



Synthesis and Characterization of the Complex of 2-BromoValero Hydroxamic Acid and Iron(III)

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Abstract:

The different, but related, problems of iron-deficient anaemia and iron overload resulting from the treatment of thalassaemia are still serious, especially in developing countries. There is therefore a serious need to develop iron chelating agents which can be used to combat iron overload. Unfortunately, those in common use today are not very satisfactory; they are by no means as effective as could be hoped and oral administration is not currently possible due to poor absorption. This thesis is therefore a report on the work carried out on the synthesis, characterization and study of the interaction of iron(III) in aqueous solution with 2-BromoValero hydroxamic acid a potential chelating agent for treating iron overload with special emphasis on the structure and bonding involved. The $\nu(\text{C}=\text{O})$ of the ligands is found at 1640cm^{-1} , and is lowered in the spectrum of the complex by 30cm^{-1} at precisely 1610 . This observation together with an increase in the $\nu(\text{C}-\text{N})$ band from around 1370cm^{-1} in the ligand to exactly 1392cm^{-1} in the complex, this is very consistent with the nature of coordination via the carbonyl and nitrogen oxygen,(O,O) of the ligand. The UV bands at $19,500\text{cm}^{-1}$ for the complex is appropriately assigned to ${}^6\text{A}_{1g} - {}^4\text{A}_{1g}$ transitions. The stoichiometric ratio of 1:3 as obtained from the job's plot for metal : ligand and assuming coordination number of 6 a structure has been proposed for the complex.

Keywords: 2-BromoValero Hydroxamic Acids, (2 -BrVHA), Chelates, Characterization, Coordination, Stoichiometry, Absorbance.

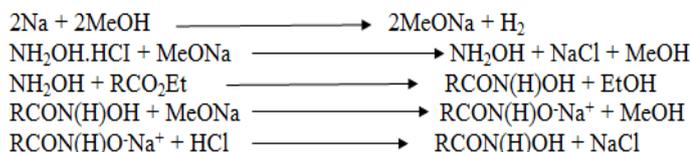
I. INTRODUCTION

Hydroxamic acids having one or more- CONHOH- groups have been extensively studied as a consequence of their biological importance which is related with their ability to form metal ion complexes (Fernandes et al.,1997). Hydroxamic acids and other compounds containing the hydroxamate group are ubiquitous in nature and are intimately associated with iron transport in bacteria (Nwabueze 1997). Iron(III) complexes of naturally occurring hydroxamate acids called siderophores, are involved in the processes of iron transport from the environment into the living organisms (Nigovic et al., 2002). Iron(III) complexes of naturally occurring hydroxamate acids called siderophores, are involved in the processes of iron transport from the environment into the living organisms (Nigovic et al., 2002). Naturally occurring hydroxamic acids such as desferrioxamine B, have typically three bidentate binding sites, making them hexadentate ligands. However, a small group of these compounds have only two hydroxamate binding sites. The most well-known example is rhodotorulic acid which forms a highly stable Fe (III) complex between pH 3 and 12 (Biruset al.,1998). Monohydroxamic acids (such as acetohydroxamic acids $\text{CH}_3\text{CONHOH} = \text{Aha}$) after deprotonation act as bidentate ligands forming octahedral complexes with a series of metal ions via co-ordination through the two oxygen atoms of the - CONHO - group. This type of co-ordination has been observed for complexes formed with Fe^{3+} , Cr^{3+} , Ni^{2+} , Co^{2+} and Zn^{2+} ions, which exhibited octahedral configuration both in the solid state and in solution (Kurzak et al.,1992).This is confirmed by x-ray diffraction studies carried out on complexes of tris (benzohydroxamic acid) with Fe(III) dihydrate and tris (benzohydroxamic acid) with chromium(III) (Brown et al.,1979). They are known to have antibacterial and

anti- fungal properties and are inhibitors of enzymes such as prostaglandin H synthase, peroxidases, urease, and matrix metallo-proteinases (MMP) which degrade the barriers holding cells in place and are involved in tumor growth. Their ability to inhibit enzymes make them ideal as drug candidates e.g Marimastat is a hydroxamic acid which is an MMP inhibitor and is at an advantage of clinical development as an anticancer drug (Celine 1972). The biological activity of hydroxamic acids appeared to be related to their iron-chelating ability. The different but related, problems of iron-deficiency anaemia and iron overload resulting from the treatment of thalassaemia (Bates et al.,1972 and Dobbin and Hider 1990) are still serious, especially in tropical countries. There is therefore, a continuous search for iron complexes which can act as suitable oral sources to counter iron deficiency and suitable ligands with high affinities for iron to relieve overload. While there are reports of studies involving iron complexes of some monohydroxamic acids, nothing is known about those derived from halogeno-substituted hydroxamic acids despite reports that other derivatives of these acids are bioactive (Nwabueze, 1996). However, complexes of isonicotinohydroxamic acid with Ni(II),Co(II) and VO(IV) have been reported (Nwabueze and Aliyu,2007; Aliyu and Nwabueze,2008,Aliyu and Nwabueze 2009;). This paper is therefore a report on the work carried out on the synthesis, characterization and study of the interaction of iron(III) in aqueous solution with a Bromo-Substituted hydroxamic acid with special emphasis on the structure and bonding involved.

1.0- Preparation of the Ligand(s):

2-BromoValero hydroxamic acids were prepared as described by Jones and Scott (1922) and also Nwabueze(1996). The various stages involved in the preparation of 2 -BrVHA are as represented by the following reactions :

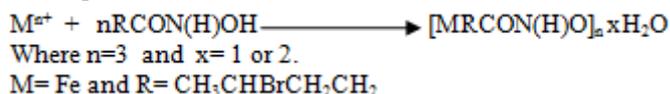


1.1- PREPARATION OF COMPLEXES.

[Fe(2BrVHA)₃]. 3H₂O was prepared as follows; (0.48g,0.002mol) in cold water was added with stirring to the 2-bromovalerohydroxamic acids (0.556g,0.004moles) in ethanol (20cm³). To this mixture, 10% solution of sodium hydrogen trioxocarbonate (IV),NaHCO₃ was added until a pink precipitate appeared. The resulting precipitate was filtered and washed with small aliquots of ethyl ethoxide,Et₂O and dried over silica gel in a vacuum dessicator. A percentage yield of 72% was obtained.

II. PRESENTATION OF RESULTS AND DISCUSSION

The ligand was prepared as reported in literature (Nwabueze,1996). The ligand reacted with the Fe³⁺ according to the equation below:



Crystallization of the ligand was achieved after concentration under laboratory conditions for four weeks and afterwards refrigeration in a deep freezer for a further two weeks. The ligand was re-crystallized in 10mL of dry ethanol after filtration. The relatively low melting point is an indication of weak intermolecular force between the molecules. Literature search confirms that the ligand was being researched for the first time.

Table.1. Analytical data and some physical constants

Compound	Formular	Formular Weight	Yield	Melting Point,M.Pt.	Molar absorptivity	Colour	Solubility
2-BromoVAH	C ₅ H ₁₁ BrNO ₂	196.9	61.0	73.50	-	White Crystal	MeOH,CHCl ₃ , H ₂ O
Fe(2-BrVAH)	C ₁₅ H ₃₄ BrNO ₂		35.50		0.050	Creamy White	MeOH,CHCl ₃ , H ₂ O

3.1.0- Determination of Stoichiometry of Complexes.

Standard solution (1 mmole) each of ferric chloride and the ligand was prepared. Different volumes (1ml, 2ml ... 9ml) of the ferric chloride solution were delivered into nine appropriately labeled test tubes using a clean burette. Different volumes of the ligand solution were added to the test tube containing the ferric chloride solution such that the total volume of each mixture is 10.00ml. This keeps the total number of mole of reactants constant throughout the series of mixtures but varies the mole fraction of each reactant from mixture to mixture. Each of the solution mixture was shaken thoroughly, stirred in a small beaker with magnetic stirrer for 30 mins and allowed to stand for 24hrs to equilibrate. Samples were removed from each test tube and placed in the cuvette of a UV-visible spectrophotometer. The absorbances were read at the λ max of the complex. A graph of mole fraction of ferric ion versus absorbance was plotted and analyzed carefully to

determine the mole fraction of ferric ion when there is the most significant change in absorbance.

Table 2. JOB'S Continous Variation Plot for the Fe(2-BrVHA) Complex.

Metal-ligand ratio	Mole fraction of Fe ³⁺	Absorbance
1:9	0.1	0.337
2:8	0.2	0.692
3:7	0.3	0.943
4:6	0.4	0.882
5:5	0.5	0.742
6:4	0.6	0.600
7:3	0.7	0.453
8:2	0.8	0.280

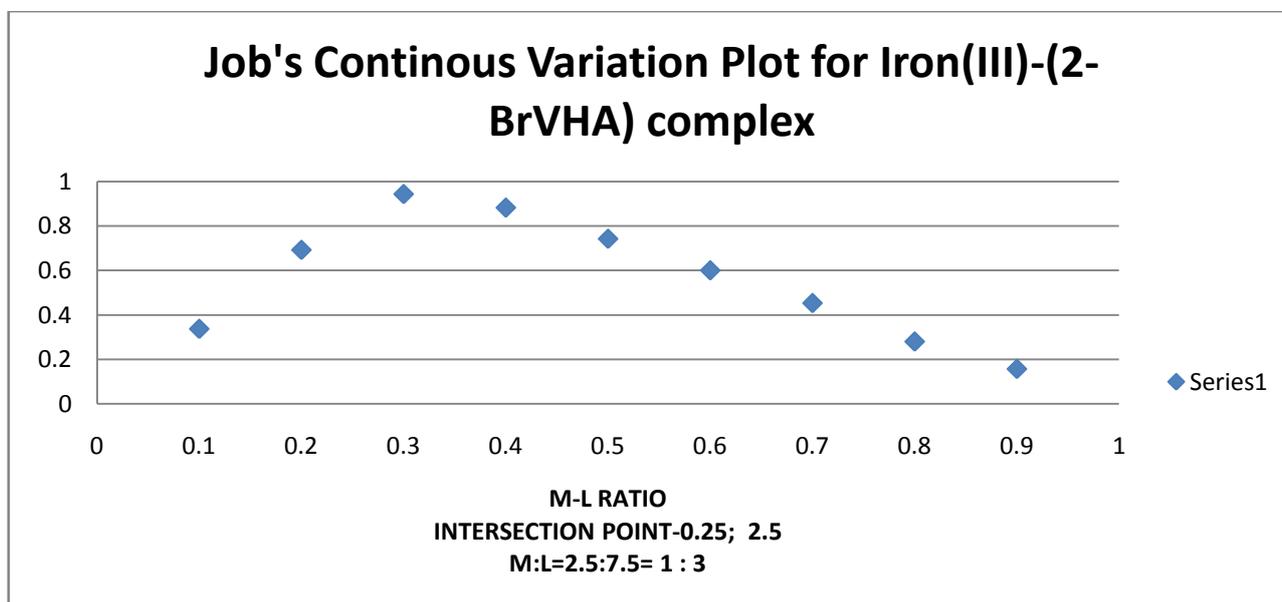


Table .3.0- IR Diagnostic Bands(cm⁻¹) for the Ligands and Complexes.

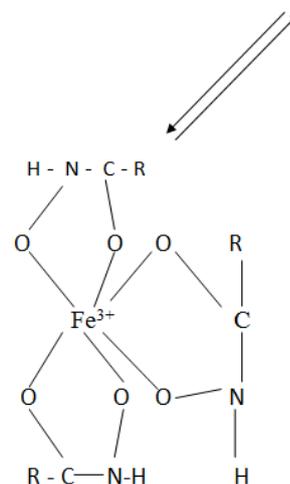
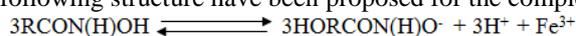
Compound	$\nu(\text{OH,NH})$	$\nu(\text{C=O})$	$\Delta\nu(\text{C=O})$	$\nu(\text{C-N})$	$\Delta\nu(\text{C-N})$	$\nu(\text{M-O})$
2-Br-VAH	3300,3125	1640		1370		
Fe(2-BrVAH) ₃	3260	1610	-30	1443	+73	495

The infrared spectra of these complex is similar to those previously reported.(Brown D.A.,1983). Electron withdrawal from the carbonyl group increases electron density in the C-N bond, resulting in a lowering of 30cm⁻¹ in the carbonyl frequency compared to the free ligand, and an increase in the C-N frequency. The diagnostic IR bands for the ligand and complex is shown in table 3.0. All the bands and nature of the spectrum are very consistent with the features reported for hydroxamic acids(Nwabueze,1996, Brown & Roche,1983, H.D Aliyu & Nwabueze,2005, Brown et al.,1982). The $\nu(\text{C=O})$ of the ligand which is found at the ligand 1640cm⁻¹, is lowered in the spectrum of the complexes by 30cm⁻¹ at precisely 1610 cm⁻¹. This observation together with an increase in the $\nu(\text{C-N})$ band from around 1370 cm⁻¹ in the ligand to exactly 1433cm⁻¹ in the complexes is very consistent with the nature of coordination via the carbonyl oxygen of the ligands.(H.D Aliyu,2005, Nwabueze,1997,Mardlik &Aswar,2003). Bands located around 3300cm⁻¹ in the ligand are assigned to $\nu(\text{N-H})$ vibrations. Bands located above 3500cm⁻¹ in the spectrum of the complex is assigned to $\nu(\text{O-H})$ of water and $\nu(\text{N-H})$ of the ligands. Therefore, it is necessary to state that, it is extremely difficult to unambiguously assign these bands and thus establish the involvement of an -amino nitrogen(-N) in the bonding. Finally, non-ligand bands below 700cm⁻¹ have been assigned to M-N and M-O vibrations.(Mandlia and Aswar,2003).

4. CONCLUSION.

Interest in metal complexes of monohydroxamic acids, RCONR'OH (R,R' = alkyl, aryl) has increased greatly in the past decade primarily because of the biological importance of the naturally occurring hydroxamic acids which may function variously as growth factors, antibiotics, antibiotic antagonists, tumour inhibitors and cell division factors. The naturally occurring trihydroxamic acids are ideally designed for octahedral coordination to iron(III) and much of their biological activity is related to their highly specific chelation to iron(III) (J.B Nielands,1966 and R.E Feeney, St. Komatsu., 1966, B.G Malmstrom.,1970). In view of the importance of naturally occurring hydroxamic acids, research continues on the design of related chelating agents, on the one hand in attempts to design iron(III) chelates as suitable oral sources of iron for mammals (D.A Brown et al.,1982;] and, on the other hand, as suitable reagents for the treatment of metal-overload and related diseases such as Cooley's Anaemia. (W.F Anderson and M.C Hiller;1986). The research ligand, 2-Bromo-valero hydroxamic acid was smoothly synthesized from the corresponding ester. It was re-crystallized from water containing drops of acetic acid. It was characterized by spectroscopic measurements to show values approximating the literature values (infrared). Iron(III) complexes of the research ligand(pale purple-red), was prepared in aqueous acidic media. The UV-Spectra of the complex observed peaks at 275nm,480nm for the Fe(2-BrVHA). Fe³⁺ has a d⁵ configuration. Thus with weak field ligands will have a high spin arrangement with five unpaired electrons .Thus d-d spectra will be 'spin forbidden'; hence the absorption will be very weak explaining the pale colours of the complexes, the UV bands at 19,500cm⁻¹ and 20,200cm⁻¹ for both complexes

are appropriately assigned to ⁶A_{1g} - ⁴A_{1g} transitions. UV - Visible spectroscopic measurements of the complexes formed at different concentrations show strict linearity. This confirms that the ligands and the metal cation are complexed uniformly. The IR- bands in the ligands and its position in the corresponding complex is reported in table 3.0. In the complexes, the $\nu(\text{C=O})$ band is lowered by about -30cm⁻¹ compared to the ligand bands and hence, suggesting coordinate bonding via the carbonyl oxygen atom.(normal O,O). Iron, just like most transition elements mainly exhibits coordination number of 6 giving an octahedral structure, though a few tetrahedral complexes, where it assumes coordination number of 4, are formed. (Lee, 1996). From the infrared spectra, stoichiometric ratio of 1:3 as obtained from the job's plot and assuming coordination number of 6 , the following structure have been proposed for the complex;



5. RECOMMENDATION.

It is recommended that further studies be carried out on the research ligand and its iron(III)-complex to obtain the stability constant and Pk_a thus, ascertain their biological relevance and hence potential medicinal uses; such studies could include anti-microbial studies, anti-tumour studies and selectivity/specificity studies of the ligand for their potential in treating iron overload.

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