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GREEN CHEMISTRY APPROACH SYNTHESIS, SPECTRAL AND BIOLOGICAL CHARACTERIZATIONS OF Cd(II) AND Hg(II) COMPLEXES WITH BIO-ACTIVE ISONIAZID AND BENZOATE ION

P. Manikandan[1]*, K. Rajasekar[1], T. Gomadurai[1], B. Sathiyamoorthy[1] and P. Sudhakar

Department of Chemistry, Government Arts College, Ariyalur-621 713 Tamil Nadu, India.

***Corresponding Author: P. Manikandan**
Department of Chemistry, Government Arts College, Ariyalur-621 713 Tamil Nadu, India.

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ABSTRACT
Novel metal complexes of Cd(II) and Hg(II) with Isoniazid and Benzoate ion have been synthesized by microwave assisted method. The Synthesized complexes have been characterized by elemental analysis, metal estimation, molar conductance, cyclic voltammetry and spectral methods viz., UV-visible, IR, Far-IR and NMR. The elemental analysis and metal estimation of the complexes show that 1:1:2 ratio of composition of metal and each ligands. The molar conductance values indicate the non-electrolyte (1:0 types) of the complexes. The redox properties of the metal complexes were investigated by electrochemical method using cyclic voltammogram. The complexes exhibited quasi-reversible one electron transfer reaction. The tetrahedral geometry from UV spectra and the metal ions coordinate in a bidentate mode of Isoniazid and monodentate mode of benzoate ion from IR and metal linked atom from Far-IR spectral data were deduced. The ^{1}H-NMR and ^{13}C-NMR spectra of diamagnetic metal ions in complexes was carried out, the chemical shift indicating the mode of coordination of ligands to the metal ions. Moreover it is concluded that isoniazid acts as a bidentate ligand, coordinating through hydrazinic nitrogen and carbonyl oxygen. The biological activity of the ligand and its complexes were tested by the antibacterial strains of *Actinobacter* and *Salmonella typhi*, antifungal strains of *Aspergillus Niger* and *Candida albicans.* The biological activities confirm that these metal complexes are more potent than of the free ligand.

KEYWORDS: Isoniazid, Benzoate ion, Cyclic voltammetry, Antibacterial, Antifungal, Metal complexes.

INTRODUCTION
Chelating ligands containing N and O donor atoms show wide biological activity and are of unique interest because of the ways in which they are bonded to the metal ions. It is known that existence of metal ions bonded to biologically active compounds may enhance their activities.[1,2] Particularly Isoniazid (INH) is the one among the well known N-donor ligand. Tuberculosis (TB) is a global crisis and is with the universal health threats today. Isonicotinic acid hydrazide (Isoniazid: INH) is one of the mostly potent anti-TB drugs, used to kill the Mycobacterium tuberculosis.[3,5] Isoniazid (INH) is capable to coordinate with metal cations through different chemical groups-heterocyclic nitrogen from the pyridine ring and/or carbonylic O and N atoms of the hydrazide group.[6,8] Benzoate ion is to be noted that the increase in pharmacological effect.[9]

Microwave irradiation of organic reactions has quickly gained attractiveness as it accelerates the reaction towards a range of synthetic transformations, solventless procedures without the use of supporting reagents and hence eco-friendly. Chemical transformations that took hours or even days to complete can now be consummate in minutes. Microwave energy offers plentiful benefits for performing synthesis such as increased reaction rates, enhanced yields and cleaner chemistries.[10,13]

The present work aims at the microwave-assisted (Green Chemistry Approach) synthesis and spectral characterization of Cd(II) and Hg(II) with Isoniazid and Benzoate ion along with the investigation of their redox behavior by cyclic voltammetry (CV) studies. The complexes were also screened for antibacterial and antifungal activities and the results were discussed.

MATERIALS AND METHOD
All the chemicals used were of AR grade from Sigma Aldrich and were used as received. Microwave irradiations were used for the synthesis of complexes from domestic microwave oven. The elemental analysis of the complex was carried out using (Thermo Finnegan make, Flash EA1112 series) CHNS(O) analyzer instrument. The metal ion estimated by volumetrically using standard procedure. The molar conductance of 10^{-3} M complex in acetonitrile was conducted using Systronic

Conductivity Bridge at 25^0c. Cyclic voltammogram of a complex were recorded in DMSO solution at room temperature on Versa Stat (Princeton Applied Research-Make) electrochemical analyzer. The three electrode cell comprised of reference calomel, auxiliary (or) counters Ag/AgCl and the working glassy carbon (part number-CHI 101) electrodes.

The diffused reflectance spectra of the complexes in the solid state were measured using Varian carry-5000 model UV-Visible spectrophotometer. IR spectra of the free INH (ligand) and its complexes were carried out using Schimadzu FT-IR8400s spectroscopy at 4000-400 cm^{-1} wave number with KBr pellet technique. The Far IR spectrum of the complexes was recorded in a Bruker make, 3000 Hyperion Microscope with Vertex 80 FTIR system model instruments.

The antibacterial and antifungal activities of INH and its complexes were done by in-vitro Agar well diffusion method using Amikacin and ketoconazole as a standard for bacterial and fungal strain respectively.

Preparation of complexes

The Cd(II) and Hg(II) complexes were synthesized by mixing Isoniazid 0.44 g (3.23 mmol), 0.50g (3.68 mmol) in 5ml methanol to the Cadmium nitrate 1g (3.24 mmol) and mercury chloridre 1g (3.68 mmol) in 5ml methanol respectively. The mixture was irradiated on a microwave oven for 10 sec, then sodium benzoate 0.93g (6.48 mmol), 1.06g (7.36 mmol) in ethanol was added to the above mixture respectively. The whole mixture was irradiated on a microwave oven for another 10 sec.

RESULT AND DISCUSSION

The synthesized Cd(II) and Hg(II) complexes were stable under ordinary condition. The molar conductance values of Cd(II) and Hg(II)) complexes at 95.3 $ohm^{-1}cm^2$ mol^{-1} and at 44.2 $ohm^{-1}cm^2$ $mol^{-}1$ respectively, indicating the non-ionic, neutral nature(1:0 type)[14,15] of the both complexes. These complexes are frequently soluble in water and DMSO on heating.

The Stoichiometry and formula of the complexes are $[M(L_1)(L_2)_2]$, these are confirmed on the basis of elemental analysis and metal estimation studies.

Table 1: Analytical data of Cd(II) and Hg(II) complexes.

Compound	Colour	Elemental analysis found (Calc)				
		M%	C%	H%	N%	O%
$[Cd(INH)(Benz)_2]$	Colourless	22.86 (24.40)	48.85 (49.50)	03.48 (04.87)	08.54 (9.43)	16.27 (17.43)
$[Hg(INH)(Benz)_2]$	Colourless	34.59 (35.40)	41.42 (43.50)	02.95 (03.69)	07.25 (07.93)	13.79 (15.43)

Redox properties of Cd(II) and Hg(II) complexes

Cyclic voltammetry study is a vital tool to give the nutshell information about the redox reaction in coordination complexes. This study reveal that the redox properties of Cd(II) and Hg (II) complexes. In Cd(II) complex the anodic peak potential Epa at 0.610 mV and the cathodic peak potential Epc at -1.00V with 100 mV/s scan rate. The peak to peak separation ΔEp is at -1.610 which is confirmed by the quasi reversible one electron transfer reaction.

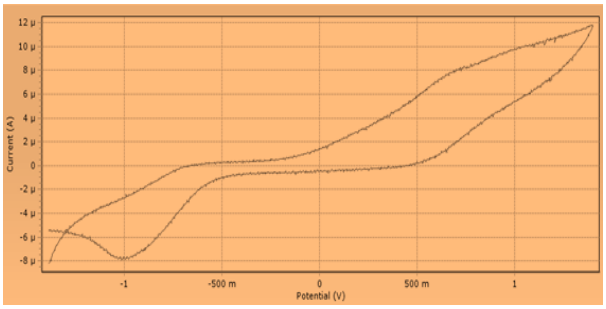

Figure-1: Cyclic voltammogram of Cd(II) complex.

Moreover in the Hg(II) Complex the anodic peak potential Epa at 0.750 mV and the cathodic peak potential Epc at -0.250 with 100 mV/s scan rate. The peak to peak separation ΔEp is at -1.000V which is also confirmed by the quasi reversible one electron transfer reaction.[16]

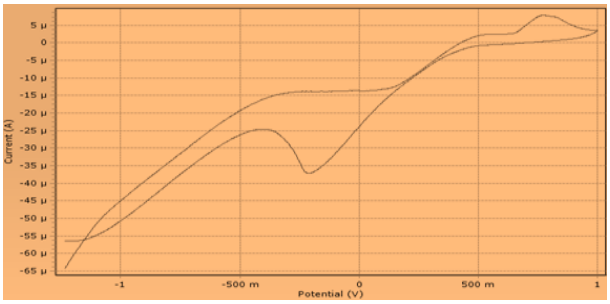

Figure-2: Cyclic voltammogram of Hg(II) complex.

UV-Visible spectrum

The Cd(II) and Hg(II) complexes shows only charge transfer spectrum (CT spectrum) at 268nm and 287nm respectively due to the presence of completely filled 'd' orbital, there is no d-d transition from lower orbital to higher level in these complexes which is confirmed the most probable geometry of these both complexes are pseudo tetrahedral.

IR and Far-IR spectra of Cd(II) and Hg(II) complexes

The IR spectral techniques are useful and significant techniques in finding the functional groups and

complexation ability in metal complexes.[17] The ligand INH shows the stretching frequencies of ν(NH_2) at 3200cm^{-1} and ν(C=O) at 1650-1660 cm^{-1}. in compexes these values shifted to slightly higher frequency as shown in table-2, which indicating that the INH forming complex with the metal ion through nitrogen and oxygen atom of ligand.

The anionic ligand shows the stretching frequency of ν(C=O) at 1680-1750 cm^{-1} and ν(C-O) at 1210-1320 cm^{-1} these frequencies are shifted to slightly lower and higher for 169for Cd(II) and Hg(II) complexes respectively, which indicating that the metal ions were coordinated through oxygen atom of the ligand.

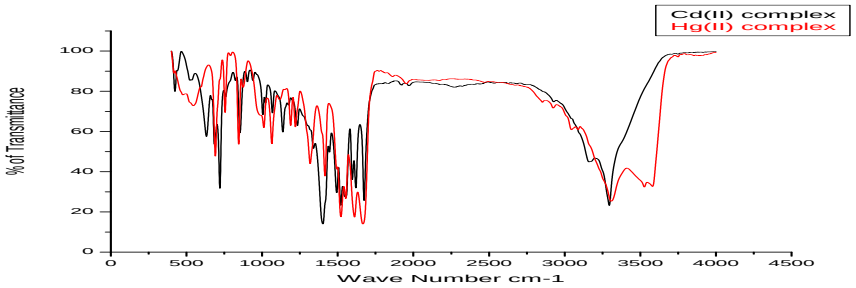

Figure-3: IR spectrum Cd(II) and Hg(II) complexes.

Table-2: IR spectral data for ligands and their Cd(II) and Hg(II) complexes.

Complex	ν(NH_2) cm^{-1}	ν (N-H) cm^{-1}	ν(C=O) cm^{-1}	ν(C-N) cm^{-1}	ν (N-N) cm^{-1}	ν (C-O) cm^{-1}	ν(C=C) cm^{-1}	ν (C=O) cm^{-1}	ν (C-H) cm^{-1}	ν (C-O) cm^{-1}
INH (ligand)	3200	3100	1650-1660	1490	1140	1020-1100	-	-	-	-
Benzoate ion		-	-	-	-	-	1400-1600	1680-1750	3000-3050	1210-1320
Cd(II) complex	3294	3160	1674	1493	1136	1068	1556	1674	2927	1233
Hg(II) complex	3307	3088	1666	1493	1188	1064	1553	1611	3044	1317

Metal-chelating (M-N&M-O) atom were predicted by Far-IR spectrum, from this, In Cd(II) complex the strong frequencies at 519cm^{-1} and at 536 cm^{-1}, Hg(II) complex at 516cm^{-1} and at 530 cm^{-1} respectively indicating the metal-nitrogen and metal-oxygen coordination of INH. The frequency at 422 cm^{-1} and 415 cm^{-1} for Cd(II) and Hg(II) complexes respectively, corresponding to the metal-oxygen coordination of benzoate ion.

^{1}H-NMR spectrum of Cd(II) and Hg(II) complexes

^{1}H-NMR spectra of INH reveal the chemical shift values at (10.10 ppm) shows of N-H proton. Two different aromatic protons present in the ligand and their chemical shift values are at 7.72 to 7.74 ppm indicating the ortho position proton where as 8.68 to 8.70 indicating the Meta position proton. These chemical shift values are slightly shifted lower/higher position upon coordination in particular the NH_2 chemical shift value shifted to lower value at 3.5ppm of Cd(II) and 3.7 of Hg(II) complexes indicating the complexation and coordination through 'N' atom of INH are confirmed.

Table 3: ^{1}H-NMR spectrum of Cd(II) and Hg(II) complexes and ligands.

Chemical shift (ppm)	(N-H)	(C-H)aromatic (Meta)	(C-H) aromatic (ortho)	NH_2	(C-H) aomatic (Benzoate)
INH	10.10	8.68-8.70	7.72-7.74	4.64	7.49-7.96
Cd(II) Complex	10.30	8.73-8.74	7.75-7.76	3.5	7.40-7.50
Hg(II) complex	10.96	8.71-8.81	7.78-7.95	3.7	7.51-7.63

^{13}C -NMR spectrum of Cd(II) and Hg(II) complexes

^{13}C-NMR spectral data of Cd(II) and Hg(II) metal ions upon coordination shows chemical shift values are slightly higher/lower when compared to INH (four different carbon atoms) and benzoate ion (Five different carbon atoms) ligands of different carbon atoms.

Table 4: ^{13}C-NMR spectrum of Cd(II) and Hg(II) complexes and ligands.

Chemical shift (ppm)	C_1	C_2	C_3	C_4	C_5	Chemical shift (ppm) of Cd(II) and Hg(II) complexes				
						C_1	C_2	C_3	C_4	C_5
INH	164.41	140.72	121.46	150.65	-	172.23	135.25	122.28	150.05	-
Cd(II) complex	167.20	141.70	122.54	150.72	132.40	166.45	139.90	122.70	150.80	127.20
Hg(II) complex	164.56	140.48	129.02	150.59	129.71	164.67	140.13	121.84	150.91	123.44

Bio-potential activity of INH and Cd(II) and Hg(II) complexes

The antibacterial activity of INH and Cd(II) and Hg(II) complex against gram negative *Salmonella* & gram

positive *Actinobacter* (pathogenic fungal strain) carried out by Agar well diffusion method using Amikacin and ketoconazole as standard respectively in DMSO as the solvent control. After incubation of disc the MIC (minimum inhibitory concentration) was measured. The results indicating these complexes have higher antibacterial and antifungal activities against the tested microorganism compared with pure ligand INH.[17]

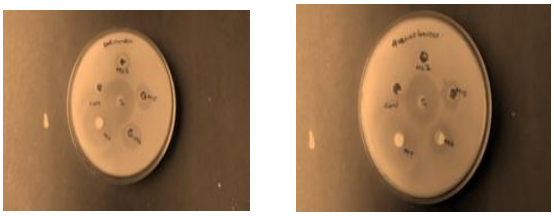

Figure-4: Antibacterial and Anti fungal activity of INH & Cd(II),(Hg(II) complexes.

CONCLUSION

In this work, the Cd(II) and Hg(II) complexes of INH and benzoate ion was synthesized using microwave assisted green chemistry approach and characterized on the basis of analytical, spectral and Biological methods. The formulae of the Cd(II) and Hg(II) complexes complex are $[Cd(INH)(Benz)_2]$ and $[Hg(INH)(Benz)_2]$ respectively. They are non-ionic, neutral and non-electrolyte. The Cyclic Voltammetry studies reveal that both the complexes are well defined redox process corresponding to the formation of one electron transfer quasi reversible Cd(II)/Cd(I) and Hg(II)/Hg(I) couple. The pseudo tetrahedral structure of the complexes confirmed by the electronic, IR, Far-IR and NMR spectral data. The bio-potential activities exposes these complexes are biologically active against the tested microorganisms than the free ligand.

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