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Synthesis, characterization and antibacterial properties of some trivalent metal complexes with [(2-hydroxy-1-naphthaldehyde)-3-isatin]-bishydrazone

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Abstract

Complexes of manganese(III), iron(III) and cobalt(III) with a bishydrazone, formed by condensation of isatin monohydrazone with 2-hydroxy-1-naphthaldehyde, have been synthesized. The spectral data reveal that the ligand acts as monobasic tridentate, coordinating through the deprotonated naphtholate oxygen, azomethine nitrogen, and carbonyl oxygen. Molar conductance values adequately support the electrolytic nature of the complexes. On the basis of the above observations the complexes have been formulated as $[M(NIB)_2]X$ where M = Mn(III), Fe(III) or Co(III); X = Cl^-, NO_3^- or OAc^-; HNIB = [(2-hydroxy-1-naphthaldehyde)-3-isatin]-bishydrazone. Based on electronic spectral data and magnetic moment values, an octahedral geometry has been proposed. The iron(III) complex has been subjected to thermal decomposition studies. The ligand and the metal complexes have been screened for their antibacterial activity and it has been observed that the complexes are more potent bactericides than the ligand.

Keywords: *Bishydrazone, metal complexes, spectral studies, TG study, antibacterial activity*

Introduction

Hydrazones form an interesting class of compounds which find extensive applications in various fields [1,2]. The coordination behaviour of hydrazones has been well studied and depends on the pH of the medium, nature of the substituents and also on the position of the hydrazone group relative to other moieties. Hydrazone derivatives containing heterocyclic moieties have interesting ligational features and several earlier workers have reported a large number of coordination compounds with such ligands [3]. Literature survey on transition metal complexes with hydrazones revealed that a major contribution to studies was based on the monohydrazone [4,5]; but those formed from the bishydrazone, especially those containing an isatin moiety, have been much less studied. It has been reported that several compounds containing an isatin moiety possess antibacterial, antifungal, anticonvulsant, anti-inflammatory and antiHIV activities [6,7]. These observations stimulated efforts for the synthesis of a bishydrazone and its metal complexes. Thus a bishydrazone derived from isatin monohydrazone and 2-hydroxy-1-naphthaldehyde has been used as a prospective chelating agent for some selective trivalent transiton metal ions.

Materials and methods

Isatin, hydrazine hydrate and 2-hydroxy-1-naphthaldehyde were purchased from Fluka /Sisco Research Laboratories (India). The C,H,N analyses were performed using a Heracus Carlo Erba 1108-CHN Analyser. The metal content of the complex was analysed using an atomic absorption spectrophotometer (GBC Avanta). Infrared spectra were recorded on a Shimadzu 8000 FT-IR Spectrophotometer. The electronic spectra were recorded on a Hitachi 320 UV-Visible spectrophotometer. ^{1}H-NMR spectra were recorded in DMSO-d_6 on a varian 400 NMR spectrometer using TMS as reference. Molar conductance measurements in DMSO were conducted

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using 10^{-3}M solutions of the complexes at room temperature with a Systronic conductivity meter type 304. Magnetic moment values of the complexes were measured at room temperature using a Gouy type magnetic balance. The diamagnetic corrections were applied using Pascals constants [8]. The thermogravimetric analysis was carried out using a thermobalance of the type Mettler Toledo STARe System.

Preparation of the ligand involved two stages.

Preparation of monohydrazone

The isatin monohydrazone was prepared by refluxing together equimolar solutions of isatin and hydrazine hydrate in methanol for 3 h. On cooling, the monohydrazone crystallised from the reaction mixture. Recrystallization from methanol afforded beautiful yellow crystals of the monohydrazone. mp. 226°C.

Preparation of bishydrazone

A solution of 2-hydroxy-1-naphthaldehyde (0.01 mol) in methanol (40 mL) was added to a solution of isatin monohydrazone (0.01 mol) in hot methanol (50 mL). The reaction mixture was then boiled under reflux for 4 h. On cooling, the solid product that crystallized was filtered and washed with methanol. The product was recrystallized from methanol to obtain orange coloured crystals that were filtered and dried in vacuum over calcium oxide. mp. 237°C.

Preparation of metal complexes

Manganese(III) and iron(III) complexes were prepared using manganese(III) acetate and iron(III) chloride respectively, according to the following general procedure.

The ligand (0.01 mol) dissolved in methanol (50 mL) was refluxed on a water-bath and a solution of metal salt (0.005 mol) was added to the above solution in small portions and the refluxing was continued for 3 h. The resulting solution was concentrated and allowed to cool. The crystalline product that separated was filtered, washed successively with methanol, ether and finally dried in vacuum.

However the cobalt(III) complex was prepared by using $[Co(NH_3)_5(CO_3)]NO_3.\frac{1}{2}H_2O$ as synthetic intermediate, which was prepared according to a reported procedure [9]. To the carbanato complex (0.005 mol) in refluxing methanol (50 mL) was added a methanolic solution (50 mL) of the ligand (0.01 mol) in small portions after adjusting the pH of the solution to 4.5 ~ 5.0. After complete addition, refluxing was continued for 3 h. The solution was filtered hot and the filtrate was concentrated over a water-bath to about half of the initial volume. The complex crystallized on cooling the solution and was filtered and washed successively with alcohol and ether and finally dried in vacuum.

Antibacterial experiments

The ligand and the metal complexes were screened for their antibacterial activity against *Escherichia coli, Staphylococcus aureus, Bacillus megaterium and Vibrio cholerea* by the agar diffusion method [10,11]. The concentration of the drug solution in DMSO was 300 μg/mL.

A hot nutrient agar solution (20 mL) was poured into sterilised petri dishes and allowed to attain room temperature. The seed layer medium consisted of peptone (1.0 g), yeast extract (0.8 g), glucose (0.2 g), sodium chloride (0.6 g) and agar (0.2 g). It was melted and cooled to about 45°C with gentle shaking. The previously grown subculture was added to the seed layer medium aseptically and mixed well. It was immediately raked into the petri dishes and allowed to attain room temperature. Then wells were made with a sterile cork borer and to these wells, the drug solution (0.01 mL) was added and the plates were allowed to cool for an hour to facilitate diffusion. The plates were then incubated at 37°C for 48 h. At the end of the incubation period the zones of inhibition around the wells were measured. Streptomycin was used as a reference.

Results and discussion

Formation of the metal complexes can be represented by the following general equations

$$MX_3 + 2HNIB \rightarrow [M(NIB)_2]X + 2HX \qquad (1)$$

Where M = Mn(III) or Fe(III); X = OAc or Cl

HNIB = [(2-hydroxy-1-naphthaldehyde)-3-isatin]-bishydrazone

$$[Co(NH_3)_5(CO_3)]^+ \xrightarrow[-CO_2,-H_2O]{H_3O^+} [Co(NH_3)_5(OH)]^{2+} \xrightarrow{H^+}$$

$$[Co(NH_3)_5(OH_2)]^{3+} \xrightarrow{2HNIB} [Co(NIB)_2]^+ + H_2O + 5NH_3 + 2H^+ \qquad (2)$$

The complexes obtained are presented in Table I. All complexes were stable at room temperature and possessed good keeping qualities. They were non-hygroscopic solids which were insoluble in benzene, chloroform, carbon tetrachloride and toluene. Formulation of these complexes has been done on the basis of elemental analysis, molar conductance and magnetic susceptibility measurement.

Molar conductance values of the complexes measured in DMSO and DMF (10^{-3}M solutions) adequately confirm the electrolytic nature of the complexes [12].

Table I. Analytical data and other details of the metal complexes.

Complex	Molecular formulae	Formula weight	Yield (%)	Analytical data (%)*				Molar conductance ohm^{-1} cm^2 mol^{-1}		Magnetic moment BM
				M	C	H	N	DMSO	DMF	
[Mn(NIB)$_2$]OAc	$MnC_{40}H_{27}N_6O_6$	743	74	7.39 (7.18)	64.69 (64.52)	3.66 (3.62)	11.31 (12.68)	53.0	73.1	4.84
[Fe(NIB)$_2$]Cl	$FeC_{38}H_{24}N_6O_4Cl$	720	79	7.75 (7.47)	63.39 (63.51)	3.36 (3.42)	11.67 (11.63)	55.1	74.8	5.81
[Co(NIB)$_2$]NO$_3$	$CoC_{38}H_{27}N_7O_7$	750	72	7.83 (7.76)	60.64 (60.58)	3.61 (3.55)	13.02 (13.37)	58.0	80.0	D

*Calculated values are given in parentheses.

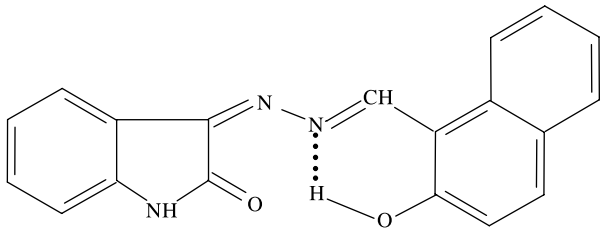

Figure 1. Structure of the ligand.

Structure of the ligand and complexes

The bishydrazone, [(2-hydroxy-1-naphthaldehyde)-3-isatin]-bishydrazone, was characterized by various spectral studies. The electronic spectra of the bishydrazone shows absorption bands at 400 nm and 340 nm assignable to $n \rightarrow \pi^*$ transitions of ketimine and aldimine group respectively. The infrared spectrum of the bishydrazone exhibited a broad band ranging from 3000–3300 and centred around 3075 cm^{-1} which can be assigned to the hydrogen bonded OH group. An intense band appearing at 1721 cm^{-1} is assigned to the $>C=O$ group of the isatin moiety [13]. Another band observed at 3200 cm^{-1} of medium intensity can be attributed to the $-NH-$ vibrations of the indole ring system. Vibrational characteristics of ketimine and aldimine groups are observed at 1642 and 1618 cm^{-1} respectively. A high intensity band at 1310 cm^{-1} can be assigned to υ(C—O) and the band at 1068 cm^{-1} can be due to the hydrazinic υ(N—N) of the free ligand.

^{1}H-NMR spectrum of the free ligand showed peak at δ 13.96 characteristic of intramolecular hydrogen bonded OH proton. The peaks at δ 9.80 and δ 8.91 are assigned to the —NH— proton of the indole ring and azomethine proton (—CH=N—), respectively, and the aromatic ring protons are observed in the range δ 6.91–7.94 as singlets. On the basis of the above spectral data an internally hydrogen bonded structure has been assigned to the ligand (Figure 1).

Infrared spectral data of the complexes are presented in Table II along with tentative assignments. In the metal complexes, the broad band due to the hydrogen bonded OH disappeared from 3000–3300 cm^{-1} indicating deprotonation and formation of C—O bond, consequently the naphtholic υ(C—O) frequency increased by about 35–45 cm^{-1} indicating the coordination of the naphtholate oxygen to the metal ion. The aldimine υ(>C=N) stretching of the ligand at 1618 cm^{-1} was shifted to lower frequency by about 20–25 cm^{-1} in the complexes. This is clear evidence for the involvement of the aldimine nitrogen in bonding. The band corresponding to υ(C=O) at 1721 cm^{-1} was shifted to lower frequency by about 50 cm^{-1} in the spectra of the complexes. This is clear evidence for coordination by the carbonyl oxygen. However vibrational characteristic of the ring υ(NH) and υ(C=N) of the ketimine moiety remained almost unaffected, indicating the non participation of these groups in coordination.

Table II. Important IR spectral bands (cm^{-1}) of the ligand (HNIB) and its metal complexes.

HNIB	$[Mn(NIB)_2]OAc$	$[Fe(NIB)_2]Cl$	$[Co(NIB)_2]NO_3$	Tentative assignment
3000–3300	–	–	–	Hydrogen bonded ν(OH) group
3200	3205	3206	3204	Indole ring NH
1721	1665	1660	1664	$\nu(C{=}O)$
1642	1643	1640	1642	$\nu(C{=}N)$ ketimine
1618	1598	1594	1596	$\nu(C{=}N)$ aldimine
1310	1344	1346	1350	$\nu(C{-}O)$ phenolic
1068	1082	1080	1081	$\nu(N{-}N)$
–	457	460	459	$\nu(M{-}N)$
–	552	548	550	$\nu(M{-}O)$

Far infrared spectra of the metal complexes showed several absorption bands which were not observed in the ligand spectrum.

The non-ligand bands of low intensity appearing in the regions 548–552 $cm^{-1}$and 457–460 cm^{-1} can be assigned to υ(M—O) and υ(M—N) vibrations, respectively [14]. Thus from the infrared spectra it is clear that the ligand is bonded to the metal ion in a tridentate fashion through the deprotonated naphtholate oxygen, aldimine nitrogen and carbonyl oxygen of the isatin moiety (Figure 2).

Magnetic measurements. Generally manganese(III) complexes are of a high-spin type except some cyanocomplexes and the spin-only value expected for a high-spin complex is 4.9 BM. The d^4 configuration of manganese(III) gives a ^5D ground term which in an octahedral field splits into $^5E_{2g}$ and $^5T_{2g}$. Although the orbital angular momentum is expected to be quenched, its contribution to the magnetic moment is not completely eliminated because of the spin-orbit coupling and the magnetic moment calculated for an octahedral complex is about 4.8 BM. But this expected value is valid only when the individual paramagnetic centres in a compound act independently of each other. In the present case, the magnetic moment is only slightly lower than the spin-only value expected for octahedral high-spin manganese(III) complexes and this value is comparable with those reported for similar type of complexes[15] of manganese(III). This value also suggests the absence of any appreciable metal-metal interaction in this complex.

Iron(III) complex exhibits an effective magnetic moment value of 5.81 BM at room temperature. Reduction in spin-only value is often caused by antiferromagnetic interaction or due to the presence of high-spin low-spin equilibrium[16]. The observed value indicates the absence of any type of metal-metal interaction in the solid state.

Trivalent cobalt(III) gives unstable simple salts because of d^6 system. The six coordinate complexes involving d^2sp^3 hybridization have octahedral structure and most of them are diamagnetic. Here also the cobalt(III) complex has been found to be diamagnetic.

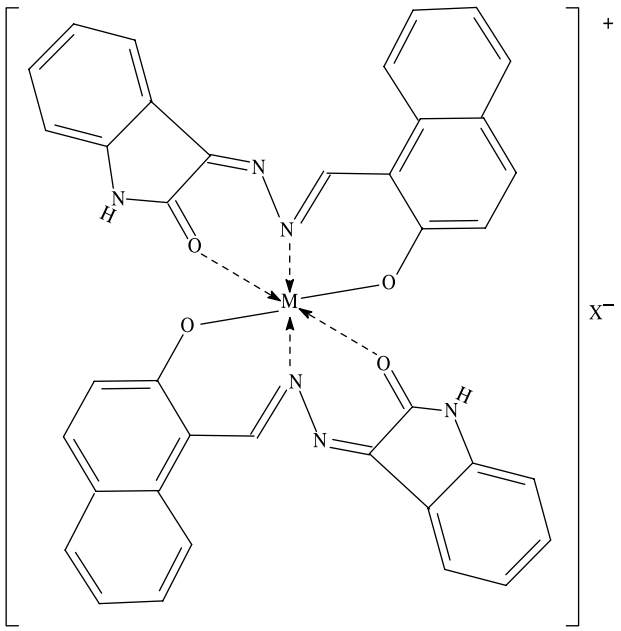

Figure 2. Structure of the metal complex.

Electronic spectra. In an octahedral field, the ^5D term of manganese(III) with d^4 configuration splits into $^5E_{2g}$ and $^5T_{2g}$ and only one d-d transition, $^5E_{2g} \rightarrow {}^5T_{2g}$ is expected. However, high-spin octahedral manganese(III) complexes are susceptible to Jahn-Teller distortion, and hence more than one transition involving the split components of $^5E_{2g}$ and $^5T_{2g}$ in low symmetry can occur. In this case a broad band centered at 545 nm with a weak shoulder at 440 nm are observed. This can be attributed to the transition resulting from the lowering of symmetry from octahedral [17].

In high-spin iron(III) complexes, the ^6S free ion ground term is the only sextuplet term arising from d^5 and it does not split in a crystal field. All the electronic transitions are thus spin-forbidden, as well as Laporte forbidden, so that the ligand field bands in the spectrum of the iron(III) complex are very weak [18]. In this case the weak ligand field bands are masked by the intense charge transfer band and hence it is difficult to have any structure correlation from the spectral data.

The cobalt(III) complex exhibited a strong band at 584 nm with a shoulder at 485 nm, arising from

$^1A_{1g} \rightarrow {}^1T_{1g}$ and $^1A_{1g} \rightarrow {}^1T_{2g}$ transitions respectively. These observations are compatible with an octahedral geometry around the cobalt(III) ion [19].

Thermogravimetric analysis. The iron(III) complex has been subjected to thermogravimetric analysis in dynamic air. Decomposition of the complex occurred in a single step process, producing Fe_2O_3 as final product. The complex was stable up to 493°K and then it started decomposing and the decomposition was complete at 533°K. In the DTG profile, this stage of decomposition of the ligand moiety and conversion of the metal into the oxide has been represented by an exothermic peak having a peak temperature 604°K. This type of single stage decomposition of the metal complexes usually occur when there is a high degree of electron delocalisation along a conjugated system which leads to uniformity in bond strength [20]. The weight loss obtained was in good agreement with the calculated value and the value obtained from an independent pyrolysis experiment. Apart from the thermal stability, this study also provided adequate support for the formulation of the complex.

Antibacterial screening

The ligand and the metal complexes were screened for their antibacterial activity and the results obtained are presented in the antibacteriogram (Figure 3). It is observed that all the metal complexes are more potent bactericides than the ligand. The observed activities of the complexes are comparable with those reported for complexes prepared using schiff bases, hydrazones, thiosemicarbazones etc as ligands [6]. This enhancement in activity can be explained on the basis of chelation theory [21,22]. Chelation reduces the polarity of the metal ion considerably, mainly because of the partial sharing of its positive charge with donor groups and possible π-electron delocalization on the whole chelate ring. Chelation can reduce not only the polarity of the metal ion, but it increases the lipophilic character of the chelate, and the interaction between metal ion and the lipid is favoured. This may lead to the breakdown of the permeability barrier of the cell, resulting in interference with the normal cellular processes. If the geometry and charge distribution around the molecule are incompatible with the geometry and charge distribution around the pores of the bacterial cell wall, penetration through the wall by the toxic agent cannot take place and this will prevent the toxic reaction within the pores.

Chelation is not the only criterion for antibacterial activity. Some important factors such as the nature of the metal ion, nature of the ligand, coordinating sites, geometry of the complex, concentration, hydrophilicity, lipophilicity and presence of co-ligands have considerable influence on antibacterial activity. Certainly, steric and pharmacokinetic factors also play a decisive role in deciding the potency of an antimicrobial agent. Apart from this, the mode of action of these compounds may also invoke hydrogen bonding though the >C═N—N═CH— group with the active centers of biomolecules and thus interfere with normal cell

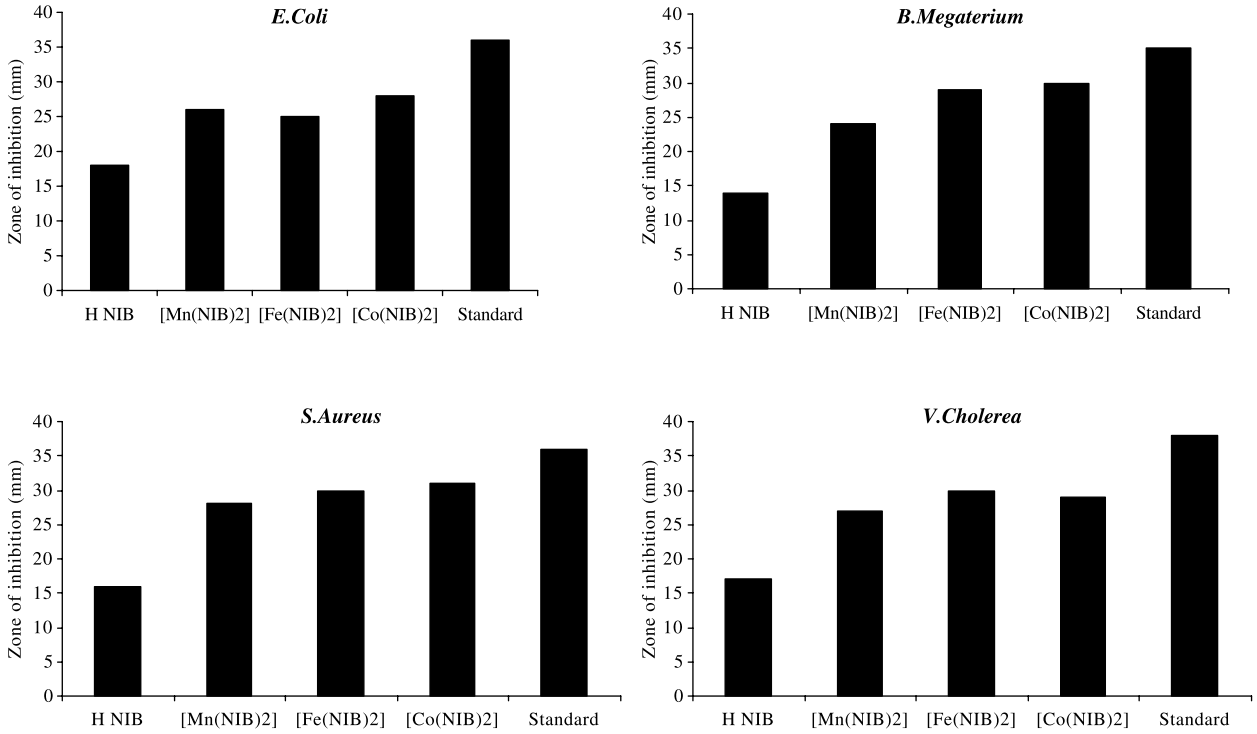

Figure 3. Antibacteriogram.

processes. Presence of lypophilic and polar substituents is expected to enhance antibacterial activity. A heterocyclic ligand with multifunctionality has a greater chance of interaction either with nucleoside bases or with biologically essential metal ions present in the biosystem and can be promising candidates as bactericides since they always tend to interact especially with some enzymatic functional groups, in order to achieve higher coordination numbers [23,24]. Moreover, enhancement in antibacterial activity on coordination with metal ion is probably due to the presence of donor systems in the uncoordinated compound or the coordinately unsaturated species formed may inhibit enzyme production since the enzymes which require these groups for their activity, appear to be more susceptible to deactivation upon coordination [25]. Thus antibacterial property of metal complexes cannot be ascribed to chelation alone but it is an intricate blend of all the above contributions.

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