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Complexes of Fe(II) & Co(II) with alpha mercapto phenylaceto hydroxamic acid

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Abstract

Complexes of the type [$M(HL)_2(H_2O)_2$][where M=Fe(II) & Co(II); H_2L=alpha mercapto phenylaceto hydroxamic acid] have been isolated by a metal ion catalysed template synthesis . The synthetic method involves the reaction of ethanolic solution of the alpha mercapto phenyl acetate, hydroxylamine hydrochloride and metal chloride in the molar ratio 2:2:1 . The compounds have been characterized on the basis of analytical, infrared and electronic spectral, magnetic moment and molar conductivity data . Infrared spectral data show that the ligand acts as a bidentate uni negative ligand coordinating through sulfur and hydroxyl oxygen. Carbonyl oxygen and amidic nitrogen do not take part in coordination as corresponding bands in infrared spectra of the ligand and complexes appear at the same position. Molar conductivity of the complexes measured in nitrobenzene has been found to lie in the range 7-12 S cm^2 mol^{-1} which indicate complexes to be nonelectrolytic in nature. Magnetic data indicate Fe(II) and Co(II) complexes to be spin free paramagnetic suggesting octahedralstructure for the complexes which is also supported by the electronic spectra of the complexes.

Keywords: Metal complexes, Schiff base ligands, Fe(II), Co(II), spectral studies, octahedral structure.

1. Introduction

Hydroxamic acid (HA) are the organic compounds with the general formula R-CO-NH-OH, where R=Alkyl or aryl (Fig-1a and 1b). Oxalohydroxamic (Fig-1c) is the first HA were discovered by Lossen in 1869, this class of organic compounds was only thoroughly studied from the nineteen eighties[1]. Due to the significant applications, the HA are well studied in modern society[2].

HA have many applications in biology and medicine[2,3], particularly against bacteria, cancer cells and fungi[4-6.] HAderivatives are known to be good antimicrobial agents for inhibiting the growth of fungi[7], but also of cancer cells[8]. They are also known to inhibit a number of enzymes[8].

Furthermore, the HA possesses multiple biological activities attributed from to their ability to bidentate chelate metal ions, interacting with a variety of metal-containing enzymes, such as matrix metalloproteases, lipoxygenase, hydrolase, urease, peptide deformylase, histone deacetylase, carbonic anhydrase *etc*.**[4]**. HA were developed as drugs used in the following diseases: cancer, cardiovascular disease, HIV, Alzheimer's disease, malaria, hypertension, tuberculosis, glaucoma, ulcers and metal poisoning, including iron. They have also been developed as insecticides, antioxidants, anticorrosive agents and siderophores**[4]**.

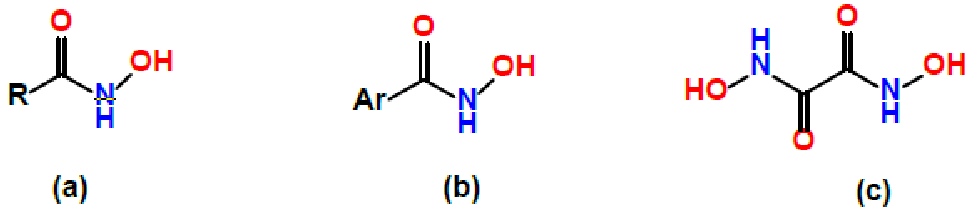
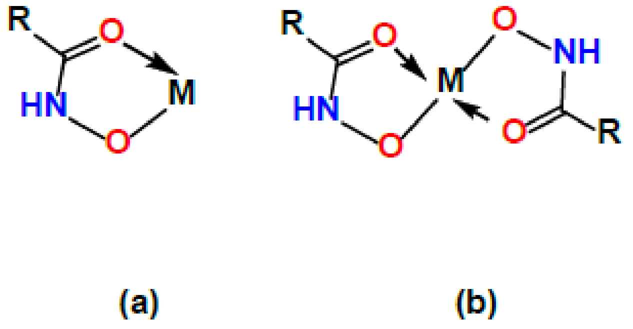


Fig-1.
General structures of HA (a and b) and oxalohydroxamic acid (c).

A number of HA derivatives are different stages of clinical trials to treat a wide range of cancers such as pracinostat (HDAC inhibition activity)**[3]**. Some HA were approved to treat different types of cancers. Suberoylanilide HA (SAHA) was approved to treat cutaneous T cell lymphoma in 2006. Resminostat is in clinical trials to treat advanced hepatocellular carcinoma in East Asian patients**[3]**. The hydroxamate group is considered to be a key element in the pharmacophores of many biomolecules and is reported to be responsible for the biological activity of HA**[9]**.

Although HA exhibit a broad spectrum of biological activities, their antimicrobial properties are generally enhanced when they are in metal chelate forms**[10-12]**. Although metal ions or complexes have been used in medicine since antiquity, the use of structurally well-defined metal complexes in coordination chemistry appeared mainly at the beginning of the 20th century (Pt anticancer agents, for example). Our interest in HA complexes is justified by the advantageous biological properties
of the complexes compared with the ligands (HA) and metals of which they are composed.



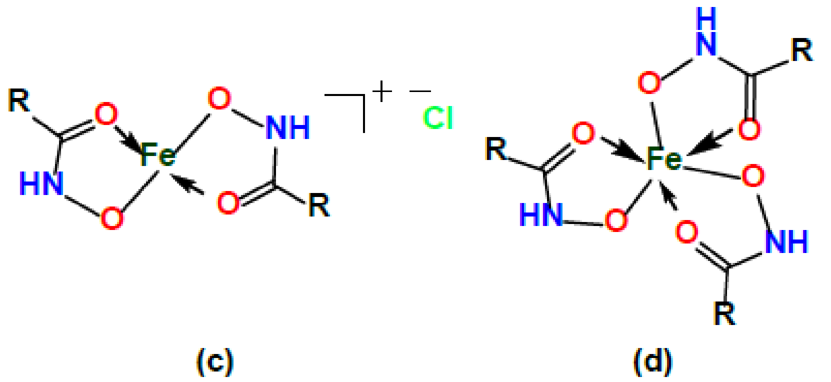
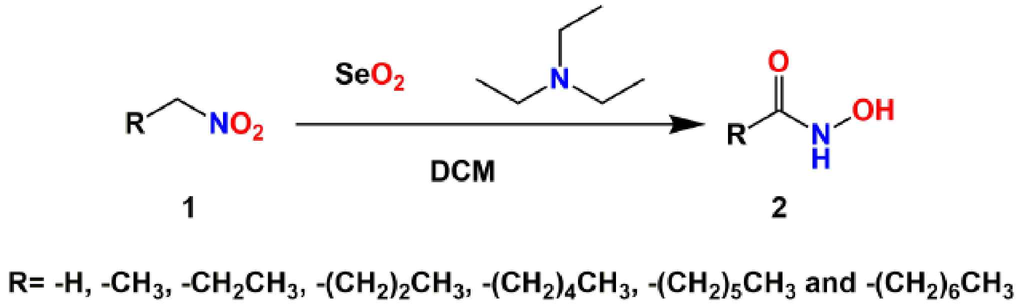


Fig-2.
General structures of HA complexes with mono(a), bi-(b and c) and tri-(d) hydroxamato (*o,o'*) coordination via C=O and deprotonated OH. M = Fe(II), Ni(II), Co(II), Cu(II) or Zn(II).



Scheme-1.
Synthesis of HA (**2**) from nitroalkanes (**1**), triethylamine and selenium dioxide in dichloromethane.

HA complexes are formed by the interaction of an HA (ligand) and a metal ion. Their structures previously known and published show a mono- which are rarely presented (Fig-2a), bi- (Fig-2b and 2c) or tri- (Fig-2d) hydroxamato (*O,O*') coordination mode via carbonyl (C=O) and deprotonated hydroxyl (OH) oxygen atoms[13].

Numerous HA complexes are reported, *e.g.* tris-chelate complex of Fe(III) with aceto-HA[14] and similar complex with heptano- and octano-HA[15]. A major study about the biological activity, the structure, the synthesis properties, the relationship of structure and biological properties have been reported recently[16,17]. Therefore, this review is to dedicate the synthesis methods of HA and HA complexes with various ions metals (Fe(II), Fe(III), Ni(II), Co(II), Cu(II), and Zn(II)).

Synthetic methods for HA are not so developed as compared to the biological application of these molecules. Sometimes synthetic chemists are content with as low yields of the

HA from its precursors. According to literature reports so far, there is not a particular reagent or condition that can be used for a wide variety of compounds[3]. Several methods for the preparation of HA have been used. An exploratory and descriptive study of methods for the synthesis of HA will help medicinal and therapeutic chemists to choose an optimal and rational method.

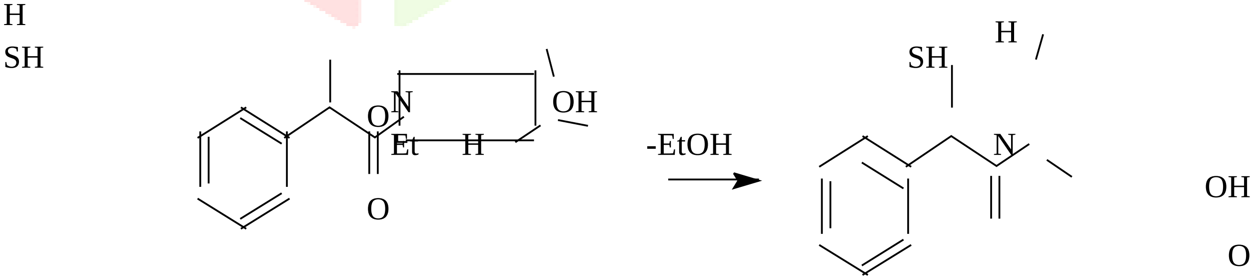
Unlike HA, the methods to synthesize their complexes are fairly similar. The number of reagent equivalents, the type of metal salt or solvent used, and the reaction conditions are the key criteria that must be sparingly observed. One of the method for synthesizing HA complexes with Fe(II) and Fe(III) was patented in 1967[18]. Other HA complexes with Fe(III), Ni(II), Co(II), Cu(II) and Zn(II) have been synthesized, similar protocols with
Bayer's[19-21]. The Failes *et al*. developed methods to synthesis HA complexes, differently from the previously described reports[14].7

The particularly interesting biological activities of HA and their complexes justify my interest in this family of chemical compounds. In this paper, I will therefore present and discuss the methods used to synthesize these chemical compounds.

2. PREPARATION OF LIGANDS

2.1. Preparation of Ligands α-Mercaptophenylaceto-hydroxamic Acid (L^1H_2):

Reacttion:



α-Mercaptophenylacetohydroxamic acid

Procedure:

2.1.a. Preparation of methanolic KOH Solution:

A 56.1 g (1 mole) of KOH was dissolved in 140 ml of methanol with continuous stirring to prepared clear solution.

2.1.b. Preparation of Hydroxylaminehydrochloride Solution:

A methanolic solution of hydroxylaminehydrochloride was prepared by adding 46.7 g of it in 240 ml of methanol.

2.1.c. Preparation of Ligand:

Both freshly prepared solutions were mixed together keepingthe temperature range at 40 ^{0}C. The mixture was left in ice-bath for five minute ensuring the complete precipitation of KCl. Thereafter 0.35 mole of 2-mercapto phenyl acetate was added in portions with constant shaking and after the addition; the solution was filtered immediately through solution. The residue in funnel was washed with a little methanol. The filtrate was keptin Erlenmeyer flask for 48 hours. Crystals of potassium salt of the acid were filtered, washed with a little absolute alcohol and dried air.

About half of the yield was mixed with 80 ml acetic acid of strength 1.25 N and stirred while heating until a clear solution was obtained. The solution was allowed to cool at room temperature and finally chilled in ice bath.

Thereafter, α-mercapto phenylacetohydroxamic acid was separarted as light brown crystals. Melting point was recorded and found to 215-216^{0}C.

The purity of ligand was checked by elemental analysis and melting point. It was also characterized by Ir and ^{1}HNMR spectral studies.

Elemental analysis of the compound is given as:

L^1H_2	% of C	% of H	% of N
Calculated	52.46	4.92	7.65
Found	52.08	4.89	7.48

3. PREPARATION OF COMPLEXES

3.1. Complexes of α-Mercaptophenylacetohydroxamic Acid (L^1H_2):

3.1. a. Complex of L^1H_2 with Fe (II) ion:

All chemicals such as iron (II) chloride, ethanol, acetone, and methanol used in this study were of analytical grade. These chemicals were purchased from CDH or Merck and used as such.

Preparation of solution:

An aqueous solution of Fe (II) chloride was prepared by mixing 0.021g of Fe (II) chloride in 40 ml of distilled water in a dried beaker with continuous stirring.

An ethanolic solution of ligand L^1H_2 was prepared by mixing 0.02 mole of ligand 35 ml of ethanol in a dried beaker with continuous stirring.

Both solutions were filtered to remove any insoluble residue left.

Preparation of complex:

An ethanolic solution of Fe (II) chloride solution was mixed with continuous stirring with a clear solution of the ligand in a dried beaker of 100 ml. After mixing, the reaction mixture was taken in a conical flask with constant shaking.

The brown precipitate was filtered and washed successively with distilled water.

A solubility test of this complex was performed. It was found soluble in dimethyl sulphoxide (DMSO), dimethyl formamide (DMF). It was sparingly soluble in water and insoluble in alcohol, ether and acetone.

Its melting point was determined using open capillary tube in kjeldal flask filled with concentrated sulphuric acid. Its melting point was ~ 175^0c.

The elemental analysis of the complex was carried out at Central Drug Research Institute (CDRI), Lucknow.

The elemental analysis of the complex is given as:

Elemental analysis:

	% of Fe	% of C	% of H	% of N
Calculated	12.25	42.12	4.39	6.14
Found	12.18	41.92	4.36	6.04

4.1. Complexes of α-Mercaptophenylacetohydroxamic Acid (L^1H_2):

4.1. b. Complex of L^1H_2 with Co (II) ion:

All chemicals such as cobalt (II) chloride, ethanol, acetone, and methanol used in this study were of analytical grade. These chemicals were purchased from CDH or Merck and used as such.

Preparation of solution:

An aqueous solution of Co (II) chloride was prepared by mixing 0.021g of Co (II) chloride in 40 ml of distilled water in a dried beaker with continuous stirring.

An ethanolic solution of ligand L^1H_2 was prepared by mixing 0.02 mole of ligand 35 ml of ethanol in a dried beaker with continuous stirring.

Both solutions were filtered to remove any insoluble residue left.

Preparation of complex:

An ethanolic solution of Co (II) chloride solution was mixed with continuous stirring with a clear solution of the ligand in a dried beaker of 100 ml. After mixing, the reaction mixture was taken in a conical flask with constant shaking.

The pink precipitate was filtered and washed successively with distilled water.

A solubility test of this complex was performed. It was found soluble in dimethyl sulphoxide (DMSO), dimethyl formamide (DMF). It was sparingly soluble in water and insoluble in alcohol, ether and acetone.

Its melting point was determined using open capillary tube in kjeldal flask filled with concentrated sulphuric acid. Its melting point was ~ 190^0c.

The elemental analysis of the complex was carried out at Central Drug Research Institute (CDRI), Lucknow. The elemental analysis of the complex is given as:

Elemental analysis:

	% of Co	% of C	% of H	% of N
Calculated	12.84	41.84	4.36	6.10
Found	12.52	41.48	4.32	6.01

5. RESULTS AND DISCUSSION

5.1. Spectral Analysis of Transition Metal Complexes Of

Ligand L^1H_2:

The complexes of L^1H_2 with transition metal(II) ions say Fe(II), Co(II),ions are anhydrous as supported by analytical and spectral studies. All these complexes are soluble in Water, alcohol and ether and insoluble in acetone, DMSO and DMF.

The molar conductances of these complexes have been recorded in nitrobenzene in digital systonic conductivitymeter-304. All complexes are non electrolytic in nature because they show very low value of its molar conductances. Magnetic moments of the complexes are in good agreement with the theoretical values calculated by Van- Vleck[1]. Analytical data, magnetic moment, molar conductance and color of all these complexes are given in following table.

S.No.	Complexes with L^1H_2	Colour	Melting point (in ^0C)	Λ_m ($Ohm^{-1}cm^2mol^{-1}$)	μ_{eff} (in B.M.)
1	$[Fe(L^1H)_2(H_2O)_2]$	Brown	175	9.2	4.91
2.	$[Co(L^1H)_2(H_2O)_2$	Pink	190	9.2	3.89

Infrared And ^{1}HNMR Spectra:

IR spectra of the ligand and complexes were recorded in a Perkin-Elmer FTIR spectrophotometer using KBR pellet method. The IR spectral data of the ligand, their complexes and their assignments are given in following table.

Functional group	ν_{S-H}	ν_{C-S}	ν_{NH-OH}	ν_{M-S}	ν_{M-O}
L^1H_2	2600	710	3550	……..	……..
$[Fe(L^1H)_2(H_2O)_2]$	……..	670	3500	340	490
$[Co(L^1H)_2(H_2O)_2]$	……..	645	3445	330	470

The NMR spectral data of the ligand, their complexes and their assignments are given in following table.

Functional group	δ_{SH}	δ_{OH}	δ_{CH}	δ_{ArH}	δ_{NH}
L^1H_2	2.8	11.5	4.2	7.27	5.2
$[Fe(L^1H)_2(H_2O)_2]$	……..	11.5	4.02	7.26	5.4
$[Co(L^1H)_2(H_2O)_2]$	……..	11.6	4.1	7.29	5.3

The ligand L^1H_2 has many donor sites such as carbonyl group nitrogen of amide and thiol.

Generally, all amides exhibit two absorption bands[2] at ~1640 cm^{-1} related to >C=O group, which is known as amide-I band and at ~1600-1500 cm^{-1}, which is known as amide-II.

The amide-I band remain at same frequency in all complexes avoiding the participation of >C=O group in coordination through the carbonyl oxygen of the ligand.

The vibrational frequency of -SH group 2600 cm^{-1} in free ligand is absent in all metal complexes. It indicates the removal
of proton before the participation of thiol group in complexation[3,4].

It has been further cinfirmed as complexes show the absence of NMR peak at about 2.8 ppm, which stands for the thiol (S-H) proton[4].

The band at 3550 cm^{-1} responsible for NH-OH group in the spectra of free ligand is shifted to lower frequency 3420-3500 cm^{-1} in complexes. It indicates the lone pair of hydroxyl group involves in coordination[5].

The presence of two new bands at 310-340 cm^{-1} and 440- 490 cm^{-1} in the spectra of metal complexes indicating the Metal- S and Metal-O bond in complexes[6,7].

The broad absorption bands at 3450 and 3470 cm^{-1} in the spectra of Fe (II) and Co (II) metal complexes respectively provide the evidences in support of coordinated water molecules to central metal ion[8].

Electronic Spectra:

Electronic spectral data for the solution of transition metal (II) complexes are given in following Table.

Table:-Electronic spectral data along with band-assignment (in cm^{-1}) of "M(II)-L^1H_2" complexes

Complexes	Band Assignments	Bands (in cm^{-1})
$[Fe(L^1H)_2(H_2O)_2]$	$^5T_{2g} \rightarrow {}^5E_g$	17685
$[Co(L^1H)_2(H_2O)_2]$	$^4F\rightarrow{}^4T_{1g}$, $\rightarrow{}^4T_{2g}$ and $\rightarrow{}^4A_{2g}$	18500, 21700 and 25300

Transition metal (II) ions have no significant absorption in the Uv-Visible region. The absorption bands of transition metal (II) ions in the visible and near infrared region appears due to the transition from their ground states to the excited state of $3d^n$- configurations[9]. The Nephelauxetic ratio (β) has been determined by the method of Jorgenson[10] using the relation:

$1 \qquad \beta$

$\nu \qquad \nu$

$\ldots\ldots\ldots\ldots 1$

The covalence factor ($b^{1/2}$), metal-ligand covalency percentage i.e. Sinhas parameter (δ%) and covalency angular
overlap parameter (η) have been calculated by using following expressions[11]:

$$\overset{/}{b}\,2 \qquad 1\ \underline{1} \qquad \beta^{\ /} \qquad \ldots\ldots\ldots\ldots 2$$

$$\delta\% \qquad 1 \quad \underline{\ \ \beta\ \ } \quad 100\ldots\ldots\ldots\ldots\ \ 3$$

$$\beta$$

$$1 \qquad \beta^{\ /}$$

$$\underline{\eta^{\ /}\qquad\quad}\ \ldots\ldots\ldots\ldots 4$$

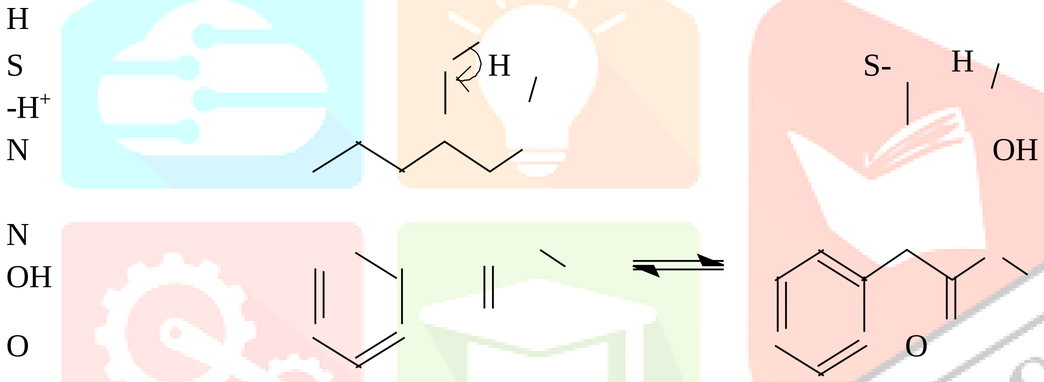
$$\beta$$

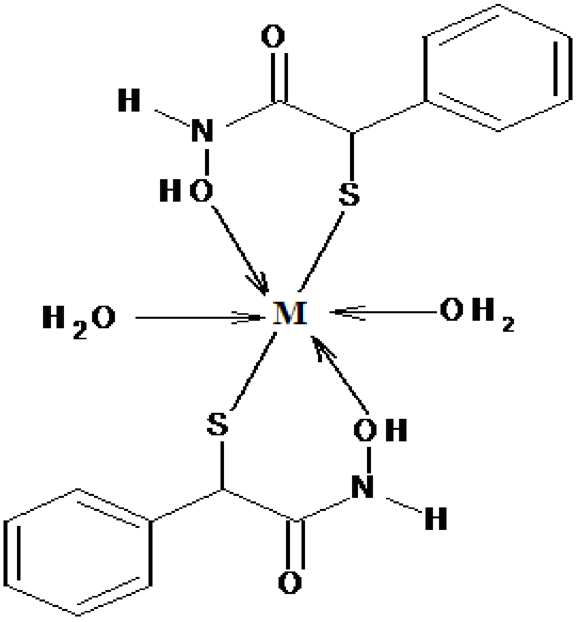
The +ve values of (1-β) and δ% supports the evidence of strong covalent bonding in all the synthesized chelated transition metal (II)-complexes[12].

CONCLUSION

IR analyses of the ligands indicate that all two ligands L^1H_2 act as uninegative bidentate ligand where as L^2H_2 act as binegative tridentate ligand.

Before ligation, ligands undergo deprotonation during condensation, which is interpreted as S–H singlet peak is absent in ^{1}HNMR spectrum of the ligands.





M= Fe(II), Co(II)

Elemental analysis shows that the complexes of Fe (II) ion and Co (II) ion with ligand L^1H_2 have two ligands and two water molecules. Hence, structures of these two complexes are six coordinated as:

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