corresponding Author's Biography:

Dr. Seema Habib is post graduated from Yeshwant Mahavidyalaya, Nanded (SRTMU-Nanded). Completed master Thesis in "Transition Metal Complexes of Chalcones." She awarded as Junior Research Fellow under the scheme of Maulana Azad National Fellowship for Minority students from UGC New Delhi, Having 7 years of teaching experience at UG and PG level. She has published 16 research articles at national and international repute.