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Microwave Assisted Synthesis, Characterization and Antimicrobial Studies of Complex of Mn(II) with 2- Hydroxynicotinamide



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Abstract

Coordination compound of Mn(II) with a pyridine based ligand, 2-Hydroxynicotinamide (2HNICAM), was synthesized using microwave irradiation and its structural aspects were investigated by elemental analysis, magnetic, FT-IR and UV-Visible spectroscopic methods. The antibacterial efficacy of the ligand and its complex were also determined by *in-vitro* method against some pathogenic bacteria stains.

Keywords: 2-Hydroxynicotinamide, Microwave irradiation, FT-IR, Antibacterial studies

Introduction

It is documented that many heterocyclic compounds especially pyridine derivatives possess significant bio-potential efficiency as well as playing crucial roles for physiological functions¹⁻⁵. Nicotinamide (Pyridine-3-carboxamide) has crucial role in various metabolic processes such as glycolysis, fatty acid synthesis, respiration⁶ and also has effects on protein and RNA synthesis⁷. Moreover nicotinamide has been successfully used in treatment of pellagra, psoriasis, and schizophrenia and Type-1 diabetes⁸. Nicotinamide, also known as Vitamin-B₃, is also an essential component of the coenzyme NAD and NADP⁹⁻¹⁰. On the other hand many complexes of nicotinamide and its derivatives with late 3d metals are reported to play a pivotal role in biological applications and their biological activities are found greater than the free ligand¹¹⁻¹³. Transition metals have a strong tendency to bound via O,O- and N,N- chelation modes to give new complexes of considerable biological activity¹⁴. The protomeric tautomerism between 2-hydroxypyridine and 2-pyridione has been a subject of much interest in heterocyclic chemistry, both theoretical and experimental, because of its significant biochemical relevance¹⁵⁻¹⁸. Such keto-enol tautomerism plays a key role in various fields of heterocyclic chemistry and biochemistry e.g. rationalization of structures, properties and reactivities of heterocyclic compounds¹⁹, concept and probes of aromaticity²⁰, even it has been related to the appearance of DNA and RNA mutations induced by proton transfer reactions²¹⁻²². The tautomeric equilibrium between 2-hydroxypyridine and 2-pyridione is sensitive to the solvent: whereas the enol form is favoured in the gas phase and the keto or oxo tautomer favoured in high dielectric solvents²³. In the present communication, we report the synthesis, spectroscopic and antibacterial properties of new complex of Mn(II) with 2-Hydroxynicotinamide i.e. 2-Hydroxypyridine-3-carboxamide (2HNICAM), a pyridine based ligand containing amide moiety.

Objectives of the Study

Transition metal complexes of nicotinamide have various applications in medicinal chemistry and shows considerable biological activity. So the present study was design to explore the biological applications of transition metal complexes of 2-Hydroxy derivative of nicotinamide. This study also provides a close insight to the protomeric tautomerism shown by most of 2-Hydroxy derivatives of pyridine ring.

Review of Literature

Tella et al. synthesized and characterized Cu(II) complex containing itaconate and nicotinamide as ligands and formulated. Spectroscopic and X-ray studies revealed that the complex contains copper(II) ion which coordinated through the two nitrogen atoms of

E: ISSN No. 2349-9443

nicotinamide, two oxygen atoms of the itaconate and two oxygen atoms of water molecules to form octahedral geometry. The ligands and their complexes were tested for bacterial activity against *E. coli*, *S. Aureus* and *P. aeruginosa* and the complexes showed enhanced activity as compared to their ligands²⁴. Icbudak et al. synthesized and characterized the mixed ligands *p*-hydroxybenzoate complexes of Ni(II), Cu(II) and Zn(II) with nicotinamide and N,N-diethylnicotinamide. Spectroscopic analysis indicated the octahedral structure of the complexes²⁵. Some complexes of 3d transition metals with nicotinic acid and nicotinamide have been prepared by Allan et al. Spectral and magnetic analysis indicated the octahedral polymeric structure²⁶. Lin et al. synthesized and characterized Co(II) complex of nicotinamide and 2-nitrobenzoate. The complex was found to have 2D supramolecular network through O-H...O and N-H...O H-bonds. Complex was an effective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with IC₅₀ value of 608 nM²⁷.

Experimental

Materials and Instrumentation

All the chemicals and solvents used were of AR grade, procured 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⁻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

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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 2-hydroxynicotinamide by microwave irradiation method

Concentrated aq. solution of NH₃ (3 ml) and catalyst NH₄Cl (0.5 g) were added to a 10 ml aqueous suspension of 2-hydroxynicotinic acid (1.39 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 3.8 minutes²⁸. 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 complex by microwave irradiation method

To prepare complex, 1.0 mmol of the divalent metal chloride (0.198 g of MnCl₂·4H₂O) was added slowly into the 10 ml aq. solution of 2-Hydroxynicotinamide (2.0 mmol, 0.27 g), 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 P₂O₅²⁹. Physico-Chemical Data of prepared ligand and complexes are shown in Table 1.

Table-1: Physico-chemical data of ligand and complexes.

Ligand/ Complexes	Colour	M.P. (°C)	Reaction period (Min.)	R _f value	Yield (%)	Elemental analysis Calculated (Found) %		
						C	H	N
2HNICAM	White	210	4.2	(0.74) ^b	67	52.16 (52.02)	4.38 (4.26)	20.29 (20.16)
Mn- 2HNICAM	Brown	215	4.0	(0.85) ^d	62	32.38 (32.27)	3.68 (3.53)	12.79 (12.62)

b = Ethanol : Benzene (5:5), c = Ethyl acetate : CCl₄ (3:7), d = Ethyl acetate : CCl₄ (4:6).

Results and discussion

IR spectral data:

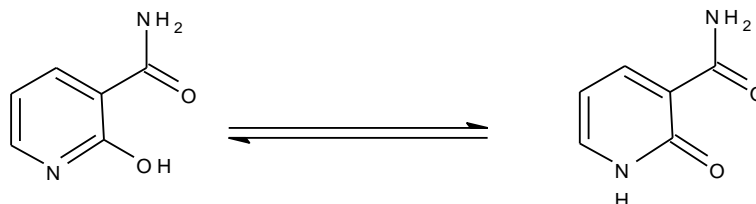
The significant infrared wave numbers for 2HNICAM and its metal complex are reported in the Table-2. Amide-I band i.e. (ν_{C=O})^a is considered as a mixed band of the ν(C=O) stretch of both the amide groups of the ligand, free amide group at position-3 and ring amide group. Complexes shows a negative shift in this band, as compared to the ligand, which clearly indicates the metal coordination through the carbonyl oxygen of both the amide groups leaving the N of both amide groups free³⁰⁻³¹. A broad band centred at 3177 cm⁻¹, in the ligand, is assigned to ν(N-H) stretch of the both the amide groups. A positive shift in ν(N-H) stretch in complexes than ligand also indirectly confirms the O,O- chelation mode of the

ligand³². Presence of coordinated water is confirmed by the strong absorption band in IR spectra of complexes, in the range 3363 to 3421 cm⁻¹, which is assigned to ν(O-H) stretch³³⁻³⁴. In IR spectra of ligand, the absence of ν(O-H) stretch (around 3400 cm⁻¹), in-plane δ(C₂-OH) bend (around 1280 cm⁻¹) and also, the strong band around 1023 cm⁻¹, indicative of pyridine structure, confirms that the ligand is possibly exist as the keto tautomer and not as enol tautomer, in solid state³⁵⁻³⁶. The keto-enol tautomeric conversion of 2-Hydroxypyridine-3-carboxamide (2HNICAM) to 2-Oxo-1H-pyridine-3-carboxamide is shown in scheme 1. In the IR spectra of all complexes absorption of medium intensity, in the region 450-550 cm⁻¹, may be attributed to ν(M-O) stretching³⁷⁻³⁸.

Table-2: Significant IR Spectral Bands (cm⁻¹) of the Ligand and Complexes

Ligand/Complexes	ν_{N-H}	$(\nu_{C=O})^a$	$(\nu_{C-N+\delta_{N-H}})^b$	$(\nu_{N-H+\delta_{C-N}})^c$	ν_{O-H}	ν_{M-O}
2HNICAM	3177	1660	1604	1555	-----	-----
Mn + 2HNICAM	3180	1634	1610	1574	3363	535

a = amide - I band, b = amide - II band, c = amide - III band



2-Hydroxypyridine-3-carboxamide

2-Oxo-1H-pyridine-3-carboxamide

Scheme 1. Keto – Enol tautomers of 2-Hydroxynicotinamide.

Electronic Spectra and Magnetic Moments

The electronic absorption spectra of the complex have been measured in DMSO. Band maxima and corresponding assignments are reported in Table-3. For the complex, absorptions bands found

in the range characteristic for the octahedral stereochemistry of the complex³⁹⁻⁴². The observed magnetic moment data of complex also support the expected octahedral geometry⁴³⁻⁴⁵.

Table 3. Magnetic Moments and Electronic Spectral Data of Complexes

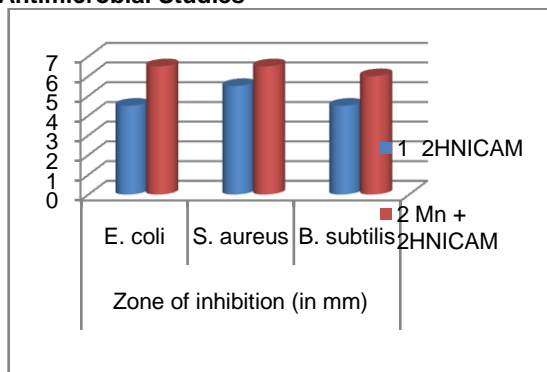
Ligand/Complexes	μ_{eff} (BM)	Electronic Spectral bands λ_{max} (cm ⁻¹)	Tentative assignments	Expected Geometry
Mn + 2HNICAM	5.82	18083, 23419, 28665	${}^6A_{1g} \rightarrow {}^4T_{1g}(G)$ ${}^6A_{1g} \rightarrow {}^4T_{2g}(G)$ ${}^6A_{1g} \rightarrow {}^4E_g, {}^4A_{1g}(G)$	Octahedral

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 the various complexes the Cu(II) complexes have been found to be most effective against these bacteria showing maximum clarity of zones. A graphical representation of antibacterial activities also provided for the purpose of comparison (Figure 1).

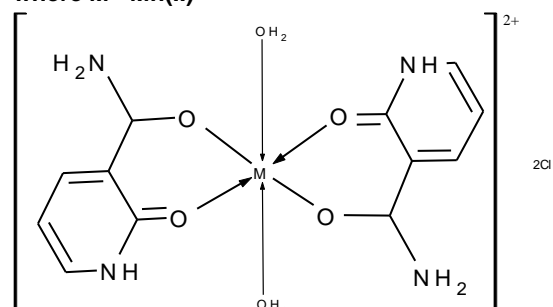
Table 4: Antimicrobial Activity of Synthesized Compounds

S. No.	Compounds (100 ppm)	Zone of inhibition (in mm)		
		<i>E. coli</i>	<i>S. aureus</i>	<i>B. subtilis</i>
1	2HNICAM	4.5	5.5	4.5
2	Mn + 2HNICAM	6.5	6.5	6.0

Figure 1: Graphical Representation of Antimicrobial Studies

Conclusion

Synthesis of 2-hydroxynicotinamide and its complex with Mn(II) have been carried out by using microwave irradiation successfully with good yield and lesser time. The synthesis of 2-hydroxynicotinamide by this green method is a first report. A comparative study of IR spectra of free ligand and its metal complex indicates that the ligand behaves as bidentate, with O,O-chelation mode, via the oxygen atom of both the amide groups, free amide group at position-3 and ring amide group. Vibrational spectroscopic analysis also confirms the existence of 2-hydroxynicotinamide as oxo-tautomer rather than its hydroxy form. Electronic spectral data, reported herein, suggest that the metal complex probably possess octahedral or nearly octahedral geometry. The antibacterial properties of the ligands and its complex were studied against *E.coli*, *S.aureus* and *B.subtilis* bacteria. The result shows that the Mn(II) complex possess considerable effective antibacterial activities against these bacteria. Tentative structure of the complexes is reported in figure 2.

Figure 2: Tentative Structure of the Complexes where M= Mn(II)

Acknowledgements

One of the author (S K Verma) gratefully thanks the University Grant Commission (UGC) CRO Bhopal (India) for awarding teacher research fellowship (TRF) to carry out the research work at GCRC, Department of Chemistry, Government Dungar College (NAAC 'A' Grade), MGS University Bikaner, Rajasthan, India.

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