MICROWAVE-ASSISTED SYNTHESIS OF SCHIFF BASE AND MIXED LIGAND COMPLEXES OF Cr(III): COMPARISON WITH CONVENTIONAL METHOD AND ANTIMICROBIAL STUDIES

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ABSTRACT

The Sustainable/Greener approach is prioritized over the conventional approach because of its environment-friendly, less time-consuming, less energy-consuming, less hazardous compounds synthesis, and low expenditure. Using a greener approach involving the use of microwave, Cr complexes were synthesized from Schiff base and various bidentate ligands and compared with conventional methods. Condensing 2-amino pyridine and isatin produced Schiff base. Complexes of Cr(III) were synthesized by using some bio-potent secondary ligands with Schiff base. Both Schiff base and complexes were characterized by FTIR spectroscopy, $^1$H NMR spectroscopy, magnetic moment analysis, elemental investigation, etc. The synthesized compounds will be further used for biological evaluation that can be further used in drugs and agrochemical design.

Keywords: 2-amino Pyridine, Isatin, Environment-Friendly, Microwave-Assisted Approach, Sustainable Approach.

INTRODUCTION

The use of microwaves for the synthesis of organic compounds has become the most popular method with respect to the environment in various fields like pharmaceutical, medicinal, academic stages, and agriculture because it is new empowering technology in drug revelation and evolution. Thermal methods are generally used for the synthesis of organic compounds because of being a source of sufficient energy. Nowadays, energy is derived through thermal heating in two ways conventional heating method or microwave-assisted heating. In a conventional way, starting materials are slowly stimulated by a conventional external heat source. Heat is reached by reactants through the walls of the container and then to the solvent and reactant. First, the molecules of the container will get excited and slowly provide energy to the next molecule. Then the surrounding reactants will get stimulated and at the end, the energy will reach the central molecules of reactants. It will take a lot of time to complete the activation. In a microwave-assisted way, microwaves provide the energy to every molecule of reactant uniformly which leads to the rise in temperature with speed. Isatin is an endogenous and heterocyclic compound and has widely been a part of various biologically potent compounds. Since its discovery, a large number of researchers had been worked on the synthesis of organic compounds, their chemical properties, and their biological application. Its molecular framework contains an indole nucleus and both lactam and keto moiety which functioned for several biological paraphernalia, viz.; anti-microbial, anticonvulsant, anti-tubercular, anti-cancer, etc. Isatin derivatives are biosignificant substrates, which can be used for the evolution of a huge variety of chemical substances, of which some entities will appear as drugs. Aminopyridines are the monoamine and diamino derivatives of pyridine. The main principle of action on the body is the dose-dependent blockade of fast voltage-gated potassium channels. It blocks the potassium channel in cell walls. A class of potassium channel-blocking agents called aminopyridines works at the level of the neuromuscular junction and the central nervous system. A simple, planar molecule called 8-hydroxyquinoline has the ability to chelate metals along with a high affinity for lipids (lipophilic action). Chemists, researchers, medicinal chemists, and professionals in health sciences have shown their great interest in the biology and chemistry of this compound. A number of specified drugs integrate this group, and several 8-
Hydroxyquinoline-based molecules can be used to synthesize various biologically important compounds with good yield, good effectiveness, and less poisonousness. Current research mainly reported an essential assemblage of very significant and highly selective thiosemicarbazide equivalents having various biological activities like antifungal property.

**EXPERIMENTAL**

**Material and Methods**
The used chemicals or materials were of A.R. grade and got from Sigma Aldrich. For characterization following methods were used: CHNX method for elemental weightage of Hydrogen, Carbon, Nitrogen, and Chlorine. Metal was evaluated gravimetrically. The melting point was measured in the melting point apparatus using capillaries. Systronic Direct Reading Conductivity Meter and Gouy's Balance Model No. HO-ED-EM-08 was employed in order to evaluate the conductance and magnetic moment. On a model SHIMADZU-JAPAN 8400 FTIR spectrophotometer and a Hitachi Perkin Elmer spectrometer, the complex's FTIR and 1HNMR spectra were analyzed respectively. The Perkin Elmer UV lambda 750 UV/Vis spectrophotometer has been employed to obtain the UV/electronic spectrum.

**Synthesis of Schiff base S-I(C_{13}H_{9}N_{3}O)**
The synthetic procedure used for preparing compounds includes two methods: the conventional method and the microwave-assisted method.

**Conventional Method**
Ethanolic solution(10ml) of Isatin (0.147g, 1mmol) and 2-aminopyridine (0.094g, 1mmol) were mixed in a 250 ml round bottom flask. The mixture was refluxed for four hours while it was heated on the heating mantle. TLC was used to monitor the status of the reaction. The refluxed content was collected on a watch glass after it had finished, recrystallized with ethanol, rinsed, and dried. Powder with an orange color was produced. It had a yield of 32.15 % and a melting point of 206.7°C.

**Microwave-Assisted Method**
The above mixture was kept under microwave irradiation of frequency approximately 2.45mHz for 20-30min. An orange-colored powder compound was obtained after recrystallization and drying. The yield of the compound was 51.45%. (Scheme-I)

**Synthesis of Complex-I (Cr C_{22}H_{15}N_{4}O_{2}Cl_{2})**
The same procedure was followed as above in both conventional and microwave-assisted methods. Here, an ethanolic solution(10ml) of Schiff base S-I (0.223g, 1mmol) and an ethanolic solution (10ml) of secondary ligand 8-hydroxyquinoline (0.145g, 1mmol) were mixed with an aqueous solution (10ml) the salt of Cr(III) (CrCl_{3}.6H_{2}O) (0.266g, 1mmol) in 250 ml Round bottom flask. This reaction mixture was treated under microwave irradiation along with the conventional method. The reaction was running for 20-30min. A dark brown colored compound was collected and dried. In the conventional method, the yield of the compound was 45.92% and, in the microwave-assisted method, it was 66.83%. The melting point of the complex was 278.9°C. (Scheme-II)
Synthesis of Complex-II (CrC_{16}H_{15}N_{4}O_{3}Cl_{2})

Here, the primary ligand was the Schiff base (0.223g, 1mmol) and the secondary ligand was an amino acid, L-Alanine (0.089g, 1mmol). Their ethanolic (10ml) solution was mixed with Cr(III) salt (0.266g, 1mmol, 10ml aqueous solution) and undergo a conventional and greener microwave-assisted method. The reaction took approximately 20-30min and we got a powder compound with having orangish-brown color. Again, the yield of the compound prepared via microwave irradiation was more than that of the conventional method (68.72%) and the compound’s melting point was 291.6°C. (Scheme-III)

Synthesis of Complex-III (CrC_{14}H_{14}N_{6}O_{3}Cl_{3})

The same conventional and microwave-assisted methods were used for the preparation of the complex of Cr(III) with ethanolic solution (10ml) of Schiff base (0.223g, 1mmol) and secondary ligand. Here, the secondary ligand was thiosemicarbazide (0.091g, 1mmol). The reaction mixture was undergoing microwave irradiation for 20-30min and the reaction was completed with a high yield (69.11%). A greyish-brown colored compound was prepared after cooling, recrystallization, and drying. The melting point was 287.4°C. (Scheme-IV)
Antimicrobial Operation
The antimicrobial operation was done by the Agar well diffusion method. (Fig.-2) It concludes following steps:
1. For both antibacterial and antifungal treatment of compounds, firstly the solution of compounds was prepared in DMSO. Here, DMSO was used as a solvent.
2. Mueller Hinton agar served as the medium to grow microorganisms on a plate and was maintained at a low temperature overnight.
3. After 24 hours, wells were prepared on a plate of 5mm in which the compounds solution of different concentrations was poured and kept for 24-48 hours at 37°C.
4. Then space was observed around the compound sample and the diameter was calculated to get the inhibition zone of the compound and got antimicrobial spectrum.
5. The diameter of compounds was compared with the standard so that the activity of compounds can be measured against the microbes.

RESULTS AND DISCUSSION
Physicochemical Data and Element Investigation
The synthesized compounds were investigated on the basis of their molecular weight, color, melting points, magnetic moment, and conductivity. On the basis of this investigation, we found that all compounds were colored with a sharp melting point and their effective conductance was obtained in the range 12.17-12.26 Ω⁻¹ cm² mol⁻¹ hence non-electrolytic. The magnetic moment of complexes was approximately 3.87BM which shows the paramagnetic property of complexes. Physicochemical data were tabulated in Table-1, elemental data were mentioned in Table-2, and FTIR data, ¹H NMR data, and antimicrobial data were mentioned in Table-3, Table-4, and Table-5 respectively.

Table-1: Physicochemical Data of Compounds

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Color/M.P.</th>
<th>Mol. Cond. (Ω⁻¹ cm² mol⁻¹)</th>
<th>μₑff BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-I(C₁₃H₉N₃O)</td>
<td>Orange/206.7°C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Complex-I</td>
<td>Dark-brown /278.9°C</td>
<td>12.17</td>
<td>3.87</td>
</tr>
</tbody>
</table>
UV-Vis Spectral Data

UV-Vis spectra were conveyed in ethanol solution in the range of 200-800 nm. The wavelength of complexes was shifted towards the longer wavelength i.e., a bathochromic shift which indicates the formation of metal-ligand bonds. The band shifted towards 380nm for the n-π* transition and 270nm for the π-π* transition in spectra.

FTIR Data

Some characteristic peaks were observed in FTIR data of ligands and complexes. The azomethine(C=N) stretching frequency was obtained in the range of 1550-1650 cm\(^{-1}\) in all synthesized compounds. Other stretching frequencies were obtained in the range 1550-1600 cm\(^{-1}\) for the C=C stretching bond and 3100-3500 cm\(^{-1}\) for the N-H stretching bond. Complexes had some peaks in the range of 450-680 cm\(^{-1}\), which shows the stretching frequency of metal with N, O, and S.

\[\text{Table-3: FTIR Data of Synthesized Compounds(cm}^{-1}\text{)}\]

<table>
<thead>
<tr>
<th>Compounds/ empirical formula</th>
<th>(\nu\ (\text{C=N}))</th>
<th>(\nu\ (\text{C=C}))</th>
<th>(\nu\ (\text{N-H}))</th>
<th>(\nu\ (\text{Cr-O}))</th>
<th>(\nu\ (\text{Cr-N}))</th>
<th>(\nu\ (\text{Cr-S}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-I (C(_{13})H(_9)N(_3)O)</td>
<td>1638</td>
<td>1573</td>
<td>3435</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Complex-I (Cr(<em>{22})H(</em>{15})N(_4)O(_2)Cl(_2))</td>
<td>1580</td>
<td>1412</td>
<td>3436</td>
<td>644</td>
<td>529</td>
<td>-</td>
</tr>
<tr>
<td>Complex-II (Cr(<em>{16})H(</em>{15})N(_4)O(_3)Cl(_2))</td>
<td>1612</td>
<td>1552</td>
<td>3131</td>
<td>679</td>
<td>543</td>
<td>-</td>
</tr>
<tr>
<td>Complex-III (Cr(<em>{14})H(</em>{14})N(_6)OSCl(_3))</td>
<td>1608</td>
<td>1544</td>
<td>3433</td>
<td>680</td>
<td>530</td>
<td>449</td>
</tr>
</tbody>
</table>

\(^1\text{H-NMR Data}\)

Proton NMR spectroscopy provides information about the position of protons in compounds that helps in the determination of the structure of the compound. For the NMR spectrum, DMSO was used as a solvent. Here, the signal aromatic hydrogens were noticed in the range 6.00-7.50 ppm, and the signals of proton directly attached to nitrogen in Schiff base and complex were observed in the range of 7.00-8.00 ppm. this high value of chemical shift for N-H is due to the high electronegativity of nitrogen and the electron-withdrawing property of the C=O group, attached to the N-H.

Antimicrobial Results

On the basis of antimicrobial activity observations, it was reported that all compounds were biologically potent against microbes at higher concentrations. Complexes were more operational than the Schiff base ligand. Complex-II had greater activity for both bacteria and fungi than other complexes and ligands. Complex-I and complex-II were more active against \textit{E. coli} and \textit{S. aureus} but complex-III showed great activity against the fungal strain \textit{A. niger}.
Table 4: $^1$H-NMR Data of Synthesized Compounds (ppm)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Aromatic C-H</th>
<th>N-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-I(C$<em>{13}$H$</em>{9}$N$_{3}$O)</td>
<td>6.34-7.06</td>
<td>7.40</td>
</tr>
<tr>
<td>Complex-I(CrC$<em>{22}$H$</em>{15}$N$_{4}$O$_2$Cl$_2$)</td>
<td>6.95-7.52</td>
<td>7.54</td>
</tr>
<tr>
<td>Complex-II(CrC$<em>{16}$H$</em>{15}$N$_{4}$O$_3$Cl$_2$)</td>
<td>6.35-7.04</td>
<td>7.39</td>
</tr>
<tr>
<td>Complex-III(CrC$<em>{14}$H$</em>{14}$N$<em>{6}$O$</em>{3}$Cl$_3$)</td>
<td>6.94-7.26</td>
<td>7.67</td>
</tr>
</tbody>
</table>

Fig. 3: FTIR spectra of S-I
Fig. 4: FTIR spectra of Complex-I
Fig. 5: FTIR Spectra of Complex-II
Fig. 6: FTIR Data of Complex-III
Fig. 7: $^1$H-NMR Spectra of S-I
Fig. 8: $^1$H-NMR Spectra of Complex-I
Fig. 9: $^1$H-NMR Spectra of Complex-II
Fig. 10: $^1$H-NMR Spectra of Complex-III
Fig. 11: Biological Activity of S-I, Complex-I, Complex-II, Complex-III (F-1, C-1, G-2, and H-2 respectively) Against E. coli (Gram-ve Bacterial strain)
Table 5: Showing Antimicrobial Operations of Compounds

<table>
<thead>
<tr>
<th>Synthesized Compounds</th>
<th>Concentration (mg/L)</th>
<th>Inhibition zone showing Antimicrobial activity (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>E. coli</td>
</tr>
<tr>
<td>S-I ((C_{13}H_9N_3O))</td>
<td>50</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>6mm</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>9mm</td>
</tr>
<tr>
<td>Complex-I ((CrC_{22}H_{15}N_4O_2Cl_2))</td>
<td>50</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>8mm</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>12mm</td>
</tr>
<tr>
<td>Complex-II ((CrC_{16}H_{15}N_4O_3Cl_2))</td>
<td>50</td>
<td>4mm</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>9mm</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>14mm</td>
</tr>
<tr>
<td>Complex-III ((CrC_{14}H_{14}N_6OSCl_3))</td>
<td>50</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>5mm</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>10mm</td>
</tr>
<tr>
<td>Positive control-I (Against bacterial strain)</td>
<td>100</td>
<td>25mm</td>
</tr>
<tr>
<td>Positive control-II (Against fungal strain)</td>
<td>100</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA=No activity

**CONCLUSION**

After analysis, on the basis of obtained results, the following facts may be concluded:

1. On the basis of the received data, it was intended that the complexes were octahedral in geometry.
2. The synthesized complexes were paramagnetic and non-electrolytic in nature.
3. On the basis of FTIR data and \(^1\)H-NMR data, it was concluded that the valency of metal in complexes was fulfilled by the halogens of metal salt.
4. The FTIR frequencies of complexes were lower than that of the Schiff base, indicating the formation of complexes.
5. The time consumption in the synthesis process via the microwave-assisted method was lower than that of the conventional method and also provided a high yield or atom economy.
6. All synthesized Schiff bases and complexes were biologically active against bacterial and fungal strains.
7. Antimicrobial activity of complexes were prominent than the ligand.
8. Complex-II exhibit more antibacterial and antifungal property than other complexes.
9. Complex-I and complex II showed more activity against the bacterial strain but complex III showed more activity against the fungal strain.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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All the authors contributes significantly to this manuscript and took part in reviewing and approving the final draft of the manuscript for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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