

Novel Complexes of Molybdenum (VI) and Oxovanadium (IV) with Cycloheptanecarbohydroxamic Acid (CPHA) and their Therapeutic Effect on Some Microorganisms

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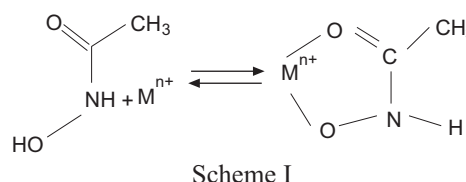
Abstract. Cycloheptanecarbohydroxamic acid (CPHA) was synthesized, characterized and their pka determined spectrophotometrically as 9.70 at 25 °C and in buffers of 0.1 mol/dm⁻³ ionic strength (*I*). The spectroscopic investigation of its reaction with Mo (VI) and VO (IV) in aqueous solution revealed the sole formation of 1:6 and 1:2 complexes at equilibrium. The isolated complexes were characterized by elemental analysis, molar conductance, magnetic moments, IR and electronic spectra studies. The magnetic and spectra studies of the isolated complexes indicate coordination via oxygen atom of the hydroxamate group. The interactions of both the ligand and its isolated complexes with some microorganisms have been studied. Both the ligand and its complexes show significant sensitivity towards the microbes and also, the related complexes can enhance antibacterial activity.

Keywords: ionic strength, square pyramidal coordination, molar conductance, molybdenum, oxovanadium, hydroxamic acid, antibacterial activity

Introduction

Hydroxamic acids are a family of organic acids of general formula RCONHOH and are much weaker acids than the structurally related carboxylic acids (RCOOH), (Nwabueze, 1996). Hydroxamic acids having one or more – CONHOH – groups have been extensively studied as a consequence of their biological importance, related to their ability to form metal ion complexes (Celina *et al.*, 1997).

Siderophores are low molecular weight iron-chelating agents produced by microbes (Etelka *et al.*, 2003). These compounds, however, are able to chelate other metal ions, for example, aluminum (III). The only drug currently available for the clinical treatment of aluminum intoxication is a natural siderophore desferrioxamine B (Hider *et al.*, 1991). It has recently been suggested that the interaction between molybdenum and siderophores has biological significance. Siderophores might be involved not only in iron, but also in molybdenum uptake in nitrogen-fixing bacteria (Duhme *et al.*, 1996). Among numerous siderophores structures, the hydroxamates are of interest due to their ability to form stable transition metal complexes through the formation of five member chelate rings as shown in Scheme I (Dessi *et al.*, 1992).



Catechols and N-hydroxylated ligands (such as L-Glutathione) which can be considered as biological sequestering agents for a large class of metal ions, are particularly effective in stabilizing high oxidation state for elements such as vanadium and molybdenum (Aliyu and Nwabueze, 2007). These ligands can utilize the capability of free vanadium ions to activate glucose uptake and glucose metabolism in rats adipocytes *in vitro* by 4-5 folds and to lower blood glucose level in hyperglycemic rats *in vivo* by 5-7 folds (Aliyu and Nwabueze, 2007).

Monohydroxamic acid form typical octahedral complexes with transition metals via coordination through the oxygen atoms and formation of reasonably ionic metal oxygen bonds (Aliyu and Nwabueze, 2008). A mononuclear penta-coordinate Mo(VI) Square pyramidal complex MoO₂L₄, a diacidic tridentate ONO donor has been reported as a model for the active oxotransfer molybdoenzyme. The chelates were found to be unusually stable and this is attributed to H-bonding

between the hydroxamate NH of the coordinated primary monohydroxamic acids oxo ligand of the Mo (Craig, 2004).

In both +5 and +4 oxidation state, vanadium can form complexes of fairly high stability with ligands being able to displace partly or fully, oxygen from the stable VO_2^+ and VO^{2+} oxocations. In highly acidic media, reversible oxygen displacement occurs from the metal ion to yield Monoxo V (IV) or V(V) complexes, which exhibits distinct EPR and ^{51}V NMR spectra features, respectively (Goldwasser *et al.*, 1999).

VO(IV) complexes have extensive clinical applications such as the oral administration of vanadate to type -1 diabetic rat lowered the high level of blood glucose to normal values. Unlike insulin, which is not absorbed orally, vanadate as low-molecular weight substance and a phosphate analog can permeate plasma membranes and intestinal wall with relative ease (Celina *et al.*, 1997).

Complexes of molybdenum (V) and (VI) with cysteine, histidine and organic sulphur compounds are of interest as model for molybdenum - containing enzymes. These enzymes are known to catalyse a number of important biological oxo-transfer reactions where the valency of molybdenum alternates between molybdenum (IV) and (VI) states in reactions with substrates and subsequent reactivation (Petrillo and Ondilti, 1982). Molybdenum complexes act as potent and specific inhibitors of metalloenzymes. The biological activities of hydroxamic acids and similar ligands are known to be positively enhanced on complexation to bio-transition metal ions like copper (II), nickel (II) and oxovanadium IV (Aliyu and Nwabueze, 2008) and molybdenum (VI) (Aliyu, 2010).

Other medicinal applications of hydroxamates which utilize their affinity for high charge density metal ions include the possible use of their complexes as imaging agent (Miller *et al.*, 1999).

Staphylococcus aureus in humans causes of a wide range of infections specially atopic dermatitis(AD) (Wertheim *et al.*, 2005),an inflammatory skin disease that usually presents itself in early age (Schultz, 2007).

As reported in many studies, *S. aureus* is the most important pathogen associated with AD. Skin colonization with *S. aureus* is known to be related to AD disease severity.

Escherichia coli strains are pathogenic and toxinogenic. In particular one can recognize an enterohaemorrhagic

strain causing very dangerous outbreaks (O157: H7: without pili "Ohne Haar") or RS218, causing meningitis. *E. coli* are widespread in the environment and pathogenic strains cause diseases of mucosal surfaces including the female genital tract. Pelvic inflammatory disease (PID; metritis) or endometritis affects ~40% of cattle after parturition. The expectation that multiple genetically diverse *E. coli* from the environment opportunistically contaminate the uterine lumen after parturition to establish PID (Baumgart *et al.*, 2007).

Pseudomonas aeruginosa survives in hot tubs, especially made of wood. *P. aeruginosa* autoinducer 3O-C12 homoserine lactone provokes hyperinflammatory responses from cystic fibrosis airway epithelial cells. The *P. aeruginosa* quorum sensing autoinducer N-3-oxododecanoyl homoserine lactone (3O-C12) is an important bacterial virulence factor that has been reported to induce pro inflammatory cytokine production (Mayer, 2002).

B. subtilis grows in the mesophilic temperature range. The optimal temperature is 25-35 °C (Entrez Genome Project). *B. subtilis* has evolved a set of strategies that allow survival under stress and starvation conditions (Bandow, 2002). Some *Bacillus* species can cause food poisoning such as *B. licheniformis* and *B. cereus*, usually by eating rice that is contaminated with *B. cereus* (EMBL EBI) (Morikawa, 2006). *B. cereus* infection can result in two different kinds of intoxications. It can either cause nausea, vomiting, and abdominal cramps for 1-6 h, or diarrhoea and abdominal cramps for 8-16 h.

Candida infection provoked by chronic diseases, medication, poor oral hygiene, reduced salivary flow, or the impairment of the immune system (Shay *et al.*, 1997). As many as 75% of elderly people in Finland harbor oral yeast (Narhi *et al.*, 1993). Even though the colonization by *Candida* may be asymptomatic, heavy growth usually leads to local candidosis, with various types of mucosal lesions and symptoms (Shay *et al.*, 1997).

Spectrophotometry. It is the quantitative measurement of the reflection or transmission properties of a material as a function of wavelength (Allen *et al.*, 2010). Spectrophotometry deals with visible light, near-ultraviolet, and near- infrared, but does not cover time-resolved spectroscopic techniques.

Fourier transform infrared spectroscopy (FTIR). FTIR is a technique which is used to obtain an infrared spectrum of absorption, emission, photoconductivity

or Raman scattering of a solid, liquid or gas. FTIR technique has made dispersive infrared spectrometers all but obsolete (except sometimes in the near infrared) and opened up new applications of infrared spectroscopy (Griffiths and Hasseth, 2007).

Isosbestic point. It is a specific wavelength at which two chemical species have the same molar absorptivity (ϵ) or more generally are linearly related. When an isosbestic plot is constructed by the superposition of the absorption spectra of two species (whether by using molar absorptivity for the representation, or by using absorbance and keeping the same molar concentration for both species), the isosbestic point corresponds to a wavelength at which these spectra cross each other. If a third one is partaking in the process the spectra typically intersect at varying wavelengths as concentrations change, creating the impression that the isosbestic point is 'out of focus', or that it will shift as conditions change. The reason for this is that it would be very unlikely for three compounds to have extinction coefficients linked in a linear relationship by chance for one particular wavelength (Ralph *et al.*, 1981).

Magnetism. Magnetism is a property of materials that respond at an atomic or subatomic level to an applied magnetic field. Ferromagnetism is the strongest and most familiar type of magnetism. Substances that are negligibly affected by magnetic fields are known as non-magnetic substances. They include copper, aluminum, gases and plastic (Fowler, 1997).

This paper reports the work carried out on the complexes of molybdenum (VI) and oxovanadium (IV) with cycloheptanecarbohydroxamic acid (CPHA) with special emphasis on identifying the number and nature of species formed in aqueous solution and the structure and nature of bonding involved. In addition, some physico-chemical properties and microbial test were investigated.

Materials and Methods

Ethylcycloheptanecarboxylic acid (purity 98%) and Na_2MoO_4 (purity 99%) was obtained from Aldrich. All other reagents used were Analar grade. NaNO_3 was used for the preparation of the background electrolytes and stock solution. Water was doubly distilled, degassed using purified N_2 and stored in glass stopped flasks. KOH (99.99%) and HNO_3 (specific gravity: 1.115) were used for adjusting pH and were stored in glass ampoules. They were standardized with potassium

hydrogen phthalate and tris (hydroxymethyl) methylamine, respectively. The pH measurements were made using a Radiometer Copenhagen Research pH calibrated with standard buffer tablets (2,4, and 9). Electronic spectra were recorded on ATI Maltson Genesis Series FTIRTM machine as Nujol Mull in the 4000-200 cm^{-1} spectra region. Room temperature magnetic susceptibility measurements were made on MSB Auto magnetic susceptibility balance. All these analyses were done at National Research Institute for Chemical Technology (NARICT), Zaria, University of Abuja and Department of Chemistry, Nigerian Defence Academy, Kaduna, Nigeria.

Equilibrium studies. Equilibrium studies of the ligand was carried out according to method described by Aliyu and Nwabueze (2009).

Preparation of the ligand. Ethyl cycloheptanecarboxylic acid was prepared as described by Nwabueze (1996). 44g of thionyl chloride were weighed into a 500 cm^3 two necked round bottom flask and 25g of the cycloheptanecarboxylic acid was added through a dropping funnel. Anti-bumping granules were added to prevent bumping. The mixture was refluxed for 30 min and the product distilled out under reduced pressure.

Ethylcycloheptanecarboxylate was obtained by adding the cycloheptanecarboxyl chloride prepared above slowly to 25 cm^3 absolute ethanol in a beaker immersed in the ice bath. The mixture was left at room temperature for about one hour and then poured into 150 cm^3 distilled water. After stirring, the ester was separated from the aqueous layer by means of a separating funnel. It was washed with saturated solution of NaHCO_3 until effervescence ceased and then with water. The ester was dried over anhydrous CaSO_4 and distilled under reduced pressure at 220 $^\circ\text{C}$ (Yield = 62.5%).

Na metal (2.3g, 0.1 mol) in MeOH (50 cm^3) was added to $\text{NH}_2\text{OH}\cdot\text{HCl}$ (6.9g, 0.1 mol) in MeOH (100 cm^3). The mixture was cooled to room temperature and ethylcycloheptanecarboxylate (17.0g, 0.1mol) was added. The mixture was stirred for 40 min, a further solution of Na (2.3g, 0.1 mol) in MeOH (50 cm^3) was added and stirring continued for further 10 min. The mixture was filtered to remove the precipitated NaCl and the filtrate was acidified with concentrated HCl . The precipitated NaCl was removed by filtration. The filtrate was concentrated in the open laboratory overnight and then refrigerated. The crystals were removed by filtration and dried in the desiccator over silica gel (Yield = 62.5%).

Preparation of complexes. Mo (CPHA)₆ was prepared as described by Aliyu (2010). (VO (IV) CPHA)₂ · 4H₂O was prepared as follows:

VOSO₄ · 2H₂O (0.33 g) in cold water was added with stirring to CPHA (0.6 g) in ethanol (20 cm³). The mixture was allowed to precipitate out as black crystals. The precipitate was washed, dried over silica gel in a vacuum desiccator (Yield = 58%).

Evaluation of the antimicrobial activities. The nutrient agar was used as the growth medium for the microbes. The nutrient agar medium was prepared by dissolving 7.0 g of the agar in 250 cm³ of distilled water. The solution was sterilized in an autoclave for 15 min, poured into petri dishes and kept in refrigerator for 24 h. After 24 h the plates were retrieved and assessed (Adetutu, 2010). Standard strains of the microbes were obtained from Nigerian Army Reference Hospital, Kaduna (NARHK).

The paper disc diffusion method was used to assess the anti microbial activity. Sterilized paper discs were impregnated with various concentrations of the ligand and the complexes dried at 37 °C before use. The microbes were inoculated into the nutrient broth and incubated for 24 h at 37 °C. The inoculums were allowed to dry and the discs were then placed evenly on the surface of the inoculation and gently pressed down to ensure contact. The plates were incubated at 37 °C for 24 h. Observation comprising, diameter of disc, zone of inhibition and Minimum Inhibitory Concentration (MIC) were made for paper evaluation. The oxford strain of *S.aureus* (National collection of type cultures No.6571) and *E. coli* NCTC 10418 was used as control. These were placed on the side of the plate under a similar condition for the test bacteria and the distance between the test complexes, the ligand and the control was 5 mm apart.

Results and Discussion

Equilibrium constants are determined in order to quantify chemical equilibria. When equilibrium constant is expressed as a concentration quotient,

$$K = \frac{[S]^{\sigma} [T]^{\tau} \dots}{[A]^{\alpha} [B]^{\beta} \dots}$$

In order for this assumption to be valid equilibrium constants should be determined in a medium of relatively high ionic strength. The equilibrium expression above is a function of the concentrations [A], [B] etc. of the

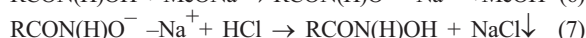
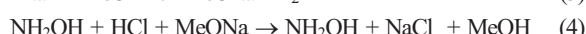
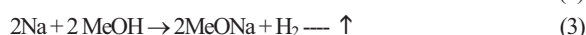
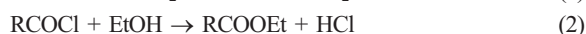
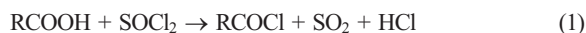
chemical species in equilibrium. The equilibrium constant value can be determined if any one of these concentrations can be measured. The general procedure is that the concentration in question is measured for a series of solutions with known analytical concentrations of the reactants. Typically, a titration performed with one or more reactants in the titration vessel and one or more reactants in the burette. Knowing the analytical concentrations of reactants initially in the reaction vessel and in the burette, all analytical concentrations can be derived as a function of the volume (or mass) of titrant added.

Spectrophotometric measurements. Absorbance. It is assumed that the Beer-Lambert law applies.

$$A = \ell \sum \epsilon c$$

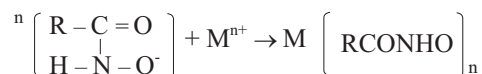
Where ℓ the optical path length, ϵ is a molar absorbance at unit path length and c is a concentration. More than one of the species may contribute to the absorbance. In principle absorbance may be measured at one wavelength only, but in present-day practice it is common to record complete spectra.

The various stages in the preparation of CPHA are as represented by the following equations.

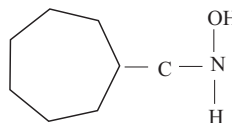


R = (Cycloheptane)

Equation of reaction for the preparation of the metal complexes



Where n is a neutral monodentate ligand



Scheme II - Structural formula of Cycloheptane carboxylic acid (CPHAH)

The structure of cycloheptanecarboxylic acid is presented in Scheme II. The ligand can release only

Table 1. Characterization data of Mo (VI) and VO(IV) – CPHA complex

Ligand/Complex	Colour	C H N M				μ B.M	Form. (Wt)	Mp/Dec (°C)
		C H N M (%)						
CPHA	Orange	-	-	-	-		157.21	101
Mo(CPHA) ₆	Light green	(55.49)	(8.67)	(8.09)	(9.24)	-1.90	1037.94	182
		55.09	8.17	7.59	9.64			
VO(CPHA) ₂ 4H ₂ O	Greyish	(42.39)	(8.39)	(6.18)	(11.96)	1.79	452.9	223
	black	42.42	8.44	6.38	11.24	-	-	-

The figures in parenthesis are calculated

one proton in the pH range of 1.5-11.4, which may be attributed to the hydroxamic group. The determined proton dissociation constant at $I = 0.01 \text{ mol/dm}^3$ $\text{Na}_2\text{CO}_3/0.025 \text{ mol/dm}^3$ NaHCO_3 buffer is 9.70 ± 0.05 . Comparison with the values for aceto-hydroxamic and benzo-hydroxamic acids, 9.37 and 8.79, respectively (Schwarzenbach and Schwarzenbach, 1963) shows a decrease in acidity, thus is in accordance with the fact that the cycloalkyl ring has a high electron donating ability than the pyridine ring. Figures 1a and 1b shows the absorption spectra of solutions containing a constant metal but variable ligand molar concentration for the Mo (VI)/CPHA and VO (VI)/CPHA systems while Fig. 2a and 2b shows graphical Matrix rank analyses of the absorbance data generated from the solutions.

The absence of an isosbestic point in Fig. 1a and 1b and the shape of graph in Fig. 2a and 2b indicates the presence of only one complex specie in the system (Hartley *et al.*, 1980).

The composition of the complex in solution was determined by Job's plot as 1:6 and 1:2, respectively.

The analytical data and some physical constants for the isolated solid complexes are shown in Table 1.

Electronic spectra. The visible spectra of the isolated complexes are shown in Table 2. The visible spectrum (electronic spectra) of Molybdenum (VI) hydroxamate

complex exhibit a band at 594nm which is assigned to ${}^2B_2 \rightarrow {}^2B_1$ ligand field transition, the position of the band together with the observed room temperature magnetic moment of - 1.90B:M is consistent with five coordinate square pyramidal geometries around Mo (VI) ions and this indicated diamagnetism (Nwabueze, 1996; Nicholls, 1974). The visible spectrum of oxovanadium(IV) hydroxamate complex shows a band located at 570nm which is assigned ${}^2B_2 \rightarrow {}^2B_1$ ligand transition, the position of the band together with the observed room temperature magnetic moment of 1.79 B.M is consistent with five coordinate square pyramidal geometries around VO(IV) ion (Nwabueze, 1996; Nicholls, 1974).

Table 2. Electronic spectra data (cm^{-3}) of Mo (VI)-CPHA and VO (IV)-CPHA. 4H₂O complexes

Complex	λ_{max} (nm)	ν (kk)	E	Assignment
Mo(CPHA) ₆	594	16.7	325	${}^2B_2 \rightarrow {}^2B_2$
VO(CPHA) ₂ 4H ₂ O	570	17.0	65	${}^2B_2 \rightarrow {}^2B_2$

Infrared spectra. Some diagnostic infrared bands for the ligand and its isolated complexes are compared in Table 3. The $\nu(\text{C}=\text{O})$ band located at 1625 cm^{-1} in the spectrum of the ligand is lowered by about 40 cm^{-1} in the spectrum of Mo(CPHA)₆ and 63.47 cm^{-1} in the

Table 3. Infrared spectra data (cm^{-1}) of Mo (VI) – CPHA and VO (IV) – CPHA.4H₂O complexes

Ligand/Complex	νNH	$\Delta\nu(\text{NH})$	$\nu(\text{C}=\text{O})$	$\Delta\nu(\text{C}=\text{O})$	$\nu(\text{C}-\text{N})$	$\Delta\nu(\text{C}-\text{N})$	M=O ($M_{\text{U}}=M_{\text{O}} \times \text{VO}$)
				(cm^{-1})			
CPHA	3200.51	-	1625	-	1157.14	-	-
Mo(VI)-CPHA	3216	16.00	1585	-40	1243	+85.86	950
VO(IV)-CPHA.4H ₂ O	3218	18.00	1561.53	-63.47	1237	+79.86	962

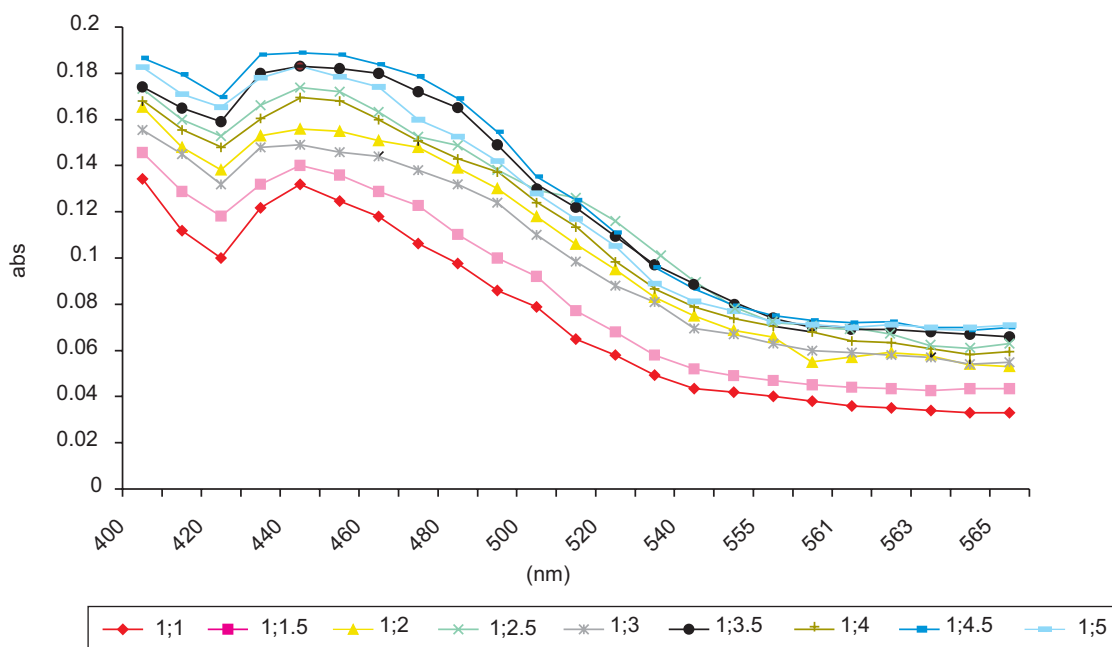


Fig. 1a. Isosbestic point search for oxovanadium (IV)-CPHA system.

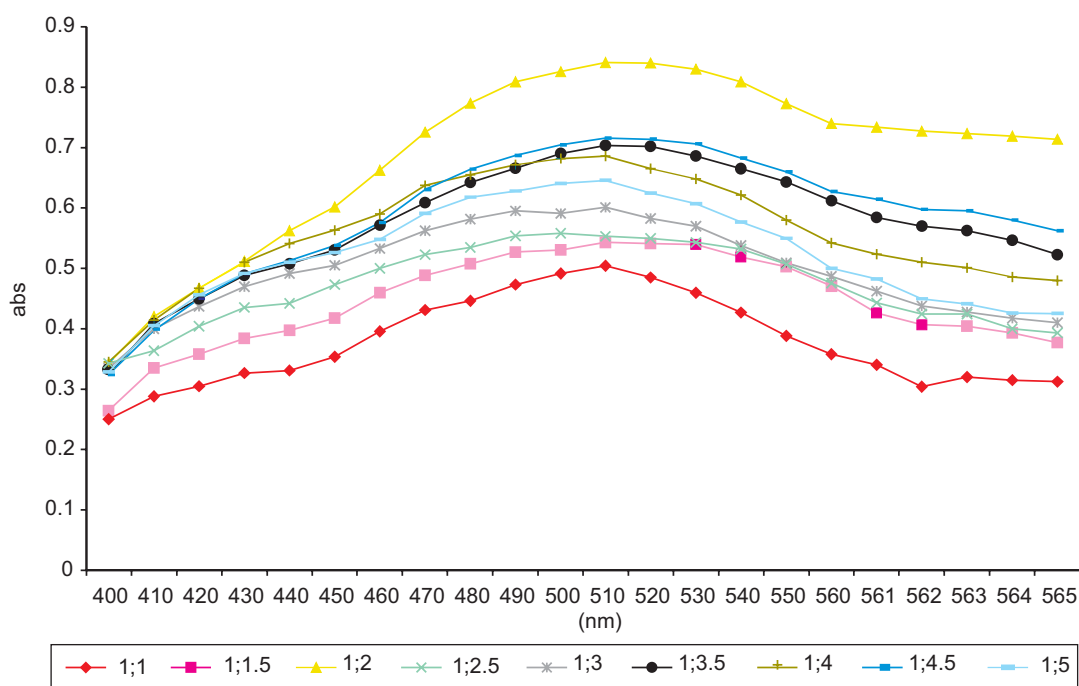


Fig. 1b. Isosbestic point search for molybdenum (VI)-CPHA system

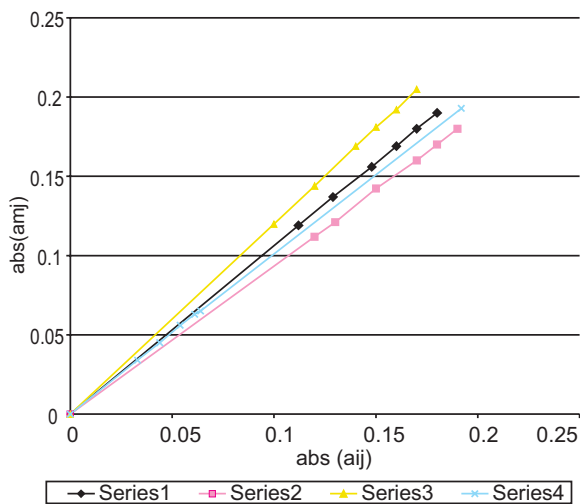
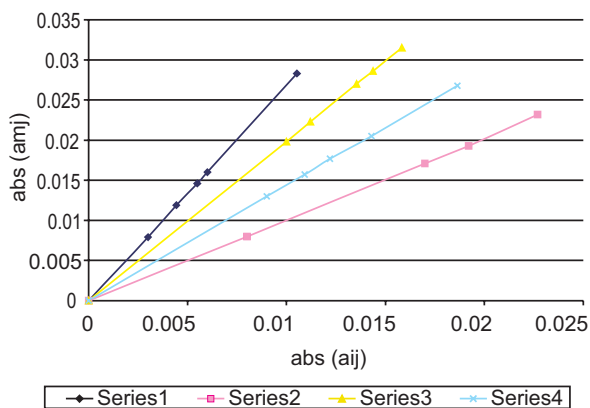
spectrum of $\text{VO}(\text{CPHA})_2 \cdot 4\text{H}_2\text{O}$. These are consistent with coordination via the carbonyl O (Jason and Pratt, 2002; Nwabueze, 1996). The $\nu(\text{NH})$ vibration which is located in the spectrum of the ligand at 3200.51 cm^{-1} is shifted to an insignificant higher frequencies in the range of about ($16\text{-}18 \text{ cm}^{-1}$) in the spectra of the

complexes indicating that there is no evidence that nitrogen atom of the hydroxamate is involved in the coordination (Nakomoto, 1997). The $\nu(\text{C-N})$ vibration band observed in the ligand is 1157.14 cm^{-1} , this band is shifted to a higher frequency of about ($\Delta 79.86$ to 85.86 cm^{-1}) which agrees with the postulates above

Table 4a. Antibacterial activity of the ligand and its isolated complexes

Compound	Symbol	<i>S.aureus</i>	<i>Candida</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>Pseudomonas</i>	Remarks
CPHA	++	18	20	17	20	16	Minimum activity
Mo(CPHA) ₆	+++	22	22	25	23	21	Moderate activity
Vo(CPHA) ₂ . 4H ₂ O	+++	23	24	22	25	22	Moderate activity

+ = activity

**Fig. 2a.** Graphical rank matrix analysis for VO(IV)-CPHA system (one specie test).**Fig.2b.** Graphical rank matrix analysis for Mo(VI)-CPHA system (one specie test).

(Hathaway and Billings, 1970; Sutton, 1968). The strong band observed at 950 cm⁻¹ and 962 cm⁻¹ assigned to molybdenum and vanadium are due to stretching modes of terminal M=O.

Magnetic moment. The room temperature magnetic moment data for the complexes are shown in Table 1. The molybdenum (VI) complex has a magnetic moment -1.90 B.M while that of oxovanadium(IV) complex is 1.79 B.M. These magnetic moments are consistent with

Table 4b. Diameter of zone of symbol comment (incubation) Adetutu, 2010

Diameter of zone of inhibition (mm)	Symbol	Remarks
12-15	+	Insignificant
16-20	++	Minimum activity
21-25	+++	Moderate activity
26-35	++++	Maximum activity

+ = activity

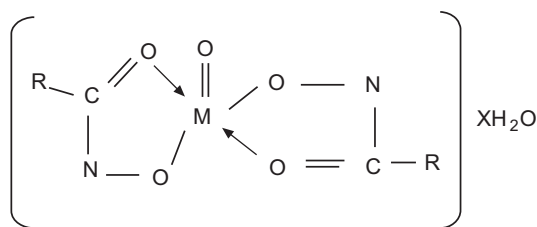
five coordinate square pyramidal geometry (Aliyu and Nwabueze, 2007; Craige, 2004).

Microbial sensitivity. The ligand and its metal complexes have been screened for their antibacterial activity and the results are presented in Tables 4a and 4b.

The complexes show moderate activity against all the bacteria tested. The enhanced activity of the complexes over the ligand can be explained on the basis of chelation theory (Mathews *et al.*, 2008). Chelation reduces the polarity of the metal ion considerably, mainly because of the partial sharing of its positive charge with donor groups. The lipid and polysaccharides are some important constituents of cell walls and membranes, which are preferred for metal ion interaction. In addition to this, the cell wall also contains amino phosphates, carbonyl and cysteinyl ligands, which maintains the integrity of the membrane acting as a diffusion barrier and also provides suitable site for bonding. Chelation can reduce not only the polarity of the metal ion, but increases the lipophilic character of the chelate, and the interaction between the metal ion and the lipid is favored. This may lead to breakdown of the permeability barrier of the cell, resulting interferences with the normal cell process. Obvious, chelation is not the only criterion for antibacterial activity. Some important factors such as nature of the metal ion, nature of ligand, coordination site, hydrophilicity, lipophilicity and presence of co-ligands have considerable influence on antibacterial activity (Rama *et al.*, 2008).

The inhibitory activity of the ligand and its isolated complexes hold promise to their potential application in the treatment of microbial induced ailment or disease conditions. Since many complexes have gained recognition as a source of curative agents for ailment, it is suggested that these complexes should not be exceptional and scientific evaluation of their active constituents be given serious consideration.

Proposed structure for the Mo (VI) and VO (IV) complexes is shown in Scheme III.



Scheme III; M = Oxomolybdenum (VI) and Oxovanadium (IV) ions where X = O, and 4.

Conclusion

The pKa of the ligand (CPHA) is 9.70 ± 0.05 and the coordination numbers of the complexes are VI and IV respectively. The antimicrobial sensitivity conducted on the test microbes indicated minimum to moderate activities which implies that it can be used as drug candidates for the treatment of the provoked diseases caused by the microbes. Furthermore, the structure shown in Scheme III is proposed for (O, O) bonding mode in square pyramidal complexes of oxomolybdenum (VI) and Oxovanadium (IV) hydroxamate.

With regard to "Proposed structure of the complexes". The author have reported synthesized complexes characterized by almost of all spectro-analytical methods. To overcome this problem, it is better, to try to obtain the crystal structure; Density Functional Theory Calculation software will be another good optional method to carry out for these complexes at the B3LYP level using the 6-31G basis set.

References

Aliyu, A.O. 2010. Cyclopropane carboxhydroxamic Acid with molybdenum (VI) ion and its microbial activity. *Current Research in Chemistry*, **2**: 35-42.
 Aliyu, A.O., Nwabueze, J.N. 2009. Studies on the complexation of cobalt (ii) with isonicotino-

hydroxamic acid and its microbial sensitivity. *Research Journal of Medical Sciences*, **3**: 170-174.
 Aliyu, A.O., Nwabueze, J.N. 2008. Complexation of cobalt (II) with nicotinohydroxamic acid and its microbial sensitivity test. *International Journal of Physical Sciences*, **2**: 167-172.
 Aliyu, A.O., Nwabueze, J.N. 2007. Complexation of vanadium (IV) with some hydroxamic acid, *European Journal of Scientific Research*, **18**: 417-428.
 Allen, D., Cooksey, C., Tsai, B. 2010. Spectrophotometry. Retrieved from <http://nist.gov/pml/div685/grp03/spectrophotometry.cfm>.
 Bandow, J.E., Brotz, H., Hecker, M. 2002. *Bacillus subtilis* tolerance of moderate concentrations of rifampin involves the β -dependent general and multiple stress response. *Journal of Bacteriology*, **184**: 459-467.
 Baumgart, M., Dogan, B., Rishniw, M., Weitzman, G., Bosworth, B., Yantiss, R., Orsi, R.H., Wiedmann, M., McDonough, P., Kim, S.G., Berg, D., Sehukken, Y., Scherl, E., Simpson, K.W. 2007. Culture independent analysis of ileal mucosa reveals a selective increase in invasive *Escherichia coli* of novel phylogeny relative to depletion of Clostridiales in Crohn's disease involving the ileum. *Multidisciplinary Journal of Microbial Ecology*, **1**: 403-418.
 Celina, M., Fernanades, M.M., Paniago, E.B., Carvalho, S. 1997. Copper (II) mixed ligands complexes of hydroxamic acid with glycine, histamine and histidine. *Journal of the Brazilian Chemical Society*, **8**: 537-540.
 Craig, J.M. 2004. Review of complexes of Molybdenum (VI) with hydroxamic acids. A review annual developments in inorganic and bioinorganic chemical research. *Annual Report on the Progress of Chemistry Section A*, **100**: 177-215.
 Dessi, A., Micera, G., Sanna, D., Erre, L.S. 1992. Formation and structure of 1:1 complexes between Aryl hydroxamic acids and vanadate at neutral pH. *Journal of Inorganic Biochemistry*, **48**: 273-282.
 Duhme, A.K., Daiuter, Z., Hilder, R.C. 1996. Complexation of molybdenum by siderophores: synthesis and structure of the double-helical cisdioxomolybdenum (VI) complex of a bis (Catecholamide) siderophore analogue. *Inorganica Chimica Acta*, **35**: 3059-3061.
 Etelka, F., Csokaand, H., Toth, I. 2003. New insights into the solution equilibrium of molybdenum (VI) – hydroxamate systems: ^1H and ^{17}O NMR spectroscopic study of Mo(VI) desferrioxamine

- B and Mo(VI) - Monohydroxamic acid system. *Dalton Transactions*, **2003**: 1645-1652.
- Fowler, M. 1997. Historical beginnings of theories of electricity and magnetism. en.wikipedia.org/wiki/Magnetism -
- Goldwasser, I., Gershonov, L.E., Armoni, M., Karnieli, E., Fit, K.M., Schecliter, Y. 1999. Synthesis of Vanadium (IV,V) hydroxamic acid complexes and *in vivo* assessment of their insulin activity. *Journal of Biological Chemistry*, **274**: 26617-26624.
- Griffiths, P., de Hasseth, J.A. 2007. *Fourier Transform Infrared Spectrometry*, 2nd edition, Wiley-Blackwell, USA.
- Hartley, F.R., Burgress, C., Alcock, R.M. 1980. *Solution Equilibria*, 2nd edition, pp. 33, Ellis Horwood, Sussex, UK.
- Hathaway, B.J., Billings, D.E. 1970. Electronic properties and stereochemistry coordination. *Chemical Review*, **5**: 143-150.
- Hider, H.C., Hal, A.D., Hay, R.W., Dilwort, J.R., Nolan, K.B. 1991. Perspectives in bioinorganic chemistry vol. **1**, pp. 209-253, JAI Press, London, UK.
- Jason, H.B., Pratt, R.F. 2002. Formation & structure of 1:1 complexes between aryl hydroxamic acids and Vanadate at neutral pH. *Inorganic Chemistry*, **41**: 2737-2753.
- Mathews, S., Kumari, B.S., Rijulal, G., Mohanan, K. 2008. Synthesis, characterization and antibacterial activity of some transition metal complexes of 2-N-(isotinamino)-3-carboxyethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene. *Spectroscopy Letters*, **41**: 154-161.
- Meyer, J.M., Geoffroy, V.A., Baida, N. 2002. Siderophore typing, a powerful tool for the identification of fluorescence and non-fluorescence pseudomonas. *Applied and Environmental Microbiology*, **68**: 2745-2753.
- Miller, M.J., Lin, Y.M. 1999. Practical synthesis of hydroxamate derive siderophores components by an indirect oxidation method and synthesis of a DIG-siderophores conjugate and biotin – siderophore conjugate. *Journal of Biological Chemistry*, **274**: 25260-25265.
- Morikawa, M. 2006. Beneficial biofilm formation by industrial bacteria *Bacillus subtilis* and related species. *Journal of Bioscience and Bioengineering*, **101**: 1-8.
- Nakomoto, K. 1997. *Infrared Spectra of Inorganic Coordination Compounds*, 200 pp., Wiley, New-York, USA.
- Narhi, T.O., Ainamo, A., Meuman, J.H. 1993. Switching of *Candida albicans* during successive episodes of recurrent vaginitis. *Journal of Clinical Microbiology*, **27**: 681-690.
- Nicholls, D. 1974. *Complexes and First Row Transition Element*, Macmillan, pp. 89-95, London, UK.
- Nwabueze, J.N. 1996. Complexes of Iron (III) with cyclopropane carbo and cyclohexyl acetohydroxamic acids. *Transition Metal Chemistry*, **21**: 258-261.
- Petrillo, E.W., Ondilti, M.A. 1982. Inhibitors of angiotensin converting enzyme containing a tetrahedral arsenic atom. *Medicine Review - A Journal of Clinical Therapeutics*, **2**: 1-4.
- Ralph, G.P., John, W.M., Arthur, A.F. 1981. *Kinetics and Mechanism*, 3rd edition, 49 pp., John Wiley and Sons. USA.
- Rama, K., Reddy, K., Suneetha, P., Karigar, C.S., Manjunath, N.H., Mahendra, K.N. 2008. Co (II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II), UO₂(VI) and Th(IV) complexes from (3-[(Z)-2-piperizin-1-yl-ethylimino]-1,3-dihydroindol-2-one (ONNN) Schiff base ligand. *Journal of the Chilean Chemical Society*, **53**: 1653-1657.
- Schwarzenbach, G., Schwarzenbach, K. 1963. Siderophore from a marine bacterium with an exceptional ferric ion affinity constant. *Helvetica Chimica Acta*, **46**: 1390-1400.
- Schultz, L.F. 2007. The epidemiology of atopic dermatitis. *Current Allergy & Clinical Immunology*, **20**: 142-148.
- Shay, K., Truhlar, M.R., Renner, R.P. 1997. Oropharyngeal candidosis in the older patient. *Journal of the American Geriatrics Society*, **45**: 863-870.
- Suton, D. 1968. *Electronic Spectra of Transition Metal Complexes*, pp. 12-13, McGraw, Hill, London, UK.
- Wertheim, H.F., Melles, D.C., Vos, M.C. 2005. The role of nasal carriage in *Staphylococcus aureus* infections. *Lancet Infectious Disease*, **5**: 751-762.