



INTERNATIONAL JOURNAL OF NANO CORROSION SCIENCE AND ENGINEERING

Microwave Promoted Synthesis of Schiff Base Ligand Using Natural Acid Catalyst and its Nickel(II) and Copper(II) Complexes

N. Punitha*[a], M. Mangalam[b], K. Vijayalakshmi[c]
and C. Sebastian Antony Selvan[d]

[a],[b],[c] Assistant Professor, Dept. of Chemistry, Rajah Serfoji Govt. College, Thanjavur, Tamil Nadu.

[d] Assistant Professor, R. V. Govt. Arts College, Chengalpattu, Tamil Nadu.

ABSTRACT

Schiff base ligands and their metal complexes are very important in medicinal and pharmaceutical fields because of their broad spectrum of biological activities. Development of new chemotherapeutic Schiff bases and their metal complexes are now attracting the attention of biochemists. In the present study, the reaction of primary aromatic amine with aryl aldehyde was found to be catalyzed by sweet lemon (*Citrus limetta*) juice as natural acid under microwave radiation to give the corresponding Schiff base in good yield. This ligand was complexed with Nickel and Copper metal ions. The ligand and its complexes have been tested for their biological activities. The synthesized compounds were characterized by melting points, elemental analysis and spectroscopic methods. These eco-friendly reactions have many advantages like economical, environmental, mild reaction conditions and simple work-up with high product yield.

Keywords: Microwave radiation, Schiff base, Natural acid catalyst, biological activities.

INTRODUCTION

The development of a simple and effective eco-friendly approach as well as an economical process is in great demand in coordination chemistry^[1]. The microwave induced enhancement of organic reactions are currently a focus of attention for chemists due to the minimum reaction time, improved yields and easier work up as compared to conventional methods.^[2,3]

Int J Nano Corr Sci and Engg 2(6) (2015) 78-84

Second International Conference on Chemical and Environmental Research (ICCER 2015), 17th December 2015,
PG and Research Department Of Chemistry JAMAL MOHAMED COLLEGE (Autonomous), Tiruchirapalli, Tamilnadu, India

Editors: Dr S Rajendran, Dr M Mohamed Sihabudeen, Dr A Zahir Hussian

The problem of resistance to microbial activity is being addressed by medicinal chemists and various strategies have been devised and attempted in order to enhance the activity or broaden the spectrum of the drugs. It has been demonstrated that transition elements play a very important role in various medicinal compounds. The antibiotic Cefotaxime is the third generation cephalosporins which possess increased activity against bacteria than the first and second generation cephalosporins. Many drugs possess better pharmacological properties when they are in the form of metal complexes.^[4-8]

Schiff base complexes may serve as models for biologically important species and were investigated for antifungal, antiviral, antibacterial, antiinflammatory, anticonvulsant and anticancer activities^[9]. Due to these beneficial properties of Schiff base, concern for the environmental demands and strong interest in the development of green chemistry, new sustainable catalysts and new environmentally benign processes have been investigated which are both economically and technologically feasible^[10,11]. The present study involves eco-friendly and inexpensive sweet lemon (*Citrus limetta*) juice as natural acid catalyst for the synthesis of Salicylidene-Cefotaxime Schiff base.

EXPERIMENTAL

Materials

All chemicals and solvents which employed in the synthesis were of analytical grade obtained from Aldrich and Merck chemical companies and used without further purification. Melting points were determined in an open capillary tube using Elico instrument. UV-Visible absorption spectrum was recorded in Systronics 2202 spectrophotometer. The IR spectra were recorded on a Perkin Elmer 157 instrument in anhydrous KBr pellets in the range of 4000–400 cm^{-1} . The micro-elemental analysis was done in Vario-EL instrument. NMR spectra were recorded on a Bruker Advance DPX 300 MHz using CDCl_3 as a solvent and tetramethylsilane (TMS) as internal standard.

Preparation of natural acid catalyst

Sweet lemon fruit (*Citrus limetta*) was peeled off and pressed manually using fruit juicer to extract juice. Then the juice was filtered through muslin cloth and then through the filter paper to remove solid material and to get clear juice which was used as a catalyst^[12].

Microwave assisted synthesis of Salicylidene-Cefotaxime (Schiff base) using sweet lemon juice as natural acid catalyst

A solution of Cefotaxime sodium (1mmol in 40mL hot ethanol) and salicylaldehyde (1mmol in 10mL ethanol) was taken in a beaker. To this reaction mixture 0.5mL of natural acid catalyst i.e., sweet lemon juice was added and then kept for 2 minutes and then subjected to microwave radiation at an interval of 0.5 min at 400 W for about 5-6 minutes. The progress of the reaction was monitored by TLC. The resulting dark yellow precipitate was filtered off, washed with ethanol and dried under reduced pressure. The product was purified by recrystallization from the same solvent. (Melting point: 150–152°C).

Synthesis of the Metal Complexes

The metal complexes were prepared by the stoichiometric reaction of the corresponding metal chloride with Schiff base ligand in the molar ratio (M : L) of 1 : 2. Metal salt (1mmol in 15mL ethanol) was added to the ligand (2mmol in 20mL methanol) with continuous stirring. The obtained colored products were separated by filtration, washed with distilled water and methanol, and dried under vacuum. Recrystallization from hot methanol gave the metal complexes. Purity of the complexes was confirmed by TLC.

Antimicrobial study

The *in vitro* biological activity of the investigated Schiff base ligand and its metal complexes were tested against *Escherichia coli* and *Staphylococcus aureus* by disc diffusion method^[13-17] using nutrient agar as medium and Cefotaxime-Na as control. The minimum inhibitory concentrations were determined for the synthesized compounds.

RESULTS AND DISCUSSION

¹H and ¹³C NMR Spectra

The ¹H and ¹³C NMR spectrum of the Schiff base was performed and the spectral data were given in the Table-1. In the ¹H NMR spectrum of the ligand, the formation of Schiff base was supported by the presence of a singlet at $\delta = 8.7$ ppm corresponding to the azomethine proton ($-\text{N}=\text{CH}-$) and a peak at $\delta = 163.62$ ppm in the ¹³C NMR spectrum^[8].

Table 1: ¹H and ¹³C NMR spectral data of the ligand

Compound	¹ H NMR δ (ppm)	¹³ C NMR δ (ppm)
Schiff base (L) <chem>C23H20S2O8N5Na</chem>	2.10 (3H, S, COOCH_3); 4.72, 4.90 (2H, AB, $J = 12.2$ Hz, C_3-CH_2); 3.40, 3.67 (2H, AB, $J = 17.2$ Hz, C_2-H_2); 5.22 (1H, d, $J = 4.6$ Hz, C_5-H β -lactam); 5.79 (1H, d, $J = 4.6$ Hz, C_7-H β -lactam); 9.53 (1H, S, $-\text{NH}-\text{CO}$); 3.99 (3H, S, OCH_3); 6.73 (1H, s, thiazolyl- $\text{C}_{16}-\text{H}$); 8.7 (1H, S, $-\text{HC}=\text{N}$); 10.2 (1H, S, $-\text{OH}$); 7.5 (4H, m, -phenyl)	163.0; 143.4; 109.9 (C_{17} ; C_{15} ; C_{16} -thiazole ring); 168.39 (C_{13}); 169.3; (C_{12}); 58.12; 65.4; 171.4 (C_5 ; C_7 ; C_6 β -lactam); 139.5; 112.2; 26.2 (C_4 ; C_3 ; C_2); 58.3 (C_9); 163.9 (C_{10}); 21.6 (C_{11}); 165.0 (C_8); 62.7 (C_{14}); 163.62 ($-\text{HC}=\text{N}$); 157.82 (C_{20} phenyl); 132.24; 130.46; 121.25; 117.43; 112.87 (C_{19} , C_{21} , C_{22} , C_{23} , C_{24} phenyl)

Infrared Spectra

The IR data of the free Cefotaxime-Na, the Schiff base and its complexes were presented in Table-2. The broad absorption band at 2800 cm^{-1} shows the presence of $-\text{OH}$ group in the ligand molecule. The spectra of the complexes contain a broad band around $3530\text{--}3545\text{ cm}^{-1}$ attributed to $\gamma(\text{OH})$. Additionally, the coordinated water presents $\delta r(\text{H}_2\text{O})$ rocking at $857\text{--}863\text{ cm}^{-1}$ and $\delta w(\text{H}_2\text{O})$ wagging at $539\text{--}545\text{ cm}^{-1}$. The band at 1657 cm^{-1} attributed to $\gamma(\text{HC}=\text{N})$ from the Schiff base was shifted to lower values ($1620\text{--}1630\text{ cm}^{-1}$) in the complexes, which suggests that the Schiff base ligand is coordinated to the metallic ion by the N atom in the azomethine group. The absorption band at 2800 cm^{-1} proves the deprotonation of $-\text{OH}$ group.

The metal complexes were characterized by the appearance of some new bands at 510–520 cm^{-1} and 419–423 cm^{-1} , which are assigned to $\gamma(\text{M-O})$ and $\gamma(\text{M-N})$ stretching frequencies, respectively. Thus, the Schiff base ligand was bidentately coordinated to the metallic ions with N and O atoms from azomethine and phenolic groups.

Table 2: IR data (cm^{-1}) of the ligand and its complexes

Compound	$\gamma(\text{OH})$	$\gamma(\text{NH}_2)$	$\gamma(\text{OH})$ associate	$\gamma(\text{C=O})$ β -lact	$\gamma(\text{C=N})$ azm.	$\gamma(\text{C=O})$ amide $\gamma(\text{C=O})$ ester	$\gamma(\text{C-O})$ phenolic	$\delta r(\text{H}_2\text{O})$ $\delta w(\text{H}_2\text{O})$ coord.	$\gamma(\text{M-O})$ $\gamma(\text{M-N})$
Cefotaxime-Na	—	3442	—	1776	—	1640	—	—	—
Schiff base	—	—	2800	1770	1657	1645	1274	—	—
$[\text{NiL}_2(\text{H}_2\text{O})_2]$	3545	—	—	1770	1623	1640	1305	863 541	420 520
$[\text{CuL}_2(\text{H}_2\text{O})_2]$	3540	—	—	1770	1620	1645	1295	860 545	427 514

Electronic Spectral studies

In order to obtain information regarding the coordination geometry of the complexes, the electronic spectra was determined at room temperature in DMF. Absorption maxima from electronic spectra for Schiff base (L) and its complexes were given in Table 3. The electronic spectra of the ligand present two absorption bands at 38460 and 28570 cm^{-1} attributed to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions respectively, determined by the C=O and C=N groups. These absorption bands also appear in the electronic spectra of the complexes, but they are shifted to ~ 1500 – 5000 cm^{-1} lower values, which prove the coordination of the ligand to the central metallic ions. The electronic spectrum of Ni(II) complex presents three $d \rightarrow d$ absorption bands at 10120, 16630, and 24880 cm^{-1} in octahedral environment corresponding to ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{2g}(\text{F})(\gamma_1)$, ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}(\text{F})(\gamma_2)$, and ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{P})(\gamma_3)$ transitions. The magnetic moment value of Ni(II) complex was 3.12 B.M. which indicates the presence of two unpaired electrons on Ni(II) ion and suggesting this complex to have an octahedral geometry. The electronic spectrum of Cu(II) complex presents only one broad band with maximum centered at 14290 cm^{-1} typical for the Cu(II) ion in an elongated distorted octahedral (tetragonal) geometry. The magnetic moment value of Cu(II) complex was 1.86 B.M. which indicates the presence of one unpaired electron on Cu(II) ion in a d^9 system.

Table 3: Absorption maxima from electronic spectra

Compound	Absorption maxima (cm^{-1})	Assignments	μ_{eff} (B.M.)
----------	--	-------------	---------------------------

Schiff base	38460 28570	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$	—
$[\text{NiL}_2(\text{H}_2\text{O})_2]$	24880 (γ_3) 16630 (γ_2) 10120 (γ_1)	$^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{P})$ $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{F})$ $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{2g}(\text{F})$	3.12
$[\text{CuL}_2(\text{H}_2\text{O})_2]$	14290 (γ_1)	$dxy \rightarrow dx^2-y^2$	1.86

Analytical data

The analytical data of the ligand and its metal complexes were shown in the Table 4.

Table-4. Analytical data of the ligand and complexes

Composition of ligand/complexes	Yield (%)	Elemental analyses(%):found (calcd)			
		C	H	N	M
Schiff base $\text{C}_{23}\text{H}_{20}\text{S}_2\text{O}_8\text{N}_5\text{Na}$	90-92	47.35 (47.50)	3.41 (3.44)	12.00 (12.04)	--
$[\text{NiL}_2(\text{H}_2\text{O})_2]$ $\text{NiC}_{46}\text{H}_{42}\text{S}_4\text{O}_{18}\text{N}_{10}\text{Na}_2$	89-91	43.89 (43.99)	3.33 (3.34)	12.13 (11.15)	4.58 (4.68)
$[\text{CuL}_2(\text{H}_2\text{O})_2]$ $\text{CuC}_{46}\text{H}_{42}\text{S}_4\text{O}_{18}\text{N}_{10}\text{Na}_2$	88-90	43.80 (43.82)	3.32 (3.33)	11.10 (11.12)	5.03 (5.04)

Antibacterial Activity

The difference in anti-bacterial activities of the parent drug, ligand and metal complexes were studied and the results are presented in Table-5. The cursory view of the data indicates the following trend in antibacterial activity of the substances against *Escherichia coli* and *Staphylococcus aureus*.

$\text{Cu(II)-complex} > \text{Ni(II)-complex} > \text{Schiff base ligand} > \text{parent drug}$

Table 5: Minimum Inhibitory Concentrations

Compound	MIC ($\mu\text{g mL}^{-1}$)	
	<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>
L	0.5	1
$[\text{NiL}_2(\text{H}_2\text{O})_2]$	0.45	0.25
$[\text{CuL}_2(\text{H}_2\text{O})_2]$	0.033	0.125
Cefotaxime-Na	1	1.5

On the basis of the above data, the proposed structures for the Schiff base and its complexes where shown in Figure 1 and 2.

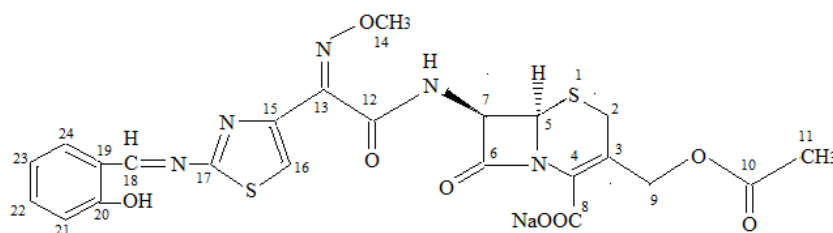
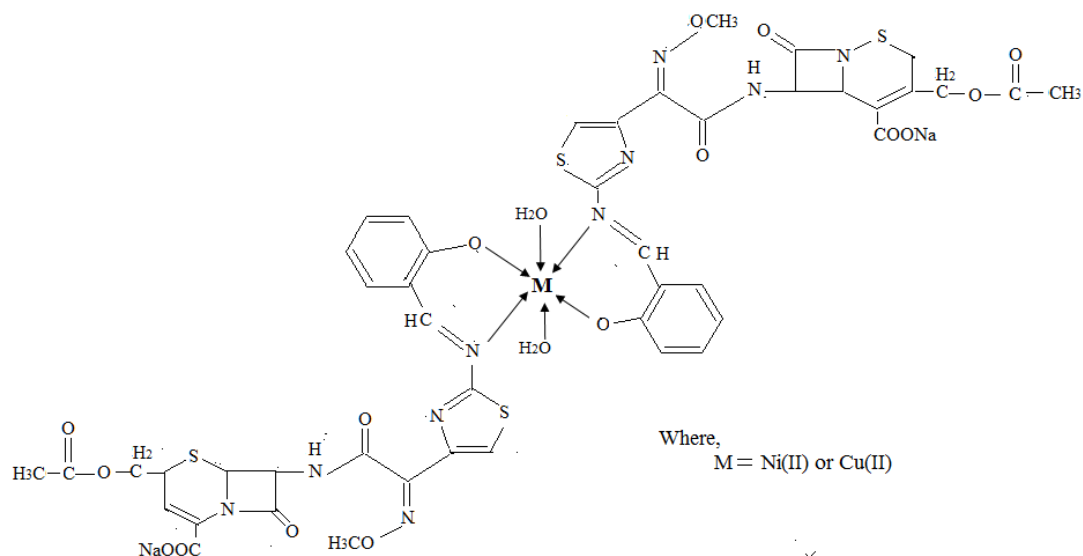


Figure -1 : Structure of Schiff base**Figure – 2 : Proposed structure of Metal(II) Complexes**

CONCLUSION

Microwave induced and natural acid catalyzed organic reaction enhancement is a simple, clean, fast, efficient and economical method for the synthesis of Schiff base and its complexes have emerged as a tool towards green chemistry. This technique can reduce the time of chemical reaction from hours to minutes. Metal complexes with the Schiff base derived from Cefotaxime with salicylaldehyde have been synthesized using sweet lemon juice catalyst under microwave radiation was a new eco-friendly route with good yield. Spectral data concluded that the Schiff base behaves as a bidentate ligand coordinated with Ni(II) and Cu(II) complexes and these newly synthesized compounds could exhibit, improved antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus*.

REFERENCES

- [1] B.L. Hayes, Recent Advances in Microwave-Assisted Synthesis. *Aldrich Chimica Acta*. 2004, 37(2), 66–76.
- [2] Aghayan M., Ghassemzadeh M., Hoseini M and Bolourtchian M, Microwave-Assisted synthesis of the tetradentate Schiff bases under solvent free and catalyst free condition. *Synth. Comm.* 2003, 33, 521–525.
- [3] Tania R., Ancker V., Gareth W.V. and Raston C.L., Benign approaches for the synthesis of bis-imine Schiff bases. *Green Chem.* 2006, 8, 50–53.
- [4] Z.H. Chohan, H. Pervez, K.M. Khan, A. Rauf, G.M. Maharvi and C.T. Supuran, Antifungal cobalt(II), copper(II), nickel(II) and zinc(II) complexes of furanyl-thiophenyl-, pyrrolyl-, salicylyl- and pyridyl-derived cephalosporins. *Journal of Enzyme Inhibition and Medicinal Chemistry*. 2004, 19(1), 85–90.

- [5] M.S. Iqbal, I.H. Bukhari, and M. Arif, Preparation, characterization and biological evaluation of copper(II) and zinc(II) complexes with Schiff bases derived from amoxicillin and cephalexin. *Applied Organometallic Chemistry*. 2005, 19(7), 864–869.
- [6] I.H. Bukhari, M. Arif, I. Akbar, and A.H. Khan, Preparation, characterization and biological evaluation of Schiff base transition metal complexes with cephradine. *Pakistan Journal of Biological Sciences*. 2005, 8(4), 614–617.
- [7] M. Arif, M.M.R. Qurashi, and M.A. Shad, Metal-based antibacterial agents: synthesis, characterization, and in vitro biological evaluation of cefixime-derived Schiff bases and their complexes with Zn(II), Cu(II), Ni(II), and Co(II). *Journal of Coordination Chemistry*. 2011, 64(11), 1914–1930.
- [8] S. Joshi, V. Pawar, and V. Uma, Antibacterial and antioxidant properties of Mn (II), Co (II), Ni (II) and Zn (II) complex of Schiff base derived from cephalexin. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*. 2011, 2(1), 61–70.
- [9] K.P. Srivastava et al., Microwave Assisted Synthesis, Characterisation and Antibacterial Study of Drug based Schiff Bases and their Zn(II) Complexes. *American International Journal of Research in Science, Technology, Engineering & Mathematics*. 2014, 6(3), 286–292.
- [10] Kajal, S. Bala, S. Kamboj, N. Sharma and V. Saini, Schiff Bases: A Versatile Pharmacophore. *Journal of Catalysts*. 2013, 1–14.
- [11] R. Pal, Fruit juice: A natural, green and biocatalyst system in organic synthesis. *Open journal of organic chemistry*. 2013, 1(4), 47–56.
- [12] S. Patil, S.D. Jadhav and U.P. Patil, Natural Acid Catalyzed Synthesis of Schiff Base under Solvent-free Condition: As a Green Approach. *Archives of Applied Science Research*. 2012, 4 (2), 1074–1078.
- [13] C. Limban and M.C. Chifiriuc, Antibacterial activity of new dibenzoxepinone oximes with fluorine and trifluoromethylgroup substituents. *International Journal of Molecular Sciences*. 2011, 12(10), 6432–6444.
- [14] R. Olar, M. Badea, D. Marinescu et al., Prospects for new antimicrobials based on N,N-dimethyl biguanide complexes as effective agents on both planktonic and adhered microbial strains. *European Journal of Medicinal Chemistry*. 2010, 45(7), 2868–2875.
- [15] C. Limban, A.V. Missir, I.C. Chirita et al., Synthesis and antimicrobial properties of new 2-((4-ethylphenoxy)methyl) benzoylthioureas. *Chemical Papers*. 2011, 65(1), 60–69.
- [16] G. M. Nitulescu, C. Draghici, M.C. Chifiriuc, L. Marutescu, C. Bleotu, and A.V. Missir, Synthesis and antimicrobial screening of N-(1-methyl-1-Hpyrazole-4-carbonyl)-thiourea derivatives. *Medicinal Chemistry Research*. 2011, 21, 308–314.
- [17] C. Limban, L. Marutescu, and M.C. Chifiriuc, Synthesis, spectroscopic properties and antipathogenic activity of new thiourea derivatives, *Molecules*. 2011, 16(9), 7593–7607.

Received: 11-12-2015

Accepted: 1-12-2015