Microwave Assisted Synthesis, Spectral and Antibacterial Studies of Complexes of 2-Hydroxy-6-methylnicotinic acid with Co(II), Ni(II) and Cu(II)

S. K. VERMA, N. BHOJAK

GCRC, P. G. Department of Chemistry, Govt. Dungar College, MGS University, Bikaner, India.
*Corresponding Author E-mail: narendarbhojak@rediffmail.com
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Abstract

New transition metal complexes of 2-Hydroxy-6-methylnicotinic acid (H\(_2\)6MnicO) Na\(_2\)[M(H6MnicO)\(_2\)Cl\(_2\)] (M = Co, Ni and Cu) have been prepared by microwave irradiation method. 2-Hydroxy-6-methylnicotinate coordinates through O,O-chelation to the transition metal(II) ions to form octahedral complexes as shown by FT-IR and UV-Visible spectral analysis. The ligand and its complexes have been screened in-vitro for antibacterial studies against Escherichia coli, Staphylococcus aureus and Bascillus subtilis bacteria.

Keywords: 2-Hydroxy-6-methylnicotinic acid, Microwave irradiation, Antibacterial studies

Introduction

Last few years there has been intense research on the synthesis of new metal complexes containing pyridine carboxylate derivatives, as many pyridine derivatives possess a diverse array of bioactivities as well as playing crucial roles for physiological functions\(^1\)-\(^3\). The studies on the coordination complexes of nicotinic acid and its derivatives reveal their antiviral, antifungal, anti-inflammatory, antitumor and antibacterial activity\(^4\)-\(^5\). Many nicotinic acid derivatives have known pharmaceutical and physiological properties and are utilized as active principle in antibacterial drugs\(^6\). 2-Hydroxynicotinic acid can be used for treatment of atherosclerosis and hypoglycaemia, for synthesizing pharmaceuticals and agrochemicals and also for synthesizing new metal complexes having versatile physiological functions\(^7\)-\(^8\). 2-Hydroxynicotinic acid undergoes Enol-ketonic tautomerism since the labile H-atom of the OH group at position-2 is in very close proximity to the pyridinic N-atom and can be easily attached to it. The ketonic tautomer is more stable, favoured even in solid state, as it is stabilized by the intramolecular H-bonding between the carboxylic group and ketonic group (at position-2)\(^9\)-\(^11\). Dogra studied the effect of solvent and acid or base concentrations on spectral characteristics of 2-Hydroxynicotinic acid under various pH conditions using various spectroscopic methods and quantum chemistry calculations\(^12\). Nicotinic acid derivatives have versatile coordinating modes and many of these ligands forms 3D metal-organic framework i.e. supramolecular association with metal via hydrogen bonding, \(\pi\)-\(\pi\) interaction and metallophilic interaction. This can be used as a power crystal-engineering tool for constructing and tailoring metal-organic architectures with desirable application\(^13\)-\(^14\). 2-Hydroxynicotinic acid can be monodeprotonated to produce 2-hydroxynicotinate anion, depending on the pH, which has multiple coordination sites, namely, monodendate, bridging, N,O-chelation (involving the pyridine nitrogen and the oxygen at position-2, forming a four membered chelate ring), O,O-chelation...
(involving the COO group and the oxygen at position-2, forming a six membered chelate ring\textsuperscript{15-17}. Herein, we report the synthesis, spectral characterization and biological activity of four new complexes of 2-Hydroxy-6-methyl nicotinic acid (H\textsubscript{2}6MnicO) with transition metals Co(II), Ni(II) and Cu(II).

**Experimental work**

**Materials and Method**

All the chemicals and were of AR grade, purchased from Sigma-Aldrich, and used without further purification. Purity of synthesized ligand and complexes was verified by TLC using different solvent systems. IR spectra are recorded on Bruker Optic Model Alpha (FT-IR) (Zn-Se Optics, ATR) (4000-500 cm\textsuperscript{-1}) using KBr disc. Magnetic susceptibility measurements were carried out on the vibrating sample magnetometer (VSM) model 155 at 5500 Gauss field strength. Microwave assisted synthesis was carried out in domestic microwave oven Model KENSTAR-OM20ACF, 2450MHz, 800W and GMBR (Green Microwave Biochemical Reactor) at GCRC, P.G. Dept. of Chemistry, Govt. Dungar College (NAAC`A` Grade) MGS University, Bikaner, Rajasthan. ECIL Double Beam UV-Visible Spectrophotometer, model UV 5704SS, with quartz cell of 10 mm light path was used for electronic spectra. All biological activities have been carried out with horizontal laminar at BIFR, Bikaner.

**Synthesis of H\textsubscript{2}6MnicO by microwave irradiation method**

Concentrated HCl (3 ml) and glacial acetic acid (3 ml) were added to a 10 ml aqueous suspension of 2-chloro-6-methyl nicotinic acid (1.72 g, 10 mmol). This mixture was taken in Erlen-Meyer flask capped with a funnel placed in a microwave oven and irradiated at 200 watt for 3.5 minutes. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to attain room temperature and solid separated was filtered. The crude product was recrystallized from redistilled ethanol.

![Synthesis of 2-Hydroxy-6-methyl nicotinic acid](image)

**Fig.1: Synthesis of 2-Hydroxy-6-methyl nicotinic acid**

**Synthesis of complexes by microwave irradiation method**

To prepare complexes, 2.0 mmol (0.08 g) of NaOH were dissolved in 5 ml of distilled water and 2.0 mmol of H\textsubscript{2}6MnicO were added. The pH value of the solution was maintained to 7-8.5 with saturated aq. solution of NaOH or a suitable acid, respectively. 1 mmol of divalent metal chloride (0.238 g of NiCl\textsubscript{2}.6H\textsubscript{2}O, 0.238 g of CoCl\textsubscript{2}.6H\textsubscript{2}O and 0.135 g of CuCl\textsubscript{2} (Anhyd.)) was added slowly into the basic solution of H\textsubscript{2}6MnicO, with constant stirring. The resulting mixture was irradiated in a microwave oven for 2 to 4 minutes at medium power level (600W) maintaining the occasional shaking. The mixture was cooled to room temperature and poured into ice chilled methanol and dried in vacuum over P\textsubscript{2}O\textsubscript{5}\textsuperscript{18}. Physico-chemical properties of prepared ligand and complexes are shown in Table-1.
Table-1: Physico-chemical data of ligand and complexes

| Ligand/ Complexes     | Colour            | M.P. (ºC) | Reaction period (Min.) | Rf value  | Yield (%) |
|-----------------------|-------------------|-----------|------------------------|-----------|-----------|
| H₂₆MnicO              | Off White         | 253       | 3.5                    | (0.74)ᵇ   | 65        |
| Na₂[Co(H₆MnicO)₂Cl₂]  | Light pink        | 250       | 2.5                    | (0.68)ᶜ   | 56        |
| Na₂[Ni(H₆MnicO)₂Cl₂]  | Off green         | 258       | 3.5                    | (0.58)ᵈ   | 63        |
| Na₂[Cu(H₆MnicO)₂Cl₂]  | Bluish white      | 261       | 3.6                    | (0.75)ᵉ   | 70        |

𝐚 = Ethanol: Benzene (3:7), 𝐛 = Ethanol: Benzene (5:5), 𝐜 = Ethyl acetate: CCl₄ (3:7),
d = Ethyl acetate: CCl₄ (4:6), 𝐞 = Methanol: Petroleum ether (2:8).

Results and discussion

IR spectral data

The significant infrared absorption frequencies for 2-Hydroxy-6-methylnicotinic acid and its metal complexes are reported in the Table-2. The strong band at 1730 cm⁻¹, in ligand, assigned to the ν(C=O) stretch of COOH group, is absent in the spectrum of complexes, which confirms the coordination of respective oxygen atom to the metal¹⁹. In complexes, the carboxylate form of the monodeprotonated ligand is confirmed by the two bands at 1624 cm⁻¹ and 1377 cm⁻¹ for Co(II), at 1626 cm⁻¹ and 1391 cm⁻¹ for Ni(II), at 1630 cm⁻¹ and 1371 cm⁻¹ for Cu(II), which are assigned to ν₁r(COO) and ν₁(COO'), asymmetric and symmetric stretch, respectively²⁰-²¹. In case of ligand, another strong band, centred at 1640 cm⁻¹, is assigned to the ν(C=O) stretch of the amide group. The strong and broad band in complex, due to ν₁r(COO') stretch, can be assumed as a mixed band with ν(C=O) stretch of the amide group²². This shifting of the band due to ν(C=O) stretch of the amide group, in form of the mixed band, towards lower frequency in the complex confirms the metal coordination via oxygen atom of the amide group²³-²⁴. The shift (Δ) between ν₁r(COO') and ν₁(COO'), for all complexes, is almost in the same range (247 cm⁻¹ to 259 cm⁻¹), shows the coordination through COO⁻ ion in unidentate mode²⁵-²⁶. The ν(N-H) stretch, in-plane δ(N-H) bending and out-of-plane γ(N-H) bending (at 3100, 1540 and 581 cm⁻¹, respectively, in the free ligand, are also present in the spectra of the complexes, at almost same range, showing the pyridine nitrogen protonation in ligand as well as in the complexes. It reveals that 2-hydroxyl-6-methylnicotinic acid exists in oxo-form rather than hydroxyl form²⁷, as shown in figure 2. In the IR spectra of all complexes absorption of medium intensity, in the region 400-500 cm⁻¹, may be attributed to ν(M-O) stretching²⁸-²⁹.

![Figure 2: Enol-ketonic tautomer of 2-Hydroxy-6-methylnicotinic acid](image-url)
Table-2: Significant IR spectral bands (cm⁻¹) of the ligand and complexes.

| Ligand/Complexes | Carbonyl group | Carboxylate group | N-H group |
|------------------|----------------|--------------------|-----------|
|                  | ν(C=O)\(^a\)   | ν(C=O)\(^b\)       | Δ         |
| H₂6MnicO         | 1730 (vs,br)   | 1640 (vs,br)       | -         |
| Na₂[Co(H₆MnicO)₂Cl₂] | '          | 1624 (vs,br)       | 1377 (s)  |
| Na₂[Ni(H₆MnicO)₂Cl₂] | '          | 1626 (vs,br)       | 1391 (s)  |
| Na₂[Cu(H₆MnicO)₂Cl₂] | '          | 1630 (vs,br)       | 1371 (s)  |

\(^a\) = ν(C=O) stretch of COOH group, \(^b\) = ν(C=O) stretch of the amide group, \(^c\) = mixed absorption band of ν\(_{as}\)(COO\(^-\)) and ν(C=O) of the amide group, ν\(_s\) = symmetric stretch, ν\(_as\) = asymmetric stretch, Δ= ν\(_{as}\)(COO\(^-\)) - ν\(_s\)(COO\(^-\)), vs = very strong, s = strong, m = medium.

**Electronic Spectra and Magnetic Moments**

The electronic absorption spectra of the complexes have been measured in DMSO. Band maxima and corresponding assignments are reported in Table-3. For all complexes, absorptions bands found in the range characteristic for the octahedral stereochemistry of the complexes.\(^{30-33}\) The observed magnetic moment data of complexes also support the expected octahedral geometry.\(^{34-36}\) The tentative structure of the complexes is shown in figure 3.

Table 3: Magnetic moments and Electronic spectral data of complexes

| Complexes                  | μ\(_{eff}\) (BM) | Electronic Spectral bands | Tentative assignments | Expected Geometry |
|----------------------------|-----------------|---------------------------|-----------------------|------------------|
| Na₂[Co(H₆MnicO)₂Cl₂]       | 4.70            | 31446, 27586, 26178, 20550, 18083, 16529 | \(^3\)T\(_1g\)(F) → \(^3\)T\(_2g\)(F), \(^4\)T\(_1g\)(F) → \(^4\)A\(_2g\)(F), \(^4\)T\(_1g\)(F) → \(^4\)T\(_1g\)(P) | Oh               |
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Antimicrobial activities

The antibacterial activity of the compounds against *E.coli*, *S.aureus* and *B.subtilis* were carried out using Muller Hinton Agar media. The activity was carried out using paper disc method is represented in Table 4, which shows that all the metal complexes have moderate antibacterial activities against these bacteria. Among these complexes Co(II), Ni(II) and Cu(II) complexes have been found to be most effective against *E.coli*, *B.subtilis* and *S.aureus* bacteria, respectively, as showing the maximum clarity of zones.

**Table 4:** Antimicrobial activity of synthesized compounds

| S. No. | Compounds (100 ppm) | Zone of inhibition (in mm) |
|-------|---------------------|---------------------------|
|       |                     | *E. coli* | *S. aureus* | *B. subtilis* |
| 1     | H$_2$MnicO          | L$_1$     | 8.0         | 5.5          | 8.0          |
| 2     | Na$_2$[Co(H$_6$MnicO)$_2$Cl$_2$] | C$_1$ | 8.5 | 5.5 | 8.5 |
| 3     | Na$_2$[Ni(H$_6$MnicO)$_2$Cl$_2$] | C$_2$ | 6.5 | 6.2 | 9.0 |
| 4     | Na$_2$[Cu(H$_6$MnicO)$_2$Cl$_2$] | C$_3$ | 6.0 | 6.0 | 8.5 |

**Fig. 3:** Tentative Structure of the complexes where M= Co(II), Ni(II) and Cu(II).
Conclusion

Synthesis of 2-Hydroxy-6-methylnicotinic acid and its complexes with Co(II), Ni(II) and Cu(II) have been carried out by using microwave irradiation successfully with good yield and lesser time. The synthesis of 2-Hydroxy-6-methylnicotinic acid by this green method is a first report. A comparative study of IR spectra of free ligand and its metal complexes indicates that the ligand behaves as bidentate, with $O,O$-chelation mode, via the oxygen atom of carboxyl group and the oxygen atom of the amide group. Infrared spectroscopic analysis also confirms the keto-enolic tautomeric existence of 2-hydroxy-6-methylnicotinic acid. Electronic spectral data, reported herein, suggest that all metal complexes probably possess octahedral geometry or nearly octahedral geometry. The antibacterial properties of the ligands and its complexes were studied against $E$.coli, $S$.aureus and $B$.subtilis bacteria. The result shows that, the Co(II), Ni(II) and Cu(II) complexes have been found to be most effective against $E$.coli, $B$.subtilis and $S$.aureus bacteria, respectively, as, showing the maximum clarity of zones.

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