



SYNTHESIS, CHARACTERIZATION AND CHELATING PROPERTIES OF INDOLE-SALICYLIC ACID COMBINED MOLECULE

Piyush Vyas¹, Prakash Patel¹ and Bhargav Trivedi²

¹Sheth M N Science College, Patan, Gujarat, India.

²J & J College of Science, Nadiad, Gujarat, India.

E-mail: uppatel2000@yahoo.com

ABSTRACT

The treatment of 2-Chloro-1-indol-1-yl-ethanone with 4-aminosalicylic acid afford a 2-Hydroxy-4-(2-indol-1-yl-2-oxo-ethylamino)-benzoic acid (HIBA). The transition metal complexes of Cu²⁺, Co²⁺, Ni²⁺, Mn²⁺, Zn²⁺ and Fe³⁺ of HIBA have been prepared and characterized by elemental analyses, spectral studies, magnetic moment determination, molar conductivity measurement and microbicidal activity.

Keywords: 2-Chloro-1-indol-1-yl-ethanone, 4-aminosalicylic acid, metal chelates, spectral studies, magnetic moment, antibacterial and antifungal activity.

INTRODUCTION

2-Chloro-1-indol-1-yl-ethanone belonging to the fused heterocyclic system prepared from amino acids are associated with diverse pharmaceutical activities such as antibacterial¹, insecticidal², fungicidal³, antimicrobial⁴, asvitronectal receptes, antagonist⁵, anthelmintic⁶⁻⁸, anti-inflamatory⁹, etc. Recently the Indole derivative has been reported with remarkable antimicrobial activity¹⁰. The reaction of Indole derivative with 4-aminosalicylic acid has not been reported so far. Though 4-amino salicylic acid is excellent anti T.B agent. Thus this may afford good chelating ligand with better microbicidal activity. Hence it was thought interesting to prepare the ligand having 2-Chloro-1-indol-1-yl-ethanone-salicylic acid moieties. Thus the present communication comprises the studies indolylsalicylic acid derivatives and its metal chelates. The research work is illustrated in Scheme-1.

EXPERIMENTAL

Materials

2-chloro-1-indol-1-yl-ethanone was prepared by method reported in literature¹⁰. p-Amino salicylic acid (PAS) (i.e. 4-Aminosalicylic acid) was obtained from local dealer. All other chemicals used were of analytical grade.

Synthesis of 2-Hydroxy-4-(2-indol-1-yl-2-oxo-ethylamino)-benzoic acid.

Formation HIBA

A mixture of 2-Chloro-1-indol-1-yl-ethanone (I) (0.02 mole) and 4-aminosalicylic acid (PAS) (0.02 mole) in ethanol (70 ml) was heated under reflux for 4h. Subsequently ethanol was distilled off and the lump mass obtained. It was triturated with petroleum ether (40-60° C). The solid designated as HIBA was isolated and dried in air. Yield was 73%. It's m.p. was 182-84° C (uncorrected).

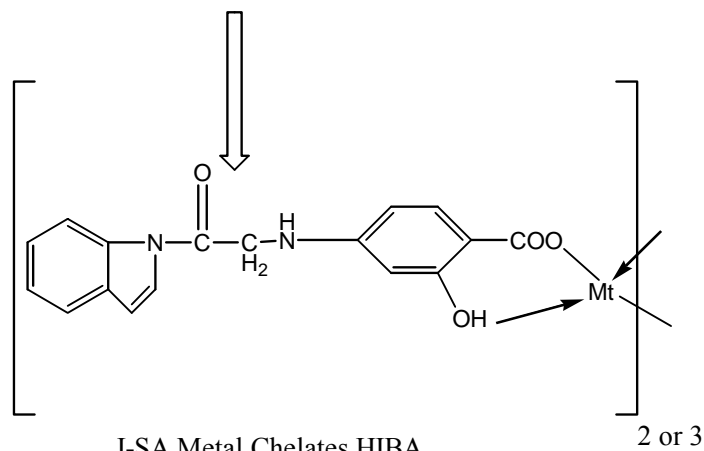
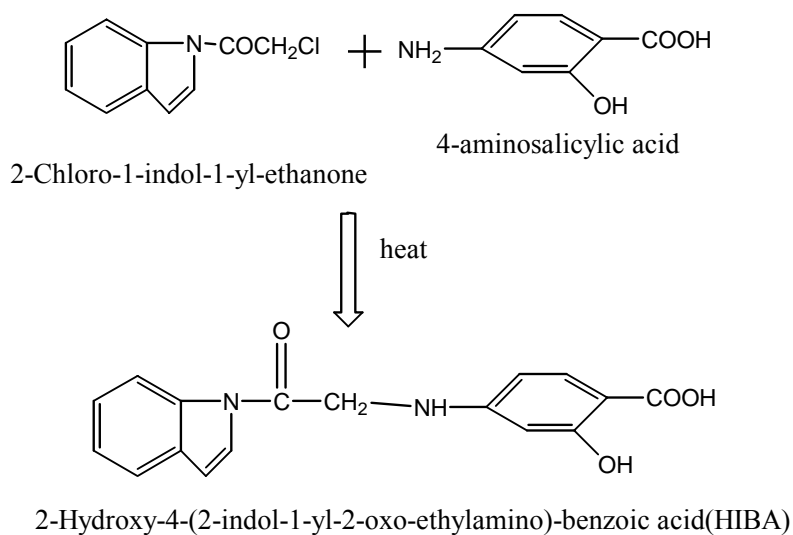
Elemental Analysis: C₁₇H₁₄N₂O₄ (310)

	C%	H%	N%
Calculated:	65.80	4.51	9.03
Found :	65.78	4.48	9.01

Acid Value Theoretical: 198.6 mg KOH/1g. Sample.
Found: 196 KOH/1g Sample.

IR Features 1190-1400 cm^{-1} C-N of Indole
3030, 1500, 1600 cm^{-1} Aromatic
1680 cm^{-1} CO of COOH
3200-3600 cm^{-1} OH 2
3400 cm^{-1} Sec.NH
2850, 2920 cm^{-1} CH_2

NMR
(DMSO) δ ppm Multiplet Aromatic
7.1 – 7.8 (7H) Multiplet Aromatic
6.5-7.8(2H) Doublet Indole CH
4.17 (2H) Singlet CH_2
10.1 (1H) Singlet (COOH)
3.9 (1H) Singlet (OH)
2.8 (1H) Singlet (NH)



Where Mt: Cu^{2+} , Ni^{2+} , Co^{2+} , Zn^{2+} , Mn^{2+} , Fe^{3+}
Scheme-1

Synthesis of metal chelates of HIBA

The Cu^{2+} , Co^{2+} , Ni^{2+} , Mn^{2+} , Zn^{2+} , and Fe^{3+} metal ion chelates of HIBA have been prepared in a similar manner. The general procedure is as follow.

To a solution of HIBA (31.3 g 0.1 mole) in ethanol-acetone (1:1v/v) mixture (150 ml), 0.1N KOH solution was added dropwise with stirring. The pasty precipitates were obtained at neutral pH. These were dissolved by addition of water up to clear solution. It was diluted to 250 ml. by water and was known as stock solution. 25 ml of the stock solution (which contains 0.01 mole HIBA) was added drop wise to the solution of metal salt (0.005 mole for divalent metal ions and 0.0033 mole for Fe^{3+} ion) in water at room temperature. Sodium acetate or ammonia was added up to complete precipitation. The precipitates were digested on water bath at 80°C for 2h. The digested precipitates of chelates were filtered washed with water and air dried. It was amorphous powder. Yield was almost quantitative. The detail are given in Table-1

Measurements

The elemental analyses of all the samples were carried out on elemental analyzer TF-EA.1101 (Italy). IR spectra of HIBA and its metal complexes were scanned on a Nicolet 760 FTIR spectrophotometer in KBr. The NMR spectrum of HIBA was scanned on Bruker NMR spectrophotometer using DMSO solvent. The metal content of the metal chelate were performed by decomposing a weighed amount of each metal complexes followed by EDTA titration as reported in literature ¹¹. Magnetic susceptibility measurement of all the metal complex was carried out at room temperature by the Gouy method. Mercury tetrathiocyanatocobalate (II) $\text{Hg}[\text{Co}(\text{NCS})_4]$ was used as a calibrant. The diffused reflectance spectra of solid metal complex were recorded on a Backman DK Spectrophotometer with a solid reflectance attachment, MgO was employed as the reflectance compound. The electrical conductivity of all the complexes was measure in acetonitrile at 10^{-3} M concentration.

Antifungal activity

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro plant pathogenic organisms listed in Table-3. The antifungal activities of all the samples were measured by cup plate method ¹². Each of the plant pathogenic strains on potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200 gms, dextrose 20gms, agar 20gms and water 1 litre. 5 days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120°C for 15 min. at 15 atm pressure. These medium were poured into sterile Petri plate and the organisms were inoculated after cooling the Petri plate. The percentage inhabitation for fungi was calculated after 5 days using the formula given below.

$$\text{Percentage of inhibition} = \frac{100(X-Y)}{X}$$

Where, X: Area of colony in control plate

Y: Area of colony in test plate

The fungicidal activity all compound are shown in Table-3

RESULTS AND DISCUSSION

The compound HIBA designated as ligand was an amorphous brown powder, soluble in various solvents like dioxane, DMSO and DMF. The results of elemental analysis of HIBA mentioned in experimental part. They are consistent with the predicted structure as shown in Scheme-I.

Examination of IR spectrum (not shown) of HIBA reveals that broad band of phenolic hydroxyl stretching is observed at $3200\text{-}3600\text{ cm}^{-1}$ as well as additional absorption bands at 3030, 1500 and 1600 cm^{-1} are characteristics of the salicylic acid ¹³. The strong bands at 1680 cm^{-1} and 3400 cm^{-1} $\nu_{\text{C=O}}$ and $\nu_{\text{sec.NH}}$. The NMR spectral data (shown in experimental part) also consists with structure of HIBA.

The Metal chelate of HIBA with ions Cu^{2+} , Co^{2+} , Ni^{2+} , Mn^{2+} , Zn^{2+} , Fe^{3+} vary in colours. On the basis of the proposed structure as shown in Scheme-1, the molecular formula of the HIBA ligand is $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_4$. Which upon complexion coordinates with one central metal atom at four coordination sites and with two water molecules. Therefore the general molecular formula of the resulting metal chelate is $[\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_4]_2$

M.2H₂O for divalent metal ions. This has been confirmed by results of elemental analysis reported in Table-1. The data are in agreement with the calculated values.

Inspection of the IR Spectra (not shown) of metal chelates reveals that all the spectra are identical in all respects. The comparison of IR spectrum of the parent ligand HIBA with that of its each metal chelates has revealed certain characteristics differences.

One of the significant differences to be expected between the IR spectrum of the parent ligand and its metal chelates is the presence of more broadened bands in the region of 3200-3600 cm⁻¹ for the metal chelates as the oxygen of the O-H group of the ligands forms a coordination bond with the metal ions¹³⁻¹⁵. This is explained by the fact that water molecule might have strongly absorbed to the metal chelates samples during their formation. Another noticeable difference is that the bands due to the COO⁻ anion at 1600 cm⁻¹ in the IR spectrum of the each metal chelates. The band at 1400 cm⁻¹ in the IR Spectrum of HL assigned to inplane OH determination¹³⁻¹⁵ is shifted towards higher frequency in the spectra of confirmed by a weak bands at 1105 cm⁻¹ corresponding to C-O-M stretching¹³⁻¹⁵. Thus all of these characteristics features of the IR studies suggested the structure of the metal chelates as shown in scheme.

Examination of data of the metal content in each compound revealed a 1:2 metal: ligand (M: L) stoichiometry in all of the chelate of divalent metal ions and 1:3 metal: ligand stoichiometry for Fe³⁺. Magnetic moment (μ_{eff}) of each of the metal chelates is given in Table-2. Examination of these data reveals that all chelates expect at Zn²⁺, are para magnetic while that of Zn²⁺ is diamagnetic.

The diffuse electronic spectrum of the [Cu HL (H₂O)₂] metal complex shows broad bands at 15865 and 22690 cm⁻¹ due to the ²T→²T_{2g} transition and charge transfer, respectively suggesting a distorted octahedral structure¹⁶⁻¹⁸ for the [Cu HL (H₂O)₂] complex. Which is further confirmed by the higher value of μ_{eff} of the [Cu HL (H₂O)₂] complex. The [Ni HL (H₂O)₂] and [Cu HL (H₂O)₂] complex gave two absorption bands respectively at 15695, 22987 and 15376, 22715 cm⁻¹ corresponding to ⁴T_{1g}→²T_{1g} and ⁴T_{1g} (p) transitions. Thus absorption bands at the diffuse, reflectance spectra and the value of the magnetic moments μ_{eff} indicate and octahedral configuration for the [NiHL (H₂O)₂] and [Cu HL (H₂O)₂] complex. The spectra of [Mn HL (H₂O)₂] shows weak bands at 15377, 17650 and 22965 cm⁻¹ assigned to the transitions ⁶A_{1g}→⁴T_{1g} (4G), ⁶A_{1g}→⁴T_{2g} (4G) and ⁶A_{1g} (F) →⁴T_{1g}, respectively suggesting an octahedral structure for the [Mn HL (H₂O)₂] chelate. The spectrum of Fe³⁺ complex has not been adequately characterized. The spectrum comprised the band ground 19018cm⁻¹ and other weak band ground 23010cm⁻¹. The latter has not very long tail. These may have the transition ⁶A_{1g}→⁴T_{2g} (4G) and ⁶A₁→⁴T₁ (4G). The high intensities of the bands suggests that they might be charge transfer in origin μ_{eff} is found to be lower than normal range. In the absence of low temperature moments it is difficult to give any significance. As the spectrum of the [Zn HL (H₂O)₂] polymer is not well resolved, it is not interpreted but it is μ_{eff} value shows that it is diamagnetic as expected.

Conductivities of all the complexes were measured in acetonitrile solvent and all the complexes were found to be electrolytic¹⁹ in nature of 1:2 type and molar conductivity values are in the range of 25.3-39.1 Ohm⁻¹ Cm⁻¹.

Table-1: Analytical Data of the Metal Chelates of HL₁ (i.e. HIBA)

Compound	Empirical Formula*	Mol. Cal. Gm/mol	Yield (%)	Elemental Analysis							
				C%		H%		N%		M%	
				Cald	Found	Cald	Found	Cald	Found	Cald	Found
HL (HIBA)	A	310	73	65.80	65.7	4.51	4.4	9.03	9.0	--	--
(L) ₂ Cu ²⁺	B	717.54	66	56.86	56.8	4.18	4.1	7.80	7.7	8.85	8.8
(L) ₂ Ni ²⁺	C	712.71	68	57.24	57.2	4.20	4.1	7.85	7.8	8.23	8.2
(L) ₂ Co ²⁺	D	712.94	65	57.22	57.2	4.20	4.1	7.85	7.8	8.26	8.2
(L) ₂ Mn ²⁺	E	708.94	62	57.55	57.5	4.23	4.2	7.89	7.8	7.74	7.7
(L) ₂ Zn ²⁺	F	719.38	64	56.71	56.6	4.17	4.1	7.78	7.7	9.08	9.0
(L) ₃ Fe ³⁺	G	1036.85	64	59.02	59.0	3.76	3.7	8.10	8.0	5.38	5.3

*Empirical Formula:

A. C₁₇H₁₄N₂O₄; **B.** C₃₄H₂₆N₄O₈ Cu²⁺ 2H₂O; **C.** C₃₄H₂₆N₄O₈Ni²⁺ 2H₂O; **D.** C₃₄H₂₆N₄O₈Co²⁺ 2H₂O; **E.** C₃₄H₂₆N₄O₈Mn²⁺ 2H₂O; **F.** C₃₄H₂₆N₄O₈Zn²⁺ 2H₂O; **G.** C₅₁H₃₉N₆O₁₂Fe³⁺ 3H₂O

Table -2: Magnetic Moment and Reflectance Spectral data of Metal Chelates of I – SA ligand

Metal chelate	Magnetic Moment μ_{eff} (B.M.)	Molar Conductivity $\Omega\text{m ohm}^{-1}\text{ cm}^2\text{ mol}^{-1}$	Absorption band (cm^{-1})	Transitions
Cu-HL	1.98	37.8	22690 15865	C.T $^2T \rightarrow ^2T_g$
Ni-HL	3.88	36.4	15695 22987	3 A _{2g} → 3 T _{1g} (p) 3 A _{1g} → 3 T _{1g} (F)
Co-HL	4.57	35.7	15376 22715	4 T _{1g} (F) → 4 T _{2g} (F) 4 T _{1g} (F) → 3 A _{2g}
Mn-HL	5.14	37.6	15377 17650 22965	6 A _{1g} → 4 T _{1g} (4E _g) 6 A _{1g} → 4 T _{2g} (4G) 6 A _{1g} → 4 T _{1g} (4G)
Fe-HL	5.90	39.4	19018 23010	6 A ₁ → 4 T _{2g} (4G) 6 A _{1g} → 4 T _{1g} (4G)

Zn²⁺ Diamagnetic in Nature.

The antifungal activity of all the compounds measured for various plant pathogens. Inspection of the result shown in Table-3 indicates that all compounds are good toxic for fungi. Out of all the compounds copper chelates is more toxic than other. These compounds almost inhibit the fungi about 72%. Hence produced metal chelates can be employed as garden fungicides. Further work in the direction is in progress.

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Table-3: Antifungal Activity of Ligand HL₁ and its metal chelates.

Sample	Zone of inhibition of fungus at 1000ppm (%)						
	PE	BT	N	T	RN	AN	TL
HL1	63	62	64	66	68	62	63
(HL1)-Cu ²⁺	75	80	79	84	77	75	78
(HL1)-Ni ²⁺	72	79	77	81	76	78	76
(HL1)-Co ²⁺	75	74	75	77	75	77	73
(HL1)-Mn ²⁺	66	73	72	73	73	73	72
(HL1)-Zn ²⁺	71	79	73	79	74	74	73
(HL1)-Fe ³⁺	73	73	76	78	79	77	78

PE= *Penicillium expansum*; BT= *Botrydepladia thiobromine*;
N=*Nigrospra sp.*; T= *Trichothesium sp.*; RN= *Rhizopus nigricans*;
AN= *Aspergillus niger*.; TL= *Trichoderma lignorum*

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