



SYNTHESIS, CHARACTERISATION AND BIOLOGICAL EVALUATION OF BIDENTATE LIGANDS (REDUCED SCHIFF'S BASE) WITH METALS OF COPPER, NICKEL AND ZINC COMPLEXES

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ABSTRACT

Schiff base ligand (L) was synthesized using p-Chlorobenzaldehyde with p-Chloroaniline followed by reduction. The complexes of copper (II), Nickel (II) and Zinc (II) with the bidentate ligand were synthesized having metal: ligand stoichiometry 1:2. The ligand and respective complexes were characterized for their analytical parameters and various spectral features. The structures of these complexes were proposed on the basis of elemental analysis, electronic spectra, molar conductivity, IR spectra, ¹HNMR spectra. Electronic spectra suggest that the band was shifted to a shorter wavelength which may be attributed to donation of the lone pairs of the nitrogen atoms. The molar conductance of the complexes indicates that the ligand is coordinated as uninegatively charged ions. The IR spectral data suggest that the coordination of phenolic oxygen to metal ion. The ¹HNMR spectral data suggest that the chemical shift observed for the OH protons in the ligand (10.63ppm) was not observed in any of the complexes. This confirms the bonding of oxygen to metal ions (C-O-M). The antibacterial and analgesic activity of the complex and non-complex compounds suggest that metal containing compounds showed good inhibitory activity than non-complex compounds.

Keywords: Cu (II), Ni (II), Zn (II), Schiff base, p-chlorobenzaldehyde and p-chloroaniline

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INTRODUCTION

Inorganic elements play crucial role in biological and biological medical processes, and it is evident that many organic compounds used in medicine do not have a purely organic mode of action, some are activated or biotransformed by metal ions metabolism¹. Many drugs possess modified toxicological and pharmacological properties in the form of metal complex and probably schiff bases are versatile C=N (Imine) containing compounds possessing broad spectrum of biological activity²⁻⁶ and incorporation of metals in form of complexes showed some degree of antibacterial⁷, antifungal⁸, antitumor⁹ and anti-inflammatory activity^{10,11}. In Schiff base azomethane nitrogen and other donor atoms like oxygen play a vital role in co-ordination chemistry¹².

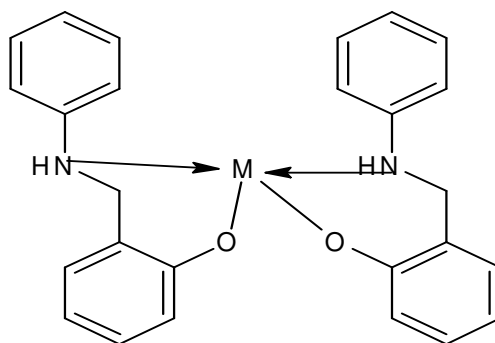
Hence an attempt is made to study the interaction of reduced Schiff base with transition of metals of biological interest and to investigate the co-ordination chemistry of such interactions. In the present work we described the synthesis and characterization of reduced Schiff base and its metal complexes. Moreover antibacterial and analgesic activity of reduced Schiff base metal complexes is also evaluated and compared with the standards.

Keeping in view, the concept of co-ordination of suitable metals as central atoms, in the present work, Schiff base p-chlorobenzaldehyde with p-chloroaniline was synthesized followed by reduction by sodium borohydride, (figure-1) and its Cu(II), Ni(II), Zn(II) complexes were prepared. The metal complexes were characterized by elemental analysis, UV visible, Molar conductance, FTIR, ¹HNMR. The co-

ordination of metals to ligand depends on various parameters like temperature of solutions, reagents, pH of solution, solvent media etc.

EXPERIMENTAL

All the chemical and solvents used were of A.R. grade. Melting points were determined in open capillaries and were uncorrected by melting point determining apparatus (SISCO). Purity of the compounds were checked by TLC. IR spectra (KBr , cm^{-1}) were recorded on a JASCO FTIR 410 spectrophotometer. ^1H NMR (CDCl_3) on a Bruker DPX 300-MHz spectrometer using TMS as an internal reference (chemical shifts in ppm). C, H and N analysis were carried out on a Euro EA (Italy) analyzer. Electronic spectrum measurements were carried out by the Jasco V-600 UV/Vis-Spectrophotometer at room temperature. The Conductivity were recorded on 'Systronics conductimeter System' at SOA University, Bhubaneswar. The analytical data are presented in table 1.



M = Cu, Ni & Zn

Fig.-1

Synthesis of Reduced Schiff base

The ligand (H_2L) was synthesized by mixing equimolar quantities of p-chlorobenzaldehyde and p-chloroaniline in ethanol, was refluxed for 4hrs with occasional shaking. The excess ethanol was then distilled off under reduced pressure, the resulting solid was washed with ethanol followed by ether and dried in vacuum. Further the synthesized compound (HL) was treated with sodium borohydride using methanol as solvent with continuous stirring in a water bath. The reaction mixture was cooled and a solid precipitated out immediately. Recrystallization of crude product from ethanol gave the desired Schiff reduced base as whitish crystalline solid. The purity was checked by M.P. and TLC technique. Further the structures of the synthesized compound were conformed by subjecting them to IR, ^1H NMR and Elemental analysis studies. Their melting points, % yields and molecular formula are given in Table-1

Synthesis of Metal complexes: (H_2L) complexes

The metal chelates were prepared by mixing methanolic solution of the respective metal (II) chloride and methanolic solution of ligand H_2L in a molar ratio 2:1. The pH of the solution was adjusted to pH 8.5 by drop wise addition of alcoholic ammonia. Then it was stirred for 8 hours at temperature $40\text{-}60^\circ\text{C}$. Then the solution was kept in a Petri dish and allowed to dry in open air. Colored crystals appeared after 3-4 days which was filtered, washed respectively repeatedly with methanol and dried in vacuum. The purity was checked by M.P. and TLC technique. Further the structures of the synthesized compound were conformed by subjecting them to IR, ^1H NMR and Elemental analysis studies which are given in table-1 and 2.

RESULTS AND DISCUSSION

All metal complexes are colored, stable in air. The solids do not melt sharply and undergo decomposition. These are insoluble in water and soluble in organic solvents such as DMF, DMSO giving respective colors to the solutions. All compounds gave satisfactory elemental analysis. Values are in the close agreement with the values calculated for expected molecular formulae assigned to these complexes,

suggesting 1:2 stoichiometries. The physical data of ligand and metal complexes are given in table-1. The molar conductance values of the complexes indicate the non-electrolytic nature of the complexes¹³.

Electronic spectrum of ligand showed two high intensity bands lying at 255 & 291 nm assigned to transition respectively in ligand. The electronic absorption spectrum of Cu (II) complex showed shifting of intense sharp bands at 251 nm and 355 nm, Ni (II) having 258 nm & 317 nm and Zn (II) having 256.1 nm & 305.6 nm respectively. This shift may be attributed to the donation of the lone pairs of the nitrogen atom of Schiff base ligand to the metal¹⁴.

The co-ordination sites of the ligand have been determined by a careful comparison of the IR spectra complexes with that of the parent ligand. The ligand shows intense absorption at 3300-3394 cm⁻¹ which may be assigned to hydrogen bonded O-H in plane stretching vibration. This sharp band has disappeared in the complexes, indicating its involvement in the bond formation process¹⁵. The ligand shows intense absorption at 1281 cm⁻¹ which may be assigned to C-N stretching frequency is lowered by 11-29 cm⁻¹ in the spectra of the complexes, indicating coordination through azomethane nitrogen of the Schiff bases¹⁶. The new bands appearing in the region 665-750 cm⁻¹ and 469-579 cm⁻¹ may probably due to coordinated water molecule and the formation of v(M-N) and v(M-O) bonds respectively^{17,18}.

The proton NMR of ligand and its metal complexes were recorded using TMS as a reference in DMSO solvent. Data related to various protons is summarized in table-2. The spectrum of ligand shows multiple signals in the range of 6.2-7.33 ppm, which are characteristic signal for aromatic ring protons. The corresponding metal chelates also show similar multiple signals with σ value in the range of 7.09-7.9 ppm. Similarly in the spectrum of ligand signal at 8.57 ppm can be assigned to (>NH) proton which was appeared signal at 8.47-8.52 ppm can be assigned to (>NH) proton in the corresponding chelates. However an important feature of the metal complexes spectrum is absence of signal due to phenolic of ligand at 10.64 ppm indicating the coordination through aromatic proton after deprotonation. The molar conductance of 10⁻³ M solutions in DMSO at room temperature of the complexes has been measured and the values are reported in table. These values were found to be ranging between 6.01- 10.95 ohm⁻¹ cm² mol⁻¹ and values indicate that all the complexes are nonelectrolytes.

The ligands and their metal chelates were screened for their antibacterial in vitro against *Staphylococcus aureus*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Klebsiella Pneumoniae*, using standard agar well diffusion assay method¹⁹. The Ni (II), Zn (II) complexes showed moderate antimicrobial activity.

The analgesic activity was determined by tail flick method²⁰. Wistar albino mice of either sex (20-30g) in the groups of six animals each were selected by random sampling technique. Indomethacin at a dose level of 10 mg/kg was administered as a reference drug for comparison. The test compounds at dose level of 100mg/kg were administered orally by intragastric tube. The animals were held in position by a suitable restrained with the tail extending out and the tail (up to 5 cm) was then dipped in a beaker of water maintained at 55°C. The time in seconds taken to withdraw the tail clearly out of water was taken as the reaction time. The reading was recorded at 0, 30, 60, 90, 120 and 180 min. after administration of compounds. A cut off point of 10 sec. was observed to prevent the tail damage. The results are presented in Table-3. The Cu (II), Ni (II) complexes showed moderate antimicrobial activity.

The purpose of the present study was to examine whether molecular modification might result in detection of new potential drugs. A series of compounds were prepared and assayed in a variety of biological test for antimicrobial and analgesic activity. The data reported in table 3 & 4 shows that effect of variation in chemical structure on activity was rather unpredictable. Seldom did a particular structural modification lead to uniform alteration in activity in all tests. However some point of interest did emerge and a few generalizations can be made. The substitution which appeared to be most important for high order of activity in the greatest number of test was the metal chelates. The introduction of Ni (II), Zn (II) in ligand reduced Schiff base produce compounds with potent antimicrobial properties and Cu (II), Ni (II) ligand compounds produce analgesic activity.

CONCLUSION

From the result one is tempted to conclude that the metal incorporation in reduced Schiff base ligands are more effective as compared to the ligand against these microbes their metal complexes seem to have developed a fair antimicrobial activity. Generally, it can be conclude that synthesized metal complexes a new represent class of analgesic agents with antimicrobial property. Obviously, the comparative evaluation of active compounds will required further studies; the data reported in this article may be helpful guide for the medicinal chemist who is working in this area.

Table-1: Colour, elemental analysis, ¹HNMR spectral data of schiff base and metal complexes.

Ligand/Complex	Colour	Elemental analysis (%) : Found (Calcd.)		¹ HNMR Chemical Shift (ppm)		
		N	M	Ar-H	NH	OH
L	Whitish Crystal	5.99	5.91	6.2-7.3	8.57	10.64
CuL	Greenish White	5.21(5.23)	11.95 (12.01)	7.08-7.8	8.34	-----
NiL	Bluish White	5.39(5.29)	11.20(11.21)	7.1-7.7	8.13	-----
ZnL	White crystal	5.27(5.28)	12.32(12.34)	7.09-7.9	8.47	-----

Table-2: IR, Molar conductance and Electronics spectral data of Schiff base and metal complexes.

Ligand/Complex	IR Spectral Data (cm ⁻¹)					Molar Conductance (S cm ² mol ⁻¹)	Electronic Spectra Data λI - λI*	N - λI*
	ν(OH)	ν(C-N)	ν(C-N)	ν(M-N)	ν(M-O)			
L	1281	1605	1450	-----	-----		291	255
CuL	1250	1594	1454	758	514	6.01	355	251
Nil	1232	1592	1232	665	469	7.78	317	258.1
ZnL	1232	1594	1454	758	514	10.95	305.6	256.1

Table-3: Antimicrobial screening of synthesized compounds by Agar diffusion method

Compound code	Molecular formula	Zone of inhibition of P.a(mm) 100µg/ml*	Zone of inhibition of K.p (mm) 100µg/ml*	Zone of inhibition of E.c (mm) 100µg/ml*	Zone of inhibition of S.a (mm) 100µg/ml*
H ₂ L ¹	C ₁₃ H ₁₄ N ₂ O ₂ Cl	14	17	19	24
CuL ¹	C ₂₆ H ₂₂ N ₂ O ₂ Cl ₂ Cu	13	11	20	21
NiL ¹	C ₂₆ H ₂₂ N ₂ O ₂ Cl ₂ Ni	22	19	18	23
ZnL ¹	C ₂₆ H ₂₂ N ₂ O ₂ Cl ₂ Zn	20	18	14	20
STD	Ampicillin trihydrate	26.4	25.3	26.2	25.6
Solvent	DMF	00	00	00	00

*Average of three readings. E. f: *Enterococcus faecalis*, P.a: *Pseudomonas aeruginosa*, K.p: *Klebsiella.Pneumoniae*, E. c: *Escherichia coli*, S.a: *Staphylococcus aureus*.

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Table-4: Analgesic activity of Synthesized compounds by tail immersion method
Results are expressed as Mean \pm SEM from six observations
*P<0.05 **P<0.01 ***P<0.001

Compound code	Molecular formula	Group (mg/kg)	Dose	Pain reaction time (min)					
				0	30	60	90	120	180
H ₂ L ¹	C ₁₃ H ₁₄ N ₂ O ₂ Cl	1	50	1.26 \pm 0.032	3.37 \pm 0.018*	6.43 \pm 0.012*	6.53 \pm 0.009	5.45 \pm 0.011*	3.19 \pm 0.014
			100	1.33 \pm 0.012	4.79 \pm 0.015*	7.64 \pm 0.040*	7.93 \pm 0.010*	5.61 \pm 0.006*	4.21 \pm 0.03*
CuL ¹	C ₂₆ H ₂₂ N ₂ O ₂ Cl ₂ Cu	2	50	1.34 \pm 0.014	3.64 \pm 0.013	5.54 \pm 0.013*	6.20 \pm 0.007*	4.94 \pm 0.013	3.73 \pm 0.010*
			100	1.24 \pm 0.004	5.03 \pm 0.028*	7.23 \pm 0.012**	7.45 \pm 0.014*	5.63 \pm 0.010* *	4.43 \pm 0.013**
NiL ¹	C ₂₆ H ₂₂ N ₂ O ₂ Cl ₂ Ni	3	50	1.32 \pm 0.013	3.33 \pm 0.010*	4.94 \pm 0.013	6.11 \pm 0.023*	4.33 \pm 0.010* *	3.63 \pm 0.016*
			100	1.36 \pm 0.009	4.63 \pm 0.010	7.13 \pm 0.010	7.24 \pm 0.015**	5.32 \pm 0.008*	4.44 \pm 0.013**
ZnL ¹	C ₂₆ H ₂₂ N ₂ O ₂ Cl ₂ Zn	4	50	1.28 \pm 0.013	3.23 \pm 0.013*	4.93 \pm 0.012*	5.83 \pm 0.012*	4.44 \pm 0.012	3.24 \pm 0.013
			100	1.25 \pm 0.004	4.53 \pm 0.011	5.94 \pm 0.013*	6.33 \pm 0.012***	4.72 \pm 0.007*	4.11 \pm 0.024***

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