An Innovative Method Designed for the Synthesis of Some New Mixed Ligand Ni(II) Complexes Its Characterization and Applications

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Abstract In the present work, a series of new mixed ligand Ni(II) complexes of the type [Ni(P)(L).2H2O] have been synthesized by using 2-amino-6-methyl pyrimidine-4-ol (HP), a primary ligand and N- and O- donor amino acids (HL) secondary ligands. Synthesis of Ni(II) complexes has been carried out by thermal and microwave methods. Results show that complexes synthesized by the microwave method were more efficient than the thermal method. Preparation time in the microwave method was short (4-7 min.) as compared to the thermal method (45 min.). Additionally, the microwave technique gave a very high yield (90%) of the complexes. The prepared complexes were characterized by Gouy experiment, FTIR, elemental analysis, TGA, and DTA at room temperature. The complexes have shown considerable antimicrobial activities such as antifungal and antibacterial activity.

Keywords: Ni(II) complexes, 2-amino-6-methyl pyridine-4-ol, amino acids, microwave, antimicrobial activity

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1. Introduction

Metal ions form different complexes with numerous biological macromolecules and with their synthetic congeners [1]. Ni(II) one of the trace elements found in certain enzymes as a co-factor. Interestingly, nine out of the ten nickel-based enzymes gives or uses gases in their reactions. These gases are CO, CO2, CH4, H2 and NH3 [2]. Amino acids contain both carboxyl and amino groups with a side chain that varies between different amino acids. However, many types of amino acids are known as α-amino acids, the monomers from which proteins are constructed. Since amino acid contains these groups, therefore they have potential donor sites such as (-COOH) and (-NH2), which they could coordinate with metals ions [3,4,5,6,7]. Amino acids are available in proteins and are categorized as essential elements for preventing and protecting harmful ailments. All the ligands are optically active from the chemical point of view and contain side chain groups to form a chelate ring with a metal ion bound at the α-β-amino nitrogen. Transition metals with potential biological activity play an essential role in the metabolism and cellular signalling of drugs and hydrogen storage media. The transition metals like Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) are essential trace elements and used as a nutritional supplement that acts as co-factors in various enzyme systems such as metalloenzymes or as enzymatic activators. Metal ions form different complexes with various biological macromolecules and their synthetic analogues will inhibit the various ailments. Nickel is indispensable trace elements found in various biological systems.

It is also present in nucleic acids, but DNA or RNA's role is still not clearly described. Nickel(II) complexes have various biological potential and it acts as an anticonvulsant and antiepileptic agents. It has antibacterial, antifungal, antimicrobial, antioxidant, and anticancer activities. Therefore, the research of Ni(II) complexes become essential in the field of bioinorganic and coordination chemistry [8,9,10,11,12]. In some literature, it is shown that complex has also been synthesized in the microwave. Microwave-assisted synthesis is a branch of green chemistry. Microwave-assisted synthesis has gained much recognition in recent years. The microwave irradiation applications are used to carry out chemical transformations, which are pollution-free, eco-friendly, low cost and offer high yields and simplicity in processing and handling. The salient features of microwave approach are shorter reaction times, simple reaction conditions, and enhancements in outcomes [12-18]. Nickel metal complexes are multifaceted compounds and exhibit a broad range of biological activities, such as antibacterial, antifungal, antimalarial, anti-inflammatory, and antiviral [19,20,21]. Bioinorganic chemistry's growth has become of greater interest in heterocyclic base transition metal complexes derived from amino acids. Many of these complexes exhibit substantial antimicrobial activity [22,23,24]. Because of the above applications, we have synthesized some new Ni(II) complexes by microwave method and thermal method. Microwave method gave very high yield in shorter time.
2. Experimental Section

All the chemicals used in the present work were of the analytical grade (A.R.) and were procured from Aldrich, E. Merck and S.D. Fine. Metal salts were purchased from E. Merck and were used as received. All solvents used were of standard/spectroscopic grade. Analytical grade nickel(II) chloride hexahydrate was used as such without further purification. Amino acids, L-Serine, L-isoleucine, L-proline, 4-hydroxy-L-proline, L-threonine were obtained from S.D. Fine Chemicals, Mumbai. In contrast, 2-amino-6-methyl pyrimidine-4-ol were obtained from Sigma Aldrich imported from U.S. Solvents ethanol, methanol, chloroform, DMF and DMSO, whenever used were distilled and purified according to standard procedures.

2.1. Physical Measurements

Elemental analysis were carried out on Thermo Finnigan Elemental Analyser model no FLASH EA 1113 series at IIT Mumbai. Metal content was estimated complexometrically by standard procedure [25,26]. Fourier transforms infrared (FTIR) spectra of the new compounds were recorded in the spectral range 4000-400 cm⁻¹ on Perkin Elmer-Spectrum FT-IR model no 1500 at IIT Mumbai. U.V. spectra were recorded using a Perkin Elmer Lambda-950 UV-VIS spectrometer using DMSO as a solvent in the range of 200-800 nm. Magnetic susceptibility measurements of complexes were carried out using Gouy balance at room temperature using Hg[Co(NCS)] as an internal reference. Thermal Analysis (TG and DTA) were carried out in a controlled nitrogen atmosphere on a Perkin Elmer Diamond TG-DTA instrument. Microwave synthesis was carried out in domestic microwave oven Model KENSTAR-OM20ACF, 2450MHz, 800W.

2.1.1. Synthesis of Ni(II) Complexes by a Thermal Method

Mixed ligand Ni(II) complexes were prepared from nickel(II) chloride hexahydrate, 2-amino-6-methyl pyridine-4-ol (HP) and different amino acids (HL) such as L-Serine, L-isoleucine, L-proline, 4-hydroxy-L-proline, L-threonine as a secondary ligand. To an aqueous solution (10 cm³) of Ni(II) chloride hexahydrate (237 mg, 1 mmol), an aqueous solution (10 cm³) of an amino acid (1 mmol) was added. The mixture was kept in a boiling water bath for 10 min. To this hot solution an aqueous solution (10 cm³) of 2-amino-6-methyl pyridine-4-ol (124 mg, 1 mmol) was added. The mixture was cooled and the solid complex obtained was filtered and washed with water and ethanol. The complexes thus prepared were dried in an oven [27].

2.1.2. Synthesis of Ni(II) Complexes by Microwave Method

To an aqueous solution (10 cm³) of nickel(II) chloride hexahydrate (237 mg, 1 mmol), an aqueous solution (10 cm³) of 2-amino-6-methyl pyridine-4-ol (HP) (124 mg, 1 mmol) was added. To this hot solution, an aqueous solution (10 cm³) of an amino acid (HL) was added with constant stirring. The reaction mixture was kept in the microwave for about 4-7 min. The complexes were obtained by raising the pH of the reaction mixture by adding a diluted ammonia solution. The mixture was cooled and the solid complex obtained was filtered and washed with water and ethanol. A comparison of these two methods is given in Table 1.

| Sr. No. | Complex                  | Thermal Method | Microwave method |
|---------|--------------------------|----------------|------------------|
|         |                          | Time in min    | % Yield          | Time in min | % Yield |
| 1       | [Ni(P)(Ser).2H₂O]        | 43             | 65               | 7           | 97      |
| 2       | [Ni(P)(Iso).2H₂O]        | 45             | 60               | 6           | 94      |
| 3       | [Ni(P)(Pro).2H₂O]        | 45             | 56               | 7           | 91      |
| 4       | [Ni(P)(HPro).2H₂O]       | 41             | 67               | 6           | 98      |
| 5       | [Ni(P)(Thr).2H₂O]        | 42             | 62               | 7           | 93      |
2.1.3. Antibacterial Activity Agar Cup Method

In the agar cup method, one compound can be tested against many organisms or a given organism against various concentrations of the same compound [28]. This method was found proper for liquid or semisolid samples and was used in the current work. In this method, a plate of sterile nutrient agar was transferred with the chosen test strain to a height of about 5 mm. Allowed to solidify and cut a particular cup of around 8 mm diameter from the centre of the plate with a sterile cork borer. Filled the cup with the sample solution of known concentration, and the vessel was incubated at 37°C for 24 hr. The degree of growth inhibition from the verge of the cup was considered a measure of the given complex's activity. Using some plates concurrently, quantitatively examined the actions of some samples.

2.1.4. Antifungal

The primary fungi toxicity screening of the synthesized complexes at different concentrations was accomplished in vitro against the test fungi, A. alternata and F. Odum, by the food poison technique [29]. The solutions of complexes were prepared by dissolving them in DMF. Clotrimazole was used as a commercial antifungal agent, and DMF served as a means of control. Potato dextrose agar medium was prepared using potato, dextrose, agar-agar and D.W. and added proper amount of the complexes in DMF were added to potato dextrose agar to form 250, 125, 62.5 ppm of the solution of the complexes in the medium. The medium was poured into a set of two Petri plates under aseptic conditions in a laminar flow hood. When the medium in the vessels was solidified, mycelial discs of 0.5 cm in diameter-cut from the edge of the 7-day old culture were aseptically inoculated upside down in the Petri plates’ centre. Petri plates were incubated at 25 ± 1°C until fungal growth in the control Petri plates nearly completed. The mycelial growth of fungi (mm) in each Petri plate was measured diametrically and growth inhibition was calculated.

3. Result and Discussion

3.1. Characterization of Metal Complexes

The synthesis of mixed ligand Ni(II) complexes may be represented as follows:

\[ \text{NiCl}_2.6\text{H}_2\text{O}+\text{HP}+\text{HL} \rightarrow [\text{Ni}(\text{P})(\text{L}).2\text{H}_2\text{O}]+2\text{HCl}+4\text{H}_2\text{O} \]

Where HP is 2-amino-6-methyl pyrimidine-4-ol and HL is an amino acid such as L-Serine, L-isoleucine, L-proline, 4-hydroxy-L-proline, L-threonine. All the complexes are coloured, non-hygrosopic and thermally stable solids (Table 2), indicating a strong metal-ligand bond. All the complexes are soluble to some extent in methanol, ethanol, chloroform, DMF and DMSO. The elemental analysis data (Table 3) of metal complexes is consistent with their general formulation as 1:1:1, mixed ligand complexes of the type \([\text{Ni}(\text{P})(\text{L}).2\text{H}_2\text{O}]\). The molar conductance values of the complexes in DMF at \(10^{-3} \text{ M}\) concentration are low (<1), indicating their non-electrolytic nature [30].

3.2. Magnetic Studies

Magnetic moments of the metal complexes calculated from the measured magnetic susceptibilities after employing diamagnetic corrections. The observed \(\mu_{eff}\) values presented in Table 3. Suggest the octahedral geometry for nickel complexes. Study also shows paramagnetic nature of synthesized complexes.

3.3. Electronic Absorption Spectra

The electronic spectra of the metal complexes in methanol recorded in the U.V. region exhibit intra ligand and charge transfer transitions. The spectra show three transitions in the range 202-262 nm, 337 nm and 383-387 nm, which can be assigned to \(\pi\rightarrow\pi^*\), \(n\rightarrow\pi^*\) and the charge transfer transitions (LMCT) from ligands to the metal, respectively. The spectra of metal complexes in chloroform recorded in the visible region show transitions in the range 400-420 nm, ascribed to charge transfer transition. Two transitions around 560-600 nm and 820-840 nm may be ascribed to d-d transitions, which are the characteristic feature of transition metal complexes. [31,32,33,34].

3.4. FTIR Spectra

The metal complexes have shown very complex FTIR spectra due to various bands with different intensities, making the interpretation difficult. However, an effort has been made to describe some of the importance. Bands based on reported infrared spectra of several -N and -O donor ligands, 2-amino-6-methyl pyridine-4-ol and their metal complexes [35,36,37]. An essential feature of these infrared spectra is the absence of band at ~3402 cm\(^{-1}\) because of the O-H stretching vibration of HP. It concludes that it leads to the complex formation that occurs by the removal of a proton from the hydroxyl group of HP moiety. A strong \(\nu(\text{CO})\) peak observed in the range 1267-1212 cm\(^{-1}\) in the spectra of the complexes indicates the 2-amino-6-methyl pyridine-4-ol moiety coordinating to metal ion through its nitrogen and oxygen atoms as an uni-negative bidentate ligand. The \(\nu(\text{N}_2\text{H}_3)\) mode observed at 3238 cm\(^{-1}\) in the spectrum of free HP ligand is found to shift to a lower wavenumber, i.e. in the range of 3000-2910 cm\(^{-1}\) indicates coordination through the tertiary nitrogen donor of HP. The in-plane and out-of-plane deformation modes observed at ~495 cm\(^{-1}\) and ~690 cm\(^{-1}\) respectively, in the spectrum of free HP, are shifted to higher wavenumbers ~505 cm\(^{-1}\) and in the range, 790-784 cm\(^{-1}\) respectively, indicates coordination through the nitrogen atom of HP with the metal ion [10,11,34].

Broad band observed in the region between 3400-3600 cm\(^{-1}\) due to asymmetric and symmetric O-H stretching modes and a weak band in 1664 cm\(^{-1}\) due to H-O-H bending vibrations, indicating the presence of a coordinated water molecule [38,39,40,41]. The \(\nu_{asymmetric}\) (COO) of the free amino acids, i.e. ~1516 cm\(^{-1}\) is shifted to a higher wavenumber, i.e. 1685- 1664 cm\(^{-1}\) and the \(\nu_{symmetric}\) (COO) mode observed at ~1426 cm\(^{-1}\) in the spectra of the free amino acids is shifted to lower wavenumber, i.e. 1160-1130 cm\(^{-1}\), in the spectra of complexes, indicating the coordination of the carboxylic
acid group via oxygen with the metal ion. The difference \((\nu_{\text{asymmetric}} - \nu_{\text{symmetric}})\) in the range 233-231 cm\(^{-1}\) indicates that the N-O bond is purely covalent [42,43]. A new peak of weak intensity observed in the regions around 600-590 cm\(^{-1}\), and 510 cm\(^{-1}\) may be ascribed to the N-O and M-N vibrations. [11,44,45]. These vibrational bands are absent in the IR spectra of free HP and amino acids.

### 3.5. Thermal Studies

The TG and DTA studies of the complexes have been recorded in the nitrogen atmosphere at a constant heating rate of 10°C/min. Thermal study on the mixed ligand nickel complexes in a controlled nitrogen atmosphere was carried out to understand the stages and temperature range of decomposition. The most probable decomposition pattern of the complexes is proposed based on the careful examination of TG and DTA curves. The thermo-analytical data were given in Table 4. The TG of the complexes shows that they are thermally stable. The complexes show the gradual loss in weight due to decomposition by fragmentation with increasing temperature. The complexes with L-serine, L-isoleucine, L-proline, 4-hydroxy-L-proline and L-threonine show similar behaviour in TG and DTA studies. Thermograms show the loss in weight corresponding to two water molecules in the temperature range 104-185°C, followed by weight loss in the range 286-522°C, which is approximately equal to the algebraic sum of weight loss due to both amino acid and HP moieties [46,47].

### 3.6. Antimicrobial Study

The studies based on the agar cup method revealed that the complexes are sensitive against *C. diphtheriae*, less sensitive against *C. Albicans*, *S. aureus*. (Table 5). The Minimum inhibitory concentration (MIC) of complexes (Table 5) ranges between 100-450 µg/mL. The biological study shows that complexes are found to be more active against *C. diphtheriae* as compared to *C. Albicans* and *S. aureus* compared to the standard antibacterial compound, doxycycline. The Ni(II) metal complexes show modest activity against the selected strains of microorganisms. In the case of antifungal activity, the result is shown in Table 6. The antifungal activity of the Ni(II) complexes shows that (Table 6) Ni(II) complexes were highly potent than the free ligand against phytopathogenic fungi, *Alternaria alternata*, and *Fusarium odum*. The studies on antifungal activity revealed that all the metal complexes show moderate activity against selected strains of microorganisms. Compared to the standard antifungal compound, clotrimazole, the complexes show less activity against the selected strains.

### Table 2. Colour, molecular weight, decomposition temperature and pH of the nickel complexes

| Sr. No. | Complex | Empirical Formula | Molecular Weight | Colour | Decomposition Temperature | pH   |
|---------|---------|-------------------|------------------|-------|---------------------------|------|
| 1       | [Ni(P)(Ser).2H2O] | NiC8H18O6N4  | 394.94          | Blue  | 385                       | 6.14 |
| 2       | [Ni(P)(Iso).2H2O] | NiC11H24O5N4   | 351.02          | Light Blue | 375 | 6.91 |
| 3       | [Ni(P)(Pro).2H2O] | NiC10H20O5N4   | 334.98          | Dark Blue | 384 | 6.65 |
| 4       | [Ni(P)(HPro).2H2O] | NiC10H20O6N4   | 350.98          | Dark Blue | 389 | 6.85 |
| 5       | [Ni(P)(Thr).2H2O] | NiC9H20O6N4    | 338.97          | Light Blue | 386 | 6.98 |

P represents the deprotonated primary ligand 2-amino-6-methyl pyridine-4-ol, whereas Ser, Iso, Pro, HPro and Thr represent deprotonated secondary ligands L-serine, L-isoleucine, L-proline, 4-hydroxy-L-proline, Threonine

### Table 3. Elemental analysis data, molar conductance and magnetic moment of nickel complexes

| Sr. No. | Complex | Elemental analysis found (calculated) | Molar conductance (Mhos cm\(^2\) mol\(^{-1}\)) | \(\mu_{\text{eff}}\) (B.M.) |
|---------|---------|--------------------------------------|-----------------------------------------------|-----------------------------|
|         |         | %M    %C %H %N                        |                                               |                             |
| 1       | [Ni(P)Ser).2H2O] | 18.06(19.76) | 29.94(30.91) | 5.08(6.86) | 17.24(18.86) | 0.031 | 3.08 |
| 2       | [Ni(P)Iso).2H2O] | 16.72(17.69) | 37.64(38.09) | 6.80(7.74) | 15.96(16.38) | 0.032 | 2.96 |
| 3       | [Ni(P)Pro).2H2O] | 17.52(18.23) | 35.86(36.49) | 6.02(6.35) | 16.73(17.30) | 0.031 | 3.17 |
| 4       | [Ni(P)HPro).2H2O] | 16.72(17.3)  | 34.22(35.2)  | 5.74(6.07) | 15.96(16.43) | 0.039 | 3.08 |
| 5       | [Ni(P)Thr).2H2O] | 17.31(18.01) | 31.89(32.22) | 5.95(6.26) | 16.53(17.89) | 0.033 | 3.12 |

### Table 4. Thermal data of nickel complexes

| Sr. No. | Complex | % Weight loss due to water | % Weight loss due to A.P. and Amino acid |
|---------|---------|---------------------------|---------------------------------------|
|         |         | Temperature Range Found   | Calculated                             | Temperature Range Found   | Calculated                             |
| 1       | [Ni(P)Ser).2H2O] | 107-185 | 9.70 | 10.40 | 286-501 | 76.57 | 72.37 |
| 2       | [Ni(P)Iso).2H2O] | 108-167 | 10.31 | 9.75 | 288-521 | 81.77 | 74.32 |
| 3       | [Ni(P)Pro).2H2O] | 110-174 | 10.72 | 10.21 | 285-522 | 79.90 | 73.15 |
| 4       | [Ni(P)HPro).2H2O] | 105-167 | 10.81 | 9.72 | 290-515 | 76.78 | 74.25 |
| 5       | [Ni(P)Thr).2H2O] | 104-175 | 9.91 | 10.08 | 292-519 | 73.61 | 73.44 |
Table 5. MIC (µg/mL) Data of Nickel complexes

| Sr. No. | Complex            | C. Albicans | S. diphtheriae | S. aureus |
|---------|--------------------|-------------|----------------|-----------|
| 1       | [Ni(P)(Ser).2H2O]  | 200         | 150            | 300       |
| 2       | [Ni(P)(Iso).2H2O]  | 150         | 100            | 400       |
| 3       | [Ni(P)(Pro).2H2O]  | 350         | 300            | 400       |
| 4       | [Ni(P)(HPro).2H2O] | 300         | 200            | 400       |
| 5       | [Ni(P)(Thr).2H2O]  | 150         | 100            | 200       |
| 7       | Doxycycline        | 2.0         | 1.5            | 1.5       |

Table 6. Antifungal screening of the Ligand and Ni(II) complexes

| Sr. No. | Complex                  | Fusarium Odum (%) | Alternaaria alternata (%) |
|---------|--------------------------|-------------------|---------------------------|
|         |                          | 250 | 125 | 63.1 | 250 | 125 | 63.1 |
| 1       | Ligand                   | 48.2 | 22.0 | --   | 56.2 | 30.1 | 11.2 |
| 1       | [Ni(P)(Ser).2H2O]        | 62.2 | 30.2 | 12.2 | 59.2 | 33.0 | 12.0 |
| 2       | [Ni(P)(Iso).2H2O]        | 49.2 | 28.0 | --   | 61.2 | 36.1 | 15.0 |
| 3       | [Ni(P)(Pro).2H2O]        | 51.0 | 23.0 | 11.2 | 57.0 | 34.2 | 12.0 |
| 4       | [Ni(P)(HPro).2H2O]       | 54.3 | 32.0 | 12.3 | 63.2 | 45.2 | 18.4 |
| 5       | [Ni(P)(Thr).2H2O]        | 65.0 | 34.2 | 12.3 | 79.0 | 48.0 | 22.0 |
| 6       | Clotrimazole (Std.)      | 94.0 | 74.0 | 42.0 | 98.0 | 86.0 | 46.0 |

Variation in the effectiveness of various compounds against different organisms depends on the impermeability of the cells of the microbes or the difference in ribosomes of microbial cells [40]. It is observed that concentration plays a vital role in increasing the degree of inhibition; as the concentration increases, the activity increases.

![Antibacterial Activity](image)

Graph 1. Antibacterial activity of Ni (II) complexes

![Structure](image)

Figure 2. The structure of Ni (II) complexes
4. Conclusion

We have improved the existing method to synthesize some new Ni(II) complexes. Microwave method is found to be energy efficient. The complex obtained in a shorter time (5-7 min) with high yield (90%), Ni(II) complexes show higher decomposition temperature indicating a strong metal-ligand bond and electrical conductance studies show non-electrolytic nature, respectively. Magnetic studies indicate the paramagnetic nature of the complexes. The IR spectra show the bonding of the metal ion through -N and -O donor atoms of the two ligands. Thermal analysis affirms the presence of coordinated water molecules. Based on these results, an octahedral structure is proposed for nickel complexes under study. The biological study shows that complexes are more active against C. diphtheriae than C. Albicans, S. aureus compared with the standard antibacterial compound doxycycline, the complexes show modest activity. The antifungal activity of the Ni(II) complexes shows that Ni(II) complexes were highly potent than the free ligand against phytopathogenic fungi, Alternaria alternata and Fusarium odum.

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