

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SOME METAL COMPLEXES WITH SCHIFF BASE CONTAINING O, N and S AS THE DONOR ATOMS

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ABSTRACT

The aim of the present work is to synthesize some Schiff base complexes of metal ion and to evaluate their antimicrobial activities. Novel Schiff base ligand derived from 2-hydroxybenzophenone with S-benzylthiocarbamate and its metal complexes with Ni (II), Cu (II), Zn (II) and Cd (II) have been synthesized and evaluated for their antibacterial activities by disc diffusion method and antifungal activities by PDA medium. The complexes have been characterized by conductance, magnetic, IR and electronic spectroscopic techniques.

KEYWORDS: Complex, Ligand, S-Benzylthiocarbamate, Schiff Base

INTRODUCTION

Multidentate ligands and their metal complexes have played an important role in the development of co-ordination chemistry. A large number of publications ranging from synthetic to modern physiochemical and biochemical relevant studies of these complexes bear testimony to their importance [1-7]. A survey of the literature shows that while much work has been done on metal complexes of ligands containing oxygen in conjunction with nitrogen or nitrogen alone as the donor atoms, ligands in which at least one of the donor atoms is sulfur, did not attract much attention in the early investigations. Similarly, data on the corresponding metal complexes of Schiff bases containing mixed donor atoms such as sulfur and nitrogen and oxygen, nitrogen and sulfur are sparse.

In the last twenty five years, a great deal of attention has been devoted to the study of metal complexes of sulfur ligands. The particular features that make sulfur an interesting donor have been discussed in a review article by Livingstone [7] in 1965 and by Akbar Ali and Livingstone [8] in 1974. Synthesis and structure characterization of this type of ligands are important because ligands containing both hard and soft donor atoms may yield metal complexes with anomalous magnetic properties and interesting stereochemistry and some of the ligands and their metal complexes are expected to show biological activity.

In fact, many metal complexes of sulfur-nitrogen chelating agents have been shown to display confirmed cytotoxic (anticancer) activities. Sulfur-nitrogen chelating agents, especially the thiosemicarbazones, in their metal complexes possess a range of biological applications that include antitumour [9], antifungal [10], antiviral [11], antibacterial [12], antifilarial [13] and antimalarial activities [14]. Thiosemicarbazones exercise their biological activity in mammalian cells by inhibiting ribonucleotide reductase, a necessary enzyme in the synthesis of DNA precursors [15]. The non-heme subunit of the enzyme has been shown to be inactivated by this thiosemicarbazones [16]. Keeping the above facts in mind in the present paper we report the synthesis and characterization of Ni (II), Cu (II), Cd (II) and Zn (II) complexes of Schiff base derived from S-benzylthiocarbamate with 2-hydroxybenzophenone.

EXPERIMENTAL

All the chemicals and solvents used for the synthesis were of analytical grade. The solvents were purified by standard methods. The infrared spectra of the ligand and metal complexes were run as KBr discs in the range $4000\text{--}400\text{ cm}^{-1}$ on a *Shimadzu* Infrared Spectrophotometer (University of Dhaka, Bangladesh). Electronic spectra in the solid state as well as in solution were recorded on a *Shimadzu* UV-160, UV-visible spectrophotometer (University of Chittagong). Conductivity measurements of the metal complexes were done in DMF bridge model PW 9501 using Philips PW 9515/10 conductivity cell.

Synthesis of Ligand H₂L

At first, the compound S-benzylthiocarbamate was prepared by the procedure adopted by Akbar Ali and Tarafdar [17]. The synthesized compound S-benzylthiocarbamate (10mmol) was dissolved in 50 ml of absolute ethanol and was mixed this with a solution of 2-Hydroxybenzophenone (10mmol) in absolute ethanol. The mixture was refluxed on a water bath for period of about 4 hours. The volume of reaction mixture was reduced to half of the original amount and there after the reaction mixture was left for slow cooling at room temperature, whereupon an yellow product had formed, which was filtered off, washed with ethanol several times and dried in a vacuum desiccators over P₄O₁₀.

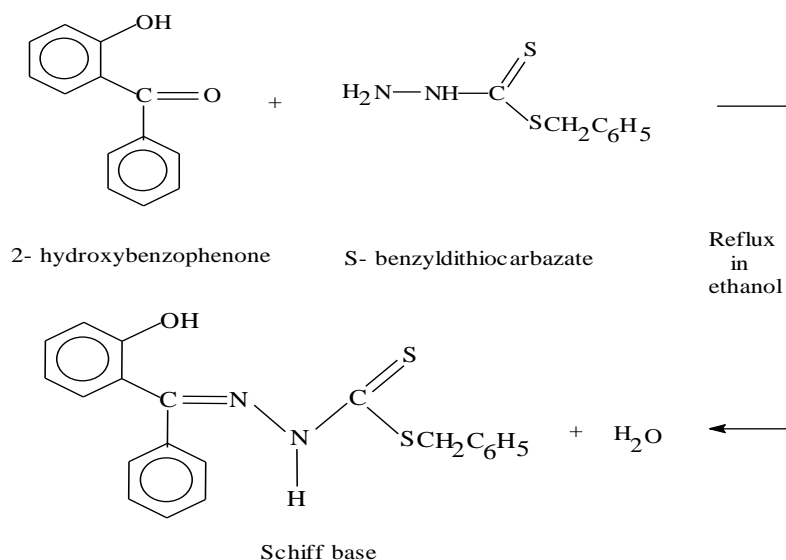


Figure 1: Scheme for Synthetic Methodology

Synthesis of Ni (II), Cu (II), Zn (II) and Cd (II) Complexes

The hot solution of the ligand H₂L (1 mmol) in absolute ethanol (40ml) was added to the solution of appropriate metal salt solution (1mmol) in ethanol (40ml). The resulting solution was heated on a water bath until the volume of the solution was reduced to half. After cooling to room temperature, solid product obtained. This was filtered off, washed several times with ethanol and dried in a vacuum desiccator over silica gel.

Collection of Test Organisms

In the present study, to detect the antifungal activities of different complexes, four plant pathogenic fungi viz. *Fusarium equiseti*, *Macrophomina phaseolina*, *Botrydiplodia theobromae* and *Alternaria alternata* were used as test organisms. The test chemicals were also screened against four human pathogenic bacteria viz. *Salmonella typhi*, *Shigella dysenteriae*, *Bacillus cereus* and *Staphylococcus aureus*. The test tube cultures of the fungal pathogens and human pathogens were collected from the laboratory of the Department of Microbiology, University of Chittagong.

Preparation of the Microbial Cultures

Standard PDA (Potato Dextrose Agar) medium was used as basal medium for the growth of fungi using the following ingredient composition: Potato: 200g, Dextrose: 20g, Agar: 15g, Distilled Water: 1000 ml.

Nutrient Agar (NA) was used as basal medium for bacteria having the following ingredient composition: Beef extract: 3g, Peptone: 5g, Agar: 15g, NaCl: 0.05g, Distilled Water: 1000ml

Detailed methodology followed during the preparation of pure cultures has been described elsewhere [18].

Efficacy of the Chemicals

Efficacies of the chemicals were tested by the 'mycelial growth tests' [19] against four selected fungal pathogens. Required amount of medium was taken in conical flasks separately and was sterilized in autoclave (at 121⁰C and 15 psi). After autoclaving, weighed amount of test chemical was added to the sterilized medium in conical flask at the point of pouring to obtain desired concentration. The flask was shaken thoroughly to mix the chemical with the medium before pouring. The medium with definite concentration (2%) of chemical was then poured at the rate of 10 ml in sterilized glass Petri dishes individually.

Proper control was maintained separately with sterilized PDA medium without chemical and three replication were prepared for each treatment. After solidification of medium the plates were of mycelial blocks (5 mm approximately) of individual test fungus, cut out from the outer margin of the growing cultures on PDA plates. The blocks were then placed at the center of each Petri dish in an inverted position. All the plates were inoculated at room temperature on the laboratory desk for five days. Radial growth of fungal colony was measured in mm after five days of incubation at 25⁰C and an average of the three replication was taken as the diameter of the colony in mm. The percentage inhibition of mycelial growth of test fungi was calculated as follows:

$$I = [(C-T)/C] \times 100$$

Where, I = Percentage of inhibition; C= Diameter of the fungal colony in DMSO (control); T= Diameter of the fungal colony in treatment.

RESULTS AND DISCUSSIONS

The new Schiff base ligand H₂L has been synthesized and characterized successfully. Different metal complexes were prepared successfully by reacting metal ions salts Ni (II), Cu (II), Zn (II) and Cd (II) with the new ligand. All the physical data of the prepared ligand and its metal complexes are shown in Table 1. The complexes prepared are stable at room temperature and are non- hygroscopic. The data from complexes correspond well with the general formula [ML]₂, where M = Ni (II), Cu (II), Zn (II) and Cd (II). The magnetic susceptibility of the complexes at room temperature was consistent with square-planar geometry around the central metal ion, except for the Zn (II) and Cd (II) complexes which show polymeric sulfur-bridged complexes.

Table 1: Color, % Yield and Melting Point Data for the Complexes of the Ligand H₂L

Compound	Color	%Yield	M.p. (°C)
[H ₂ L]	Yellow	60	171
[NiL] ₂	Dark brown	68	165
[CuL] ₂	Green	61	197
[ZnL] ₂	Yellow	60	173
[CdL] ₂	Yellow	66	169

Infra-Red Spectra

The main stretching frequencies of the IR spectra of the ligand and its complexes are tabulated in Table 2. The IR spectra of ligand and its complexes are found to be very similar to each other. Hence significant frequencies are selected by comparing the IR spectra of the ligand with its complexes.

The very strong and sharp band located at 1620 cm^{-1} due to the azomethine group of the ligand underwent a shift to lower frequency (by $20\text{-}30\text{ cm}^{-1}$) after complexation, indicating the coordination of azomethine nitrogen to metal ion and this can be explained by the donation of electrons from nitrogen to empty d-orbital of the metal ions [20]. The imino nitrogen is involved in complexation with the metal ion is clearly evident from the appearance of new medium intensity band at $560\text{-}545\text{ cm}^{-1}$, assignable to (M-N) in the spectra.

Table 2: Selected Characteristics IR Bands ($4000 - 500\text{ cm}^{-1}$) of Ligand and its Complexes

Compound	O-H	N-H	C-H Aromatic	C-H Aliphatic	C=N	C=S	CO	CSS	M-S	M-N	M-O
H ₂ L	3510	3300	3050	2970	1620	1580	1460	960	-	-	-
[NiL] ₂	-	-	3005	2975	1597	-	1490	980	690	560	460
[CuL] ₂	-	-	3015	2950	1595	-	1510	975	699	550	490
[ZnL] ₂	-	-	3010	2960	1595	-	1465	1010	695	545	465
[CdLi] ₂	-	-	3020	2960	1598	-	1470	965	696	550	470

A broad band is found at 3510 cm^{-1} in the spectra of the ligand due to the O-H of the phenol. Absence of the phenolic O-H vibration indicates that it is deprotonated in complexes. Shift of C-O stretch of phenol to higher wave number confirms that metal ions are bound to the phenolic oxygen [21]. The proposed coordination site is further supported by the appearance of medium band at $(460\text{-}490)\text{ cm}^{-1}$ which could be attributed to M-O bond.

The IR spectrum of the ligand does not show any peak at around 2570 cm^{-1} attributable to the S-H stretching mode [22] indicating that in the solid state it remains in the thioketo form. The spectrum of the Schiff base exhibits band at 1580 cm^{-1} may be attributed to stretching vibration of C=S group which confirm the thioketo form of the ligand.

Although the Schiff base remains in the thioketo tautomeric form, both in the solid state as well as in solution, like most of the other Schiff bases derived from S-alkyldithiocarbamic acid, it readily tautomerizes to the thioenol form in the presence of metal ions with the concomitant formation of metal complexes containing the thiolato form.

The band of C=S disappeared in spectra of the Schiff base complexes confirmed thiolato form in the complexes. The CSS band which is found in the ligand is split in the complexes. The splitting of the CSS mode in the complexes is in keeping with the assumption that bonding of the ligand occurs via one of the sulfur atoms which is confirmed from the appearance of new medium intensity band at $690\text{-}699\text{ cm}^{-1}$ assignable to (M-S) in the spectra.

Study of the Electronic Spectra

Electronic spectral studies of compounds were carried out in DMF solution ($1 \times 10^{-3}\text{ M}$). The ligand shows three bands in UV and visible region ($321, 284$ and 247 nm) which can be attributed to $(\pi \rightarrow \pi^*)$ transition for the aromatic system, $(\pi \rightarrow \pi^*)$ transition of imines group and $(n \rightarrow \pi^*)$ transition [23] which was shifted to a longer wavelength (red shift) upon formation of the complexes. All the complexes show two different bands in different positions. The first band is attributed to the charge transfer, while the second is returned to $(d-d^*)$ transitions [24]. The intensity of these bands in all complexes is consistent with square planar structure [25].

Study of the Magnetic Susceptibility and Conductivity

The magnetic moment value of the nickel (II) complex and copper (II) complex are 1.61 B.M. and 1.21 B.M. respectively, which are lower than 1.73 B.M. This indicates the formation of square planar geometry of the complexes [26]. Conductivity measurements show that the complexes are non-electrolytes. As ligand is doubly deprotonated tridentate ligand so when metals are bonded to the ligand the complexes might possess a three- coordinate geometry.

As three coordinate nickel (II) and copper (II) complexes are highly unlike, so the compounds must dimerize in order to achieve a four coordinate square-planar geometry. The molar conductance values of zinc (II) and cadmium (II) complexes indicate that both complexes are non-electrolytes. Due to their d^{10} electronic configurations, both complexes are inherently diamagnetic and their electronic spectra do not show any d-d transition bands.

The bands observed in their electronic spectra are due to their ligand transitions, since these bands are also observed in the electronic spectrum of the ligand and in addition to the ligand bands, these complexes also display charge transfer bands at 409-400 nm attributable to $S \rightarrow M^II$.

The stoichiometric composition of $[ML]$ suggests a three coordinate geometry for these complexes. However, such three coordinate zinc (II) and cadmium (II) complexes are not found in the literature and therefore, the only possible structure that can be envisaged for these complexes is a mercaptide sulfur-bridged dimeric or a polymeric structure. The very low solubility of these complexes in most of the non-donor organic solvents suggests that a polymeric geometry is most likely.

Table 3: Magnetic Moment, Molar Conductance and Electronic Spectra of the Schiff Base Ligand and its Complexes

Compound	μ_{eff} (B.M.) at ca. 303 °K	Λ (ohm ⁻¹ cm ² mol ⁻¹) (State DMF)	λ_{max} (nm) (DMF)
[H ₂ L]	-	-	247, 284, 321
[NiL] ₂	1.61	1	300,400, 309
[CuL] ₂	1.21	1	350,428,575
[ZnL] ₂	Dia	5	309,364,400
[CdL] ₂	Dia	8	350, 409, 612

Antimicrobial Activity

The investigations included 4 strains of bacteria and 4 strains of fungi. Minimum inhibitory concentration (MIC) of Schiff base metal complex required to inhibit the growth of bacteria and fungi was determined. The derivatives tested exhibited differential activity against bacteria and fungi. The results were given in table no 4 and 5.

The results of the antibacterial activity of the compounds compared with standard drug (Ampicillin) have indicated that compounds were active but activity was lesser than the standard drug except cadmium complex. Cadmium complex showed equipotent against *Bacillus cereus*. Comparative studies of the ligand and their metal complexes indicated that metal complexes exhibits higher antibacterial activities than the free ligand.

The higher activity of metal complexes compare to free ligand can be explained on the basis of Overtone's concept [27] and chelation theory [28].

Table 4: Antibacterial Activities of the Ligand and its Metal Complexes

Compounds	Diameter of Zone of Inhibition in mm (100mg dw/disc)			
	<i>S. dysenteriae</i>	<i>S. typhi</i>	<i>B. cereus</i>	<i>S. aureus</i>
H ₂ L	-	-	8	-
[NiL] ₂	10	7	10.5	9.5
[CuL] ₂	9	13	8	10
[ZnL] ₂	-	12	-	11
[CdL] ₂	-	-	20	9
Ampicillin	30	24	20	20

N.B:- ‘(-)’ means no inhibition; dw: denotes dry weight

If the inhibition activity of the newly prepared Ni (II), Cu (II), Zn (II) and Cd (II) complexes of the Schiff base ligand are compared, it is observed that an individual complex has a superior inhibition action over a particular fungus. When compared with the Nystatin, which is clinically useful therapeutic agent, the copper complex are almost effective as Nystatin on all the fungi.

Table 5: Antifungal Activities of the Ligand and its Ni (II), Cu (II) and Zn (II) Complexes

Sample	% Inhibition of Mycelia Growth in Presence of Test Organism			
	<i>Botrydipodia theobromae</i>	<i>Macrophomina phaseolina</i>	<i>Alternaria alternate</i>	<i>Fusarium equiseti</i>
Ligand L	3.3	7	4.2	4.4
[NiL] ₂	20	29	17.1	11.7
[CuL] ₂	65*	70*	42*	35*
[ZnL] ₂	21	10.7	14*	16
[CdL] ₂	4	27	8.5	8.8
Nystatin (100µg dw./disc)	70	71	51	44

N.B:- ‘*’ means good inhibition; dw: denote dry weight

CONCLUSIONS

The Schiff base formed by condensation of 2-hydroxybenzophenone with S-benzylthiocarbamate, abbreviated in this chapter as (H₂L) readily reacts with nickel (II), copper (II), zinc (II), and cadmium (II) acetate salts yielding intensely colored complexes, which on the basis of analysis, can be formulated as [NiL]₂, [CuL]₂, [ZnL]₂, and [CdL]₂ respectively. The ligand behaves a dinegatively charged ONS tridentate chelating agent forming oxygen-bridged dimeric nickel (II) and copper (II) complexes but polymeric sulfur-bridged complexes were found for Zn (II) and Cd (II) complexes.

The antimicrobial studies suggested that the Schiff base was found to be biologically active and their metal complexes showed significantly enhanced antimicrobial and antifungal activity against microbial strains in comparison to the free ligand. Thus, exhibiting their broad spectrum nature can be further used in pharmaceutical industry for mankind, as an antimicrobial agent, after testing its toxicity to human beings.

ACKNOWLEDGMENTS

Financial support by the Department of Chemistry, University of Chittagong is gratefully acknowledged. I am also grateful to Dr. Nazimuddin and Dr. M. Akbar Ali for their valuable advice and unfailing suggestion during the entire course of this research work.

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