

A Review on Biological Studies of Metal Complexes of Macrocyclic Schiff Base Ligands

Archana Singh, Suman Malik and Sheeraz Ahmad Teli

Department of Chemistry, Sadhu Vaswani Autonomous College, Sant Hirdaram Nagar (Bairagarh),
Bhopal-462030 (M.P.) India

Abstract - During the past few years there has been a great deal of activity in the field of macrocyclic Schiff base metal complexes. It has been recognized that many complexes containing synthetic macrocyclic ligands may serve as models for biologically important species. Macrocyclic Schiff bases have been of great importance in chemistry because they can selectively coordinate with certain metal ions and form rearranged complexes. The formation of polynuclear metal complexes was only considered highlighting the key role played by the phenoxide oxygen atom in binding two metal centres in a bridge disposition. This arrangement allows two metal ions to stay close to each other and consequently these binuclear centres are able to mimic many biological sites, especially those where the two metals can cooperate to form an active centre. The metal complexes of macrocyclic Schiff base ligands display a broad spectrum of biological activities like antibacterial, antifungal activity etc. with Schiff base ligands since it contain a metabolised (HC=N) biocidal unit.

Keywords- Macrocyclic Schiff base, metal complexes, active centres, biological activities, biocidal unit.

I. INTRODUCTION

Over the past few years macrocyclic Schiff base ligands have received vital attention not only because of their pharmacological properties [1,2], soft-hard donor character and coordination behavior [3,4] but also for their capacity for chemical recognition of anions and metals of biochemical and environmental importance [5,6]. Macrocyclic Schiff base ligands showed good extraction abilities for the removal of different metal ions [7,8]. The precise molecular

recognition between macrocyclic ligands and their guest provides a good opportunity for studying key aspects of supramolecular chemistry, which are also significant in a variety of disciplines including chemistry, biology, physics, medicine and related science and technology [9]. The recent growing interest in the electrochemistry (reduction and oxidation process) of macrocyclic complexes derived from recognition of biological importance of the less common oxidation states of Cu and Ni [10, 11]. Redox potentials of Cu(II)/Cu(I) depends on the relative thermodynamic stabilities of the two oxidation states in a given ligand environment. The biological activities [12-14] of the metal complexes may be associated to the redox properties of these complexes

II. BIOLOGICAL STUDIES

The increase in the mortality rate associated with infectious diseases is directly related to bacteria that exhibit multiple resistances to antibiotics. The lack of effective treatments is the main cause of this problem. The development of new antibacterial agents with novel and more efficient mechanisms of action is definitely an urgent medical need. Schiff bases have been pointed to as promising antibacterial and antifungal agents.

A new type of macrocyclic ligand, 1,4,7,10-tetrakisbenzyl 1-1,4,7,10 tetraazacyclododecane with four neutral pendent groups at N residuals and its Co(II), Ni(II) and Cu(II) complexes have been synthesized and characterized by Kong *et al.* [15].

These complexes show high antitumor activity. Schiff base macrocyclic ligands derived from thiosemicarbazides are of significant interest for their pharmacological properties as antibacterial, anticancer, antiviral and antifungal agents [16-18]. Natarajan Raman et al. [19] have reported the synthesis of a novel 14-membered *macrocyclic* Schiff base derived from 3-cinnamalideneacetanalide and *o*-phenylenediamine which acts as a tetradentate and strongly conjugated ligand to form a cationic solid complex with Cu(II), Ni(II), Co(II) and Zn(II). The ligand and the complexes were characterized by the usual spectral and analytical techniques. The antimicrobial tests were also recorded and gave good results in the presence of metal ions in the ligand system. Sing *et al.* [20] synthesized a novel series of complexes of the type $[M(C_{28}H_{24}N_4)X]X_2$, where M = Cr(III), Fe(III), and Mn(III), X = Cl⁻, NO₃⁻, OAc⁻ and (C₂₈H₂₄N₄) corresponds to the tetradentate macrocyclic ligand, by condensation of 1,8-diaminonaphthalene and 2,3-butanedione(diacetyl) in the presence of metal salts. All the complexes were tested for their *in vitro* antifungal activity against some fungal strains. The results obtained were compared with the standard antifungal drug which revealed that the complexes exhibit moderate activity. Sharma *et al.* [21] synthesized tetraaza macrocyclic complexes of transition metals of Ni(II), Cu(II), Cr(III), Fe(III), and Mn(II) in methanolic media by template method. *In vitro* antibacterial activity of these macrocyclic complexes against five pathogenic bacterial strains were tested to assess their inhibiting activities and compared with standard drug. Sellappan and coworkers synthesised the new macrocyclic Schiff base ligands by the condensation reaction between 9,10-phenanthrenequinone and *o*-phenylenediamine. The ligands react with vanadylsulphate to form metal complex. Further the complexes have been subjected to antimicrobial activity and it was concluded that the complex show antibacterial activity [22]. New complexes of 12-membered macrocyclic Schiff base ligand containing thiosemicarbazone moiety have been prepared by Kumar *et al.* with general composition [MLX₂] where M = Mn(II) and Cu(II), L = 3,4,9,10-tetra-2-furanyl-1,2,5,6,8,11-hexaaza cyclo-dodeca-7,12-dithione-2,4,8,10-tetraene, X = Cl⁻, NO₃⁻ and NCS. All the examined complexes have also been tested *in vitro* against a number of pathogenic fungi. Results indicated that the complexes exhibited good antifungal activities [23]. Tyagi et al. [25] synthesized Co(II), Ni(II), and Cu(II) complexes with a tetradentate macrocyclic ligand, 6,15-dimethyl 8,17-diphenyl-7,16-dihydrodibenzo[b,i][1.4.8.11] tetraazacyclo tetradecine. The ligand and its complexes showed fungicidal. Kumar and coworkers [26]

prepared new Co(II) and Ni(II) complexes of 12 membered macrocyclic Schiff base ligand containing thiosemicarbazone moiety as a part of ring having general composition [MLX₂] where M=Co(II), and Ni(II), L=3,4,9,10-tetra-2-furanyl-1,2,5,6,8,11-hexaazacyclododeca-7,12-dithione-2,4,8,10-tetraene, X = Cl⁻, NO₃⁻, NCS. The antifungal activities of complexes have been studied against a number of pathogenic fungi. The complexes showed good antifungal results. Pawar *et al.* [26] synthesized macrocyclic Schiff bases by the condensation of acetyl acetone with semicarbazide hydrochloride and thiosemicarbazide in presence of methanol. Further, their oxovanadium complexes have been synthesized by using vanadium acetylacetone. The structural assignment of these compounds has been made on the basis of various spectral techniques. The synthesized compounds were screened for their *in vitro* growth inhibiting activity against different strains of bacteria viz., *S. aureus*, *B. licheniformis*, *E. coli* and *M. luteus* and were compared with the standard antibiotic ofloxacin. Also *in-vitro* antioxidant activity of all compounds was determined by nitric acid free radical scavenging assay. Ahmad *et al.* [27] synthesised a new mixed thia-aza-oxo macrocyclic schiff base viz., 1,10-dithia-3,8,12,17-tetraoxo-4,7,13,16tetraazacyclooctadecane with a series of transition metals Cu(II), Co(II), Ni(II) and Mn(II) by the [2+2] condensation of thiodiglycolic acid and ethylenediamine. Different spectral techniques were used for their analysis. The redox behaviour was investigated by cyclic voltammetry and show metal centered reduction process for all complexes. The complexes of Cu(II) show both oxidation and reduction process. These metal complexes were also tested for their *in vitro* antimicrobial activities against some bacterial and fungal strains to assess their inhibiting potential and the activities shown by these complexes were compared with standard drugs.

Riyadh *et al.* [28] reported the synthesis of a new macrocyclic multidentate Schiff-base ligand Na₄L by condensation reaction of sodium 2, 4, 6-triformyl phenolate with ethylenediamine in mole ratios of 2:3 and its tetranuclear metal complexes with Mn(II), Co(II), Ni(II), Cu(II), and Zn(II). Na₄L was prepared via a template approach. The tetranuclear macrocyclic-based complexes were prepared from the reaction of the corresponding metal chloride with the ligand. The physicochemical and spectroscopic studies revealed tetrahedral geometries about Mn, Co, and Zn atoms. However, square planar geometries have been suggested for Ni(II) and Cu(II) complexes. Biological activity of the ligand and its metal complexes against Gram positive bacterial

strain *S.aureus* and Gram negative bacteria *E. coli* revealed that the metal complexes become more potentially resistive to the microbial activities as compared to the free ligand. However these metal complexes don't exhibit any effects on the activity of *P. aeruginosa* bacteria. Eissa [29] reported the synthesis of three new Macrocyclic Hydrazone Schiff bases by condensation of intermediate compounds: 1,6- bis (2-formylphenyl) hexane and glutaraldehyde with both dihydrazide of isophthalic acid and dihydrazide of terephthalic acid). Different spectral techniques were used for their analysis. The new Macrocyclic Hydrazone Schiff bases were tested for antibacterial activities against Gram positive (*B. subtilis* and *S. aureus*) and Gram negative (*S. typhi* and *E. coli*). The compound ligands exhibited a variable activity of inhibition on the growth of the bacteria. Singh *et al.* [30] reported the synthesis of novel macrocyclic Schiff's base ligand 1,4-bis(2-formylphenoxy)butane. The metal complexes of ligand with Mn(II), and Co(II) have been prepared by the condensation of 1,4-bis(2formylphenoxy)butane and thiourea in the presence of divalent metal salts in 1:1:1 ratio. All metal complexes were characterized by elemental analyses, molar conductance, magnetic moment measurements and spectral (UV-Vis, IR, and ESR) studies. The macrocyclic ligand acted as tetradentate ligand and coordinate with metal ions through nitrogen and oxygen atoms. The magnetic moments and electronic spectral data suggested octahedral geometry for the Mn(II) and Co(II) complexes. The ligand and metal chelates were screened *in-vitro* for antibacterial and antifungal activity. Metal complexes were studied for antimicrobial activity including antibacterial, and antifungal. Among all Co(II) complexes showed good results.

Gull *et al.* [31] have synthesized macrocyclic Schiff base ligand ($C_{26}H_{28}N_8O_4$) from 1,4-dicarbonylphenyl-dihydrazide and pentane-2,4-dione (2:2) and complex of type $[M(C_{26}H_{28}N_8O_4)X]$ where $M=(Co(II), Cu(II) \text{ and } Ni(II))$ and $X=Cl^-$. The compounds were characterized by the analytical and spectroscopic methods. The ligand behaves as a tetradentate ligand and coordinates to the metal ions via the nitrogen atoms and the complexes have the mononuclear structures. The antimicrobial activities of the ligand and its complexes, as growth inhibiting agents, have been screened *in vitro* against different species of bacteria and fungi and the results concluded that the metal complexes are effective drugs against the tested strains as compared to the macrocyclic ligand.

III. CONCLUSION

The macrocyclic Schiff base metal complexes have been investigated as potential biological agents in long history of medical application. Up to now, a great variety of these complexes containing hetero atoms represent good antimicrobial activity. However, the biological activity of these Schiff base metal complexes deserves further investigation for better result in research field. Although the research on this subject is incipient, a number of reports disclosing the effects of the Schiff bases on the pathogens of clinical interest have recently been increasing. Schiff base compounds have been shown to be promising leads for the design of more efficient biologically active metal complexes.

REFERENCES

- [1] W. Min, W. Liu-Fang, L. Yi-Zhi, L. Qin-Xi, X. Zhi-Dong, Q.Dong-Ming. *Trans Metal Chem.* 2001; 26(3):307-310.
- [2] MA. Abdullah, AK. Salman. *Molecules.* 2010; 15(10):6850-6858.
- [3] M. Maji, S. Ghosh, S K. Chattopadhyay, Wu BM, Mak TCW. *J. Chem. Soc., Dalton Trans.* 1999; 135-140.
- [4] P. Sengupta, R. Dinda, S. Ghosh, WS. Sheldrick. *Polyhedron.* 2003; 22(3):447-453.
- [5] B. Priyanka, PP. Om, KS. Soumitra. *Appl Organometallic Chem.* 2009; 23(1):19–23.
- [6] KD. Dimitra, K. Nikolaos, AD. Mavroudis, RM. John, SF. Christopher, KS. John, XW. Douglas. *Eur J of Inorg Chem.* 2000; 2000(4):727-734.
- [7] K. Souad, A. Nadeem, K.Farouk. *Jordan J of Chem.* 2012; 7(1):73-80.
- [8] K. Farouk, KC. Mohamad, Z.ALWail . *ISRN Org Chem.* 2012; Article ID 208284.
- [9] E. Labisbal, A. Sousa, A. Castineiras, A. Gracia-Vazquez, J. Romero, D.X. West, *Polyhedron,* 2000; 19, 1255.
- [10] J.A. Streeky, D.G. Pillsburg, D.H. Busch, *Inorg. Chem.* 1980; 19, 3148.
- [11] A.A. Isse, A. Gennaro, E. Vianello, *J. Chem. Soc., Dalton Trans.* 1993; 2091.
- [12] D.X. West, E. Liberta, S.B. Padhye, R.C. Chikate, P.B. Sonawane, A.S. Kumbar, R.S. Yeranda, *Coord. Chem. Rev.* 1993; 123, 49.
- [13] Y. Haiduc, A. Silvestru, *Coord. Chem. Rev.* 1990; 99, 253.
- [14] M.A. Malik, S.A. Al-Thabaiti, M.A. Malik, *Int. J. Mol. Sci.* 2012; 13, 10880.
- [15] D. Kong, L. Meng, Lin Sang and YuyuanYie, *Trans. Met. Chem.* 1999; 24, 553. 11
- [16] L.D.S. Yadav and S. Singh, *Indian J. Chem.* 2001; 40B, 440.

- [17] M.K. Srivastava, B. Mishra and M. Nizamuddin, Indian J. Chem. 2001; 40 B, 342.
- [18] M. Wang, L.F. Wang, Y.Z. Li, Q.X.Li, Z.D. Xuand, D.M. Qu, Trans. Met. Chem. 2001; 26, 307.
- [19] N. Raman and C. Thangaraja, Transition Metal Chemistry. 2005; 30, 317.
- [20] DP. Singh and K. Kumar. Chem. Soc., 2010; 75 (4): 475-482.
- [21] R. Sharma, Prabhat, R. Singh, S. Pawar and A. Chauhan. J. Am. Sci., 2010; 6(9):559-564.
- [22] R. Sellappan, S. Prasad, P. Jayaseelan and R. Rajavel. Rasayan J Chem., 2010; 3:556-562.
- [23] U. Kumar and S.J. Chandra. Nepal Chem. Soc., 2010; 25: 46-52.
- [24] S. Chandra, M. Tyagi and S.J. Agarawal. Serb. Chem. Soc., 2010; 75(7): 935-941.
- [25] U. Kumar and S.E.J. Chandra. Chem. Soc., 2010; 7(4): 1238-1245.
- [26] V. Pawar, S. Joshi & V. Uma. Biokemistri Nigerian Society for Experimental Biology 2011 Vol. 23.
- [27] R. Ahmad Shiekh, I. Ab.Rahman, M. Ahmad Malik, N. Luddin S. Malik Masudi, S. Ahme Al-Thabaiti Int. J. Electrochem. Sci. 2013; 8.
- [28] R.M. Ahmed, E. Yousif, A.Hasan and H. Mohamad J.Al-Jeboori; Hindawi Publishing Corporation The Scientific World Journal; 2013.
- [29] HH. Eissa Organic Chem Curr Res. 2013; 2:3 Volume 2, Issue 3 , pp. 2-8.
- [30] J. Singh, P. Jain, M. Tyagi. World Journal of Pharmacy & Pharmaceutical Sciences 2014; Volume 3, Issue 10, PP. 953 -964.
- [31] P. Gull and A. Adil Hashmi, J.Braz. Chem. Soc. 2015; Vol. 26, No. 7, pp 1331-1337.

Dr. Archana Singh

Assistant Professor
Department of Chemistry
Sadhu Vaswani Autonomous College
Sant Hirdaram Nagar (Bairagarh)
Bhopal-462030 (M.P.) India

Dr. Suman Malik

H.O.D. Chemistry
Sadhu Vaswani Autonomous College
Sant Hirdaram Nagar (Bairagarh)
Bhopal-462030 (M.P.) India

Sheeraz Ahmad Teli

Research Scholar
Department of Chemistry
Sadhu Vaswani Autonomous College
Sant Hirdaram Nagar (Bairagarh)
Bhopal-462030 (M.P.) India