

Synthesis and Characterization of Copper Complexes with Schiff base Macrocyclic Ligands

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ABSTRACT

A series of novel multidentate copper (II) complexes with macrocyclic Schiff base ligands of the type $[Cu(L^{1-3})Cl_2]$ have been synthesized by metal ion catalyzed macrocyclization of vicinal diketones and vicinal diamines. The multinuclear macrocyclic based complexes were synthesized from the reaction of the corresponding metal chloride with the ligand. The modes of bonding and over all geometry of the complexes were determined through physicochemical, magnetic moment, molar conductance and spectroscopic methods. Present study revealed tetrahedral geometry about Cu atom. However, square planar geometries have also been suggested for Cu(II) complexes. Biological activity of the ligand and its metal complexes were studied. Results obtained indicate that all the complexes are soluble in organic solvents and stable to atmosphere.

Keywords: *Macrocyclization, Physicochemical properties, Tetrahedral geometry, Multinuclear complexes.*

INTRODUCTION

Macrocyclic compounds have attracted increasing interest owing to their mixed soft-hard donor character, versatile coordination behaviour and in the understanding of molecular processes.¹⁻² Macrocyclic metal complexes are of significant attention in terms of structural and coordination chemistry. The study of metal complexes of macrocyclic ligands appears to be fascinating in view of the possibility of obtaining coordination compounds of unusual structure and stability. Now a days it has become the subject of extensive research due to their potential applications in building block of macrocyclic-based chemistry,³ biomedical and environmental chemistry as well. The chemistry of Schiff-base macrocyclic compound is an important field in coordination chemistry⁴. This is due to their ability to react with a range of metal ions forming stable complexes which have applications in different fields⁵. Schiff base macrocyclic complexes are considered to be among the most important stereo chemical models in main group and transition metal coordination chemistry due to their preparative accessibility and structural variety. Study of the interaction between drugs and transition metals is an important and active research area in bioinorganic chemistry. It is well known that the action of many drugs is dependent on the coordination with metal ions.

In addition, the well-established coordination chemistry of copper allows for its reaction with a wide variety of chelator systems that can potentially be linked to antibodies, proteins, peptides and other biologically relevant small molecules. The aqueous solution coordination chemistry of copper is limited to its three accessible oxidation states (I-III).⁶ The lowest oxidation state, Cu (I) has a diamagnetic d^{10} configuration and forms complexes without any crystal-field stabilization energy. Complexes of this type are readily prepared using relatively soft polarizable ligands. Cu (I) complexes are typically not used for *in vivo* imaging due to their lability. Copper (II) is a d^9 metal of borderline softness which favors amines, imines, and bidentate ligands. A third oxidation state Cu (III) is relatively rare and

difficult to attain without the use of strong π -donating ligands.

A large number of Schiff bases and their complexes have been studied for their interesting and important properties, like the ability to reversibly bind oxygen, catalytic activity in the hydrogenation of olefins and transfer of an amino group, photochromic properties and complexing ability toward some toxic metals. The high affinity for the chelation of the Schiff bases toward the transition metal ions is utilized in preparing their solid complexes. Complexes based on Schiff-base ligands play important roles in biomedical,⁷⁻⁸ biomimetic, and catalytic systems and in supporting liquid crystalline phases.⁹

Schiff bases are potential anticancer drugs and, when administered as their metal complexes, the anticancer activity of these complexes is enhanced in comparison to the free ligand. Some biologically active Schiff base ligands like hydrazine-pyrrole-2-carboxaldehyde, hydrazine-furan-2-carboxaldehyde and hydrazine-thiophene-2-carboxaldehyde and their phenyl derivatives and their Co(II), Cu(II) and Ni(II) mixed complexes have been synthesized and characterized.

A number of Schiff-base complexes have been used as oxygen carriers to mimic complicated biological systems.¹⁰ Furthermore, metal complexes of chromium, manganese, nickel, copper, zinc, and ruthenium with a wide variety of Schiff-bases are active oxidants for stoichiometric conversion and have been used as catalysts for carbonylation, hydrogenation, hydroformylation, and epoxidation reactions. It is to explore the use of multidentate Schiff-base ligands for the building blocks of macrocyclic compounds. We describe here the formation of macrocyclic species of some phenoxo-bridged tetranuclear transition metal ions with the new macrocyclic Schiff-base. The ligand was derived via a template approach in which ethylenediamine parts facilitated the linkage of the two units.

Candidiasis, a fungal disease caused by a diploid opportunistic fungal pathogen *Candida* proves to be life threatening mycoses fatal for immuno compromised patients, e.g. AIDS and transplantation surgery. A number of antifungal agents are available for the treatment of Candidal infections. Majority of them are polyenes such as Amphotericin B and Nystatin or the azoles, such as Itraconazoles and Fluconazole. Presently, use of standard antifungal therapies is scarce due to the high toxicity, low efficacy rates, and drug resistance. Recent studies indicated *c.-albicans* resistance to azoles or hepatotoxicity and nephrotoxicity linked to polyene use, particularly amphotericin B. Therefore, present study was conducted to synthesize some macrocyclic tetradentate ligand of copper complexes and screen them for their properties.

MATERIALS AND METHODS

Organic reagents and solvents purchased from Sigma Aldrich, Merck and Loba Chemie were used without further purification. Melting point determination was performed by using a Mel-temp. instrument. Elemental analyses were performed on Heraeus Vario EL (III) analyzer at the C.D.R.I; Lucknow. The results were within $\pm 0.4\%$ of the theoretical values. Electronic spectra were recorded on a Shimadzu UV 1601 PC UV-Visible spectrophotometer. IR spectra were recorded on Perkin-Elmer model 1600 FT-IR RX1 spectrophotometer as KBr discs. Magnetic susceptibility measurements were carried out from a microanalysis laboratory by Gouy method at room temperature.

Synthesis of Ligand:

25ml of ethanolic solution glacial acetic acid with 25 ml of hot ethanolic solution of ethylene diamine (0.05 mol) were mixed slowly with constant stirring. This mixture was refluxed at 60–70°C for 6-7 hrs with few drops of concentrated hydrochloric acid. On keeping

it overnight at 0°C a blue precipitate was formed, which was filtered, washed with ethanol and dried in vacuum over P₄O₁₀ and recrystallized from methanol. Yield: 77%; mp > 300°C; IR (KBr) cm⁻¹ : 3448 (O–H), 3198(N–H), 3016 (C–H), 1620 (C=O), 1414 (C–N), 1066, 886, 776; ¹H NMR (300 MHz, d ppm from TMS in DMSO_{d6}, 300 k): d 11.70–12.60 (4H, Br N–H), d 4.22–4.37 (s, 4H, C–H), d 2.90–3.05 (s, 8H, C–H₂); ¹³C NMR (CDCl₃) (d, ppm): 173.5 (C=O), 38.08 (4CH₂); ESI MS (m/z) 345 [M]⁺, 345 [M⁺]⁺; Elem. Anal. Calcd. C = 40.62%, H = 5.64%, N = 15.79%, Cl = 20.02%; found C = 41.02%, H = 5.69 %, N = 16.94%, Cl = 20.22%.

Synthesis of Complexes:

Copper(II) complexes with 12-membered macrocyclic Schiff base ligands can be synthesized and measurements of their physical properties can be estimated by established methods. The constituent parts of each compound have been estimated by established analytical methods, such as copper by iodometry, halides as their respective silver halides and carbon, hydrogen and nitrogen by semimicro combustions methods.

A series of copper(II) complexes with macrocyclic schiff base ligands of the type [Cu(L¹⁻³)Cl₂] have been synthesized by metal ion catalyzed macrocyclization of vicinal diketones and vicinal diamines.

Ethanol solutions of biacetyl (0.01 mol) and ethylenediamine (0.01 mol) were mixed and refluxed with CuCl₂·2H₂O (0.005 mole) for an hour when blue crystals of complexes were obtained. It was filtered, washed with suitable solvent dried and analyzed.

RESULT AND DISCUSSION

A series of macrocyclic Cu (II) complexes were synthesized by treating CuCl₂·2H₂O with three macrocyclic Schiff base ligands. All the complexes are stable to the atmosphere. The complexes are soluble in chloroform, DMSO, DMF and aqueous methanol. The elemental analyses (Table-1) are consistent with the proposed structure of the complexes. The low molar conductance values of the complexes in DMF at room temperature (16.2, 14.0 and 13.5 ohm⁻¹·cm²·mol⁻¹) confirm their non-electrolytic nature.

Table-1
Physical, analytical and electronic spectral data of macrocyclic Cu(II) complexes.

Comp. No.	Cu(II) Compound/ Molecular Formula	Λ _M	μ _{eff} (B.M.)	λ _{max} (cm ⁻¹)	Analyses (%) Found / (Calculated)				
					N	C	H	Cl	Cu
1.1	[Cu(L ¹)Cl ₂]	16.2	1.96	16008, 21226	16.94 (15.79)	41.02 (40.62)	5.69 (5.64)	20.22 (20.02)	18.08 (17.91)
1.2	[Cu(L ²)Cl ₂]·2H ₂ O	14.0	1.98	17348, 22801	12.66 (12.54)	54.26 (53.73)	3.61 (3.58)	16.05 (15.90)	14.36 (14.22)
1.3	[Cu(L ³)Cl ₂]	13.5	1.96	17857, 21988	9.38 (9.29)	64.36 (63.73)	4.68 (4.64)	11.89 (11.78)	10.63 (10.53)

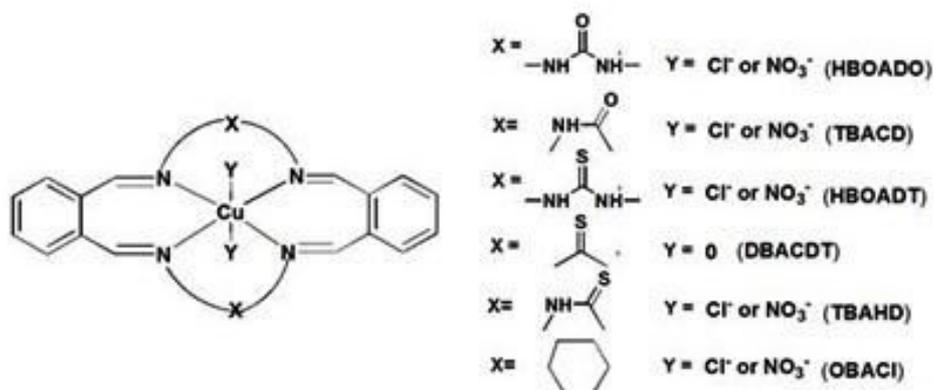
Infrared Spectral Data

In the IR spectra of macrocyclic Cu(II) complexes, a medium intensity band due to ν(C=N) was shifted towards lower side about 20–33 cm⁻¹ compared to the ligand spectra and was appeared in the range of 1598–1573 cm⁻¹. The appearance of a lower intensity band in the region of 524–505 cm⁻¹ corresponds to the ν(M–N) vibration supports the fact that the ligands coordinate to the metal ions through the nitrogen of C=N group in all the complexes.¹¹ A band present in the range of 318–302 cm⁻¹ in the spectra of 1.1, 1.2 and 1.3 complexes indicating the presence of two chlorides in trans position around copper center.¹² The presence of chloride ions in 1.1, 1.2 and 1.3 complexes are detected by the addition of

silver nitrate reagent leading to the formation of white precipitate. The additional bands observed around ~ 1410 , 1300 and 1020 cm^{-1} were obtained in the spectra of the nitrate complexes¹³, which are consistent with the monodentate nature of the nitrate group¹⁴. The macrocyclic Cu(II) compounds 1.2 contain a broad band in the region $3505\text{--}3374\text{ cm}^{-1}$ due to the presence of lattice water molecules.¹⁵

On the basis of physico-chemical and spectral studies the tentative structures proposed for the complexes are shown in Scheme-1.

Scheme 1. Representative structures of copper complex.



CONCLUSION

Present programme is able to synthesize a new series of macrocyclic tetradentate nitrogen donor (N_4) ligand 6,7,14,15-tetrahydroxy-1,4,9,12-tetraazacyclohexadecane-5,8,13,16-tetrone based transition metal complexes of the type $[M(L^{1-3})Cl_2]$ where $M = Cu(II)$ and screened them for their anticandidal property. Antimicrobial results showed that metal complexes have high killing activity compared to the ligand. A whole line of current antifungals target ergosterol biosynthesis pathway or its end product which is unique to fungi. The macrocyclic molecules can be used as antibacterial, antidiabetic, antitumor, antiproliferative and anticancer.

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Sinha and Yadav

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