IJCPS Vol. 7, No. 2 , Mar-Apr 2018
www.ijcps.org
ISSN:2319-6602
International Journal of Chemical and Physical Sciences

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

doi: 10.30731/ijcps.7.2.2018.67-74

Abstract

*New transition metal complexes of 2-Hydroxy-6-methylnicotinic acid ($H_26MnicO$) $Na_2[M(H6MnicO)_2Cl_2]$ (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 co-ordination 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, π-π 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[15-17]. Herein, we report the synthesis, spectral characterization and biological activity of four new complexes of 2-Hydroxy-6-methylnicotinic acid ($H_2$6MnicO) with transition metals Co(II), Ni(II) and Cu(II).

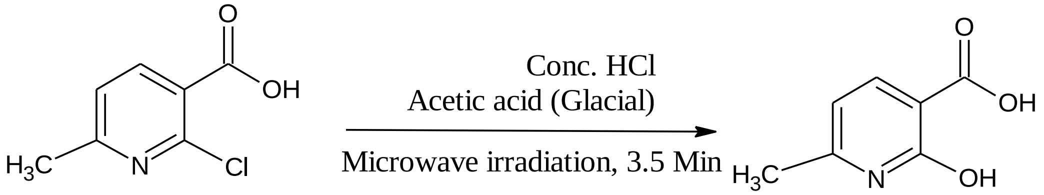
Experimental work

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^{-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_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-methylnicotinic 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 recrystalized from redistilled ethanol.



2-Chloro-6-methylnicotinic acid 2-Hydroxy-6-methylnicotinic acid

Fig.1: Synthesis of 2-Hydroxy-6-methylnicotic 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_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 $NiCl_2.6H_2O$, 0.238 g of $CoCl_2.6H_2O$ and 0.135 g of $CuCl_2$ (Anhyd.)) was added slowly into the basic solution of $H_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_2O_5[18]. Physico-chemical properties of prepared ligand and complexes are shown in Table-1.

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

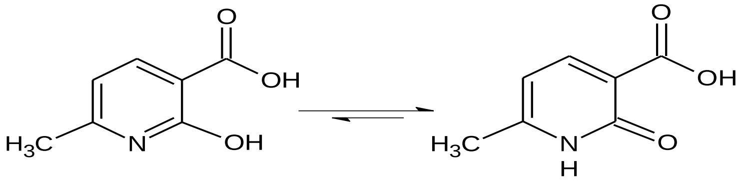
Ligand/ Complexes	Colour	M.P. (°C)	Reaction period (Min.)	R_f value	Yield (%)
$H_26MnicO$	Off White	253	3.5	$(0.74)^b$	65
$Na_2[Co(H6MnicO)_2Cl_2]$	Light pink	250	2.5	$(0.68)^d$	56
$Na_2[Ni(H6MnicO)_2Cl_2]$	Off green	258	3.5	$(0.58)^e$	63
$Na_2[Cu(H6MnicO)_2Cl_2]$	Bluish white	261	3.6	$(0.75)^a$	70

a = Ethanol: Benzene (3:7), **b** = Ethanol: Benzene (5:5), **c** = Ethyl acetate: CCl_4 (3:7), **d** = Ethyl acetate: CCl_4 (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 $\nu(C=O)$ stretch of COOH group, is absent in the spectrum of complexes, which confirms the coordination of respective oxygen atom to the metal[19]. 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 $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$, asymmetric and symmetric stretch, respectively[20-21]. In case of ligand, another strong band, centred at 1640 cm^{-1}, is assigned to the $\nu(C=O)$ stretch of the amide group. The strong and broad band in complex, due to $\nu_{as}(COO^-)$ stretch, can be assumed as a mixed band with $\nu(C=O)$ stretch of the amide group[22]. This shifting of the band due to $\nu(C=O)$ 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 group[23-24]. The shift (Δ) between $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$, for all complexes, is almost in the same range (247 cm^{-1} to 259 cm^{-1}), shows the coordination through COO^- ion in unidentate mode[25-26]. The $\nu(N\text{-}H)$ stretch, in-plane $\delta(N\text{-}H)$ bending and out-of-plane $\gamma(N\text{-}H)$ 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 form[27], 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 $\nu(M\text{-}O)$ stretching[28-29].



2-Hydroxy-6-methylpyridine-3-carboxylic acid 2-Oxo-1H-6-methylpyridine-3-carboxylic acid

Fig.2: Enol-ketonic tautomer of 2-Hydroxy-6-methylnicotinic acid

Table-2: Significant IR spectral bands (cm^{-1}) of the ligand and complexes.

Ligand/ Complexes	**Carbonyl group**		**Carboxylate group**			**N-H group**			
	$\nu(C{=}O)^a$	$\nu(C{=}O)^b$	$\nu_{as}(COO^-)^c$	$\nu_s(COO^-)$	Δ	ν(N-H)	δ(N-H)	γ(N-H)	ν(M-O)
$H_26MnicO$	1730 (*vs,br*)	1640 (*vs,br*)	-	-	-	3100	1540	581	-
$Na_2[Co(H6MnicO)_2Cl_2]$	-	-	1624 (*vs,br*)	1377 (*s*)	247	3138	1567 (*s*)	565	452 (*m*)
$Na_2[Ni(H6MnicO)_2Cl_2]$	-	-	1626 (*vs,br*)	1391 (*s*)	235	3131	1556 (*s*)	549	446 (*m*)
$Na_2[Cu(H6MnicO)_2Cl_2]$	-	-	1630 (*vs,br*)	1371 (*s*)	259	3117	1551 (*s*)	543	454 (*m*)

a = ν(C=O) stretch of COOH group, ***b*** = ν(C=O) stretch of the amide group, ***c*** = mixed absorption band of $\nu_{as}(COO^-)$ and ν(C=O) of the amide group, ν_s = symmetric stretch, ν_{as} = asymmetric stretch, $\Delta = \nu_{as}(COO^-) - \nu_s(COO^-)$, *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** $\lambda_{max}(cm^{-1})$	**Tentative assignments**	**Expected Geometry**
$Na_2[Co(H6MnicO)_2Cl_2]$	4.70	31446, 27586, 26178, 20550, 18083, 16529	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$, $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$	*Oh*

$Na_2[Ni(H6MnicO)_2Cl_2]$	3.30	31950, 28011, 25646, 22529, 18116, 16584, 11414	$^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$	*Oh*
$Na_2[Cu(H6MnicO)_2Cl_2]$	1.87	30441, 27027, 26109, 22900, 18030, 16584, 11014	$^2E_g \rightarrow {}^2T_{2g}$ $^2B_{1g} \rightarrow {}^2A_{1g}$	*Oh*

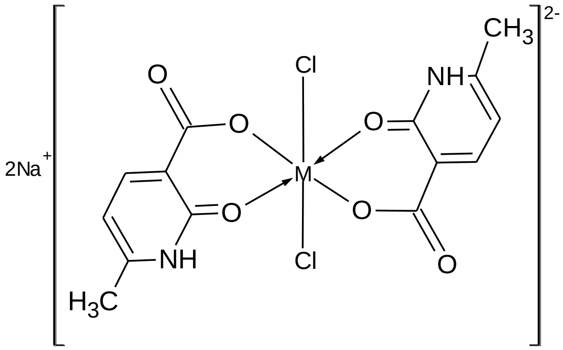


Fig. 3: Tentative Structure of the complexes where M= Co(II), Ni(II) and Cu(II).

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	$H_26MnicO$	L_1	8.0	5.5	8.0
2	$Na_2[Co(H6MnicO)_2Cl_2]$	C_1	8.5	5.5	8.5
3	$Na_2[Ni(H6MnicO)_2Cl_2]$	C_2	6.5	6.2	9.0
4	$Na_2[Cu(H6MnicO)_2Cl_2]$	C_3	6.0	6.0	8.5

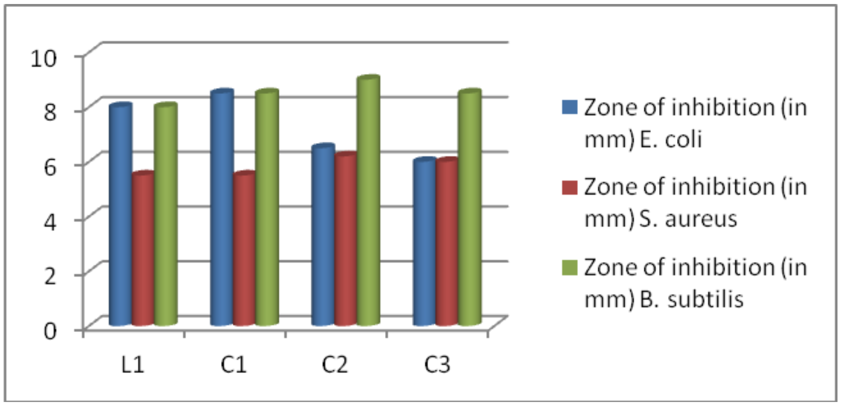


Fig.4: Graphical Representation of Antimicrobial Studies.

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.

Acknowledgement

One of the author (SKV) 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-334001.

References

[1] F. Depeint, W. R. Bruce, N. Shangari, R. Mehta and P. J. O'Brien, *Chem Biol Interact*, 2006, 163, 94.
[2] B. G. Brown and X. Q. Zhao, *Am J Cardiol*, 2008, 101, B58-B62.
[3] T. Suksrichavalit, S. Prachayasittikul, C. Nantasenamat, C. I. N. Ayudhya, and V. Prachayasittikul, *European Journal of Medicinal Chemistry*, 2009, 44, 3259.
[4] D. Wang, X. Cheng, Y. Shi, E. Sun, X. Tang, C. Zhuang and T. Shi, *Solid State Sci*, 2009, 11, 195-199.
[5] R. Singh, R. S. S. Rao, *J Mol Struct*, 1981, 71, 23–30.

[6] A. G. Gilman, L. S. Goodman, and A. Gilman, *The pharmacological basis of therapeutics, 6th ed*., 1980, Macmillan, New York.

[7] A. R. Victoria and D. W. Michael, *Chem. Mater. Rev*., 1994, 137, 357- 401.

[8] A. M. Beatty, *Coord. Chem. Rev*., 2003, 246, 131-143.

[9] A. J. Boulton and A. Mckillop, *Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds*, Vol. 2, 1984, Pergamon, Oxford.

[10] C. Y. Sun, X. J. Zheng and L. P. Jin, *Zeitschrift Fur Anorganische und Allgemeine Chemie.*, 2004, 630, 1342-1347.

[11] S. K. Verma and N. Bhojak, *World Journal of Pharmacy and Pharmaceutical Sciences*, 2017, 6(6), 490-514.

[12] S. K. Dogra, *J. Mol. Struct*., 2005, 737, 189-199.

[13] C. L. Ma, Q. L. Li and R. F. Zhang, *Inorg Chim Acta*, 2009, 362, 2937-2940.

[14] H. H. Zou, S. H. Zhang, Y. Xiao, C. Feng and Y. G. Wang, *Struct Chem*, 2011, 22, 135-140.

[15] S. M. O. Quintal, H. I. S. Nogueira, V. Felix and M. G. B. Drew, *Polyhedron*, 2002, 2, 2783-2791.

[16] Y. M. Li, Y. X. Che and J. M. Zheng, *Chinese J. Struct. Chem*., 2006, 5, 572-576.

[17] S. M. O. Quintal, H. I. S. Nogueira, V. Felix and M. G. B. Drew, *Dalton Transactions*, 2002, 7, 4479-4487.

[18] N. Yadav and N. Bhojak, *The Int.J.Eng.Sci.*, 2013, 2(2), 166-168.

[19] Y. F. Yue, W. Sun, E. Q. Gao, C. J. Fang, S. Xu and C. H. Yan, *Inorganica Chimica Acta*, 2007, 360, 1466-1473.

[20] D. A. Kose, H. Icbudak and H. Necefoglu, *Hecettepe J. Biol. & Chem*., 2007, 35(2), 123-128.

[21] W. Lewandowaski, B. Desiewicz, P. Koczon, J. Skierski, K. D. Teperek, R. Swislocka, L. Fuks, W. Priebe and A. P. Mazurek, *Journal of Molecular Structure*, 2002, 604, 189-193.

[22] J. Miklovic, P. Sega, D. Miklos, J. Titis, R. Herchel and M. Melník, *Chemical Papers*, 2008, 62(5), 464-471.

[23] P. C. R. Soares-Santos, H. I. S. Nogueira, J. Rocha, V. Felix, M. G. B. Drew, R. A. S. Ferreira, L. D. Carlos and T. Trindade, *Polyhedron*, 2003, 22, 3529-3539.

[24] V. B. Di-Marco, A. Tapparo, A. Dolmella and G. G. Bombi, *Inorganica Chimica Acta*, 2004, 357, 135-142.

[25] K. Nakamoto, *Infrared and Raman spectra of inorganic and coordination compounds, Part B (5th. Ed.)*, 1963, New York, Willey.

[26] C. F. Edward, W. P. Griffith, A. J. P. White and D. J. Williams, *J. Chem. Soc., Dalton Trans.*, 1993, 12, 3813.

[27] S. K. Verma and N. Bhojak, *Microwave Assisted Synthesis, Characterization and Antimicrobial Studies of Complexes of Mn(II), Co(II), Ni(II) and Cu(II) with 2-Hydroxynicotinic acid, Chem. Sci. Trans.*, 2018, in press.

[28] M. S. Saleh, J. *Indian Chem. Soc*., 1993, 70, 202.

[29] K. A. Idriss, M. S. Saleh and H. Sedaira, *Monat. Chem*., 1991, 122, 507.

[30] Raja Ram, K. K. Verma, H. S. Bhandari, and N. Bhojak, *IARJSET*, 2015, 2(11), 40-43.

[31] S. F. A. Kettle, *Physical Inorganic Chemistry*, 1996, Springer-Verlag Berlin-Heidelberg.

[32] B. N. Figgis and M. A. Hitchman, *Ligand Field Theory and Its Applications*, 2000, Willey-VCH, New York.

[33] K. F. Purcell and J. C. Kotz, *Inorganic Chemistry*, 1977, W. B. Saunders, Philadelphia.

[34] R. N. Prasad, M. Jindal and M. Jain, *J Indian Chem Soc*., 1984, 9, 1-3.
[35] K. K. Verma, Raja Ram, K. Sharma and N. Bhojak, *World Journal of Pharmacy and Pharmaceutical Sciences*, 2016, 5(4), 1307-1318.
[36] J. Lewis and R. Wilkins, *Modern Coordination Chemistry*, Interscience, 1960, New York.