ISSN 1996-5052

Current Research in Chemistry

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Current Research in Chemistry 2 (2): 35-42, 2010
ISSN 1996-5052

Cyclopropane Carbohydroxamic Acid with Molybdenum (VI) Ion and its Microbial Activity

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Abstract: Complex of molybdenum (VI) with cyclopropane carbohydroxamic acid (CAPH) has been investigated. Spectrometric pH method at 25±0.1°C in aqueous medium of 0.1 mol dm^{-3} ionic strength. Mo (VI) form ML_6 complex. The pKa of the ligand was 9.80±0.04. The isolated complex was characterized by elemental analysis, molar conductance, magnetic and spectra studies (IR, electronic and ^{1}HNMR studies). The complex indicates square pyramidal coordination via (O, O) atom of the hydroxamate group. The interaction of both the ligand and its isolated complex with some microorganism has been studied . Both the ligand and it's isolated complex shows significant sensitivity towards the microbes.

Key words: Ionic strength, square pyramidal coordination, molar conductance, ligand, magnetic and spectra studies

INTRODUCTION

Siderophores are known as naturally 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, aluminium (III) and the only drug currently available for the clinical treatment of aluminum intoxication is a natural siderophore desferroxamine 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 five (5) member chelate rings (Hewitt, 1959). Catechols and N-hydroxylated (such as L-Glutathion) ligands which can be considered as biologically sequester ring agents for large class of metal ions are particularly effective in stabilizing high oxidation state for elements such as vanadium and molybdenum (Kay and Mitchell, 1970). Molybdenum as a trace element play an important role in metabolic processes (Keshavan and Gowda, 2001). Complexes of molybdenum (V) and (VI) with cystein, histedine and organic sulphur compounds are of interest as models for molybdenum-containing enzymes (Keshavan and Gowda, 2001). These enzymes are known to catalyze a number of important biological oxo-transfer reactions where the valence of molybdenum alternates between molybdenum (IV) and (VI) states in reactions with substrates and subsequent reactivation (Petrillo and Ondilti, 1982). A mononuclear penta-coordinate Mo (VI) square pyramidal complex MoO_2L_4, a diacidic tridentate ONO donor, has also been reported as a model for the active centre of oxotransfer molybdoenzymes. 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 and oxo ligands of the Mo. L-Tartaric acid has been used to form an enantiopure 1-D double helicate $[NH_4]$ $[Mo_2O_4Gd\text{-}(H_2O)_6(L\text{-}C_4H_6O_6)_2]4H_2O$ (Craig, 2004).

A mononuclear penta-coordinate Mo(VI) square pyramidal complex MoO_2L_4, a diacidic tridentate ONO donor, has also been reported as a model for the active centre of oxotransfer molybdoenzymes. Oxo-transfer ability was also tested for a series of addition compounds of alkylidene complexes EtMo[N(But)Ar] (Salzer, 2003) as catalysts for alkyne metathesis has been dichloro dioxomolybdenum (VI) with sulfoxides $MoO_2Cl_2L_2$ (L ~ sulfoxide) (Arnaiz *et al.*, 2003). A facile entry to related (g 5-C_5R_5) chlorodioxomolybdenum (VI) complexes (R~H, Me CH_2Ph) is described and their potential as olefin epoxidation catalysts explored. A high catalytic activity of molybdenum (VI) cis-dioxo complexes bearing sugar-derived Schiff-base ligands (L) of general formula MoO_2(L) (solv) for epoxidation is described by Zhao *et al.* (2003).

Complexes of molybdenum (VI) with the catecholamide siderophore ligands aminochelin, azotochelin and protochelin undergo electrochemical reduction solution studies, via 17O NMR and ^{1}HNMR, onmolybdenum (VI)-hydroxamate systems (aceto, N-methylaceto, benzo, hydroxamicacids and desferrioxamine) have been undertaken and complete equilibrium models for all the systems studied are presented (Duhme-Klair *et al.*, 2003).

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 and oxo ligands of the Mo. The ligand HBNO forms binuclear oxomolybdenum-(VI) $[Mo_2O_5(HBNO)_2]$ and -(IV) $[Mo_2O_2(HBNO)_4]$ complexes that display diamagnetic and paramagnetic behavior, respectively (Farkas and Csóka, 2002).

Monohydroxamic acids forms typical octahedral complexes with transition metals via coordination through the oxygen atoms and formation of reasonably ionic metal oxygen bonds (Aliyu and Nwabueze, 2008). The earlier studies indicated that the tittle ligand possess a high affinity for iron (III) (Nwabueze, 1996b), also the complexation of the tittle ligand with Co^{II}, Ni^{II} and Cu^{II} have been reported by Nwabueze (1996a). 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 oxo-vanadium IV (Aliyu and Nwabueze, 2008). It is therefore, necessary to study the interaction of the tittle ligand with other biometals in other to ascertain its selectivity for molybdenum and its potential as drug candidates for ailments associated with molybdenum deficiency. Furthermore, the interaction of hydroxamic acids with Mo (VI) is of importance since, they act as potent and specific inhibitors of metalloenzemes.

In this study, the affinity of the tittle ligand for Mo (VI) is studied with special emphasis on the structure and nature of bonding involved. In addition, some physico-chemical properties were investigated together with its anti-microbial activity which are included in this study.

MATERIALS AND METHODS

Material

The molybdenum (VI) stock solution was prepared from Na_2MoO_4 (Renal). Cyclopropane carbohydroxamic acid (CAPH) was prepared as previously reported by Aliyu and Nwabueze (2008). The purity of the ligand and its exact concentration in the stock solution was determined by Gran's method (Gran, 1950). The research was carried out between 2006/2007 and 2007/2008 academic session at the Laboratory of the Department of Chemistry, Nigerian Defence Academy, Kaduna.

Potentiometric and Spectroscopic Studies

The pH-metric and spectrophotometric measurements were carried out at an ionic strength of 0.1 mol dm^{-3} KCl at 25±0.1°C. Carbonate-free KOH solutions of known concentrations were used as titrant. The HCl stock solutions were prepared from HCl (both the acid and base were Merck products) and their concentrations were determined by pH-Metric titration. A PHM64 Radiometer instrument equipped with a CTWL45244/2 combined electrode and an ABU13 burette was used for the pH-metric measurements. The electrode system was calibrated according to the method of Irving *et al.* (1967) and the pH-metric reading could therefore be converted into hydrogen ion concentrations.

The water ionization constant, pKw is 13.74 under the condition employed. The pH metric measurements were performed throughout the pHrange ca 2.0-10.5. The initial volume of the sample was 10.00 mL. The ligand concentrations were varied in the range 1.50×10^{-3}-6.0×10^{-3} mol dm^{-3}. The sample was completely deoxygenated by bubbling argon for 20 min before measurements were started.

A HP 8453 spectrophotometer was used to record the UV-visible spectra over a range 200-650 nm for molybdenum complex. The concentration of MoO_4^{2-} was 2.5 ± 10^{-4} mol dm^{-3}.

The ^{1}HNMR measurement of CPAH was made in D_2O on a bucker AM 360 instrument. The CPAH concentration was 2.5 ± 10^{-4} mol dm^{-3}.

The IR spectra were recorded on ATI Maltson Genesis series FTIR™ machine as nujol mulls in the region 4000-200 cm^{-1} spectra region. Room temperature magnetic susceptibility measurements were made on AUTO magnetic susceptibility balance. The Mo was estimated by standard method (Basset *et al.*, 1979).

Preparation of the Ligand

The CPAH was prepared as described by Aliyu and Nwabueze (2008).

Preparation of the Complex

$Mo[CPAH]_6$: 2.47 g of Na_2MoO_4 in 20 cm^3 of distilled water was added with stirring to CPAH (1.01) g in ethanol (30 cm^3). To this mixture a solution of sodium bicarbonate was added until a green gelatinous precipitate appeared. The precipitate was removed washed with small aliquot of diethyl ether and dried over silica gel in a vacuum desicator. Yield = 73%.

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 250 mL 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. Standard strains of the microbes were obtained from Nigerian Army Reference Hospital, Kaduna (NARHK).

The paper disc diffusion method was used to assess the antimicrobial activity. Sterilized paper disc were impregnated with various concentration of the ligand and the complex 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 after incubation.

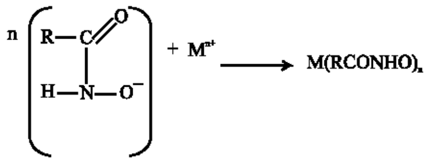
Observation comprising, diameter of disc, zone of inhibition and Minimum Inhibitory Concentration (MIC) were made for paper evaluation. Two other sterile blank discs were impregnated with water to serve as negative controls.

RESULTS AND DISCUSSION

The various stages in the preparation of NHA are as represented by the reactions below:

- $2Na + 2MeOH \rightarrow 2MeONa + H_2$
- $NH_2OH.HCl + MeONa \rightarrow NH_2OH + NaCl\downarrow + MeOH$
- $NH_2OH + RCO_2Et \rightarrow RCON(H)OH + EtOH$
- $RCON(H)OH + MeONa \rightarrow RCON(H)O{\rightarrow}Na^+ + MeOH$
- $RCON(H)O^{-}\text{-}Na^+ + HCl \rightarrow RCON(H)OH + NaCl\downarrow$

where, R is Pyridine ring for the complex of NHA model.



where, n is the number of molecules of the ligand involved in ligation.

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

The pKa value of CPAH is 9.80±0.04. The high basicity of the ligand may be ascribed to positive inductive effect of the methylene group attached to the functional group. The ligand CPAH has a formula $C_4H_7NO_2$ and a relative molecular weight of 101.10 g. It has a melting point of 125°C, the color is golden as compared to its isolated complex $[MoO_4(CPAH)_6]$ which has a formula $C_{24}H_{36}N_6O_{16}Mo$ and it is light green in color. The ligand is soluble in water and methanol while the complex is insoluble in various organic solvents such as ethanol, chloroform, petroleum ether and methanol. The complex is soluble in water.

Figure 1 shows the vis., absorption spectra of solutions containing a constant metal but variable ligand molar concentration of the Mo^{VI}/CPAH system; while Fig. 2 shows the graphical matrix rank analysis for the absorbance data generated from similar solutions for the Mo^{VI}/CPAH system. The two systems show similar behavior. The absence of an isosbentic point and the shape of the graph is typical of systems containing only one complex species (Hartley *et al.*, 1980).

Electronic Spectra

The visible spectrum of the isolated solid complex was shown in Table 3.

The visible spectrum (electronic spectrum) of molybdenum (VI) hydroxamate complex exhibit two bands at 690 and 546 nm which are assigned $^2B_2 \rightarrow ^2B_1$ ligand field transition (Nicholls, 1974; Nwabueze, 1996a).

Table 1: Characterization data of Mo(VI)-CPAH complex

Complex	Color	C	H	N	µ B.M	Form. wt (g)	Mp/Dec
Mo(VI)CPAH	Light green	39.94 (39.89)	5.75 (5.81)	11.58 (11.63)	1.90	722	180°C
CPAH	Golden	47.52 (47.47)	6.98 (6.92)	13.88 (13.84)		101	125°C

Values in brackets indicate percentage

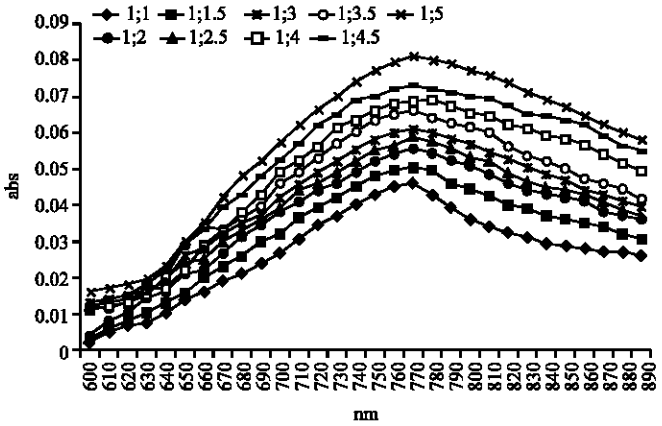


Fig. 1: Sosbestic point search for Mo^{IV}-CPAH system

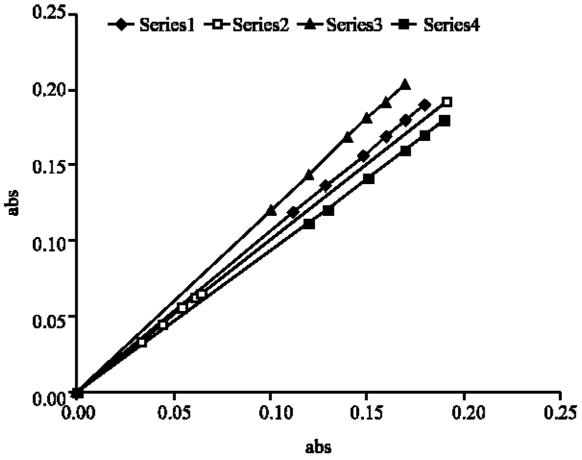


Fig. 2: Graphical rank matrix analysis for Mo^{IV}-CPAH system (one specie test)

Table 2: Infrared spectra data (cm^{-1}) of Mo(VI)-CPAH complex

Complex	νNH	Δν (NH)	ν (C=O)	Δν (C=O)	N (C-N)	Δν (C-N)	M=O
$MoO_4(CPAH)_6$	3164.05	-26.95	1644	21.19	1413	99.47	950
CPAH	3191		1624		1314		

Table 3: Electronic spectra data (cm^{-1}) of Mo(VI)-CPAH complex

Compound	Λmm	υ(kk)	E	Assignment
$MoO_4(CPAH)_6$	690	15.8	286	$^2B_2 \rightarrow {}^2E$
	546	18.6	728	$^2B_2 \rightarrow {}^2B_1$

Infrared Spectra

The relevant infrared spectra bands for the ligand and its isolated complex are shown in Table 2.

The infrared spectra of the ligand is observed at 3191 cm^{-1} region may be assigned to ν(NH). In the infrared spectra of the corresponding complex, this band is shifted to an insignificant higher frequency (Δν = 16.95 cm^{-1}), indicating that the nitrogen atom of the hydroxamate is not involved in the coordination. The infrared band observed at 1630 cm^{-1}

Table 4: ^{1}HNMR for the ligand in D_2O, ∂(PPM)

Compound	NH	OH	H(cyclopropane ring)
CPHA	1.4 (d, 1H) (NH)	4.6 (s,IH)(OH)	0.6-1.0 (5H, m)

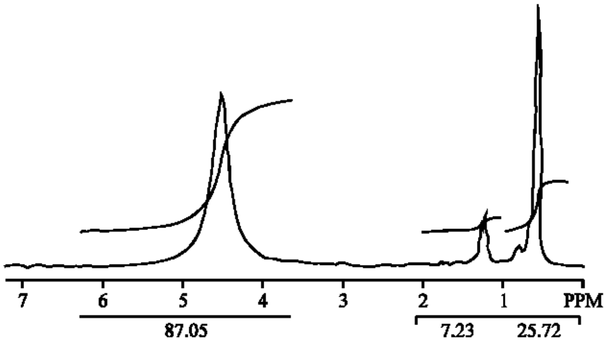


Fig. 3: ^{1}HNMR spectrum of CPAH ligand

in the ligand may be assigned to (νC=O) carbonyl. The infrared spectrum of the corresponding complex, this band is shifted to a lower frequency (Δν = 31.19 cm^{-1}) suggesting coordination through the carbonyl oxygen atom. The ν(C-N) vibration band in the ligand is located at 1314 cm^{-1}, this band is shifted to a higher frequency of about (Δν = 89 cm^{-1}). The strong band observed at 950 cm^{-1} is assigned to molybdenum is due to stretching modes of terminal M=O bond. This is consistent with coordination via carbonyl O (Nakamoto, 1963). The position of these bands together with the observed room temperature magnetic moment of 1.90 B.M are consistent with square pyramidal coordination around molybdenum (VI) ion (Craig, 2004; Nwabueze and Aliyu, 2007).

^{1}HNMR

The ^{1}HNMR data for the ligand is shown in Table 4. The signal to the protons of cyclopropane ring appears as multiplets at approximately ∂0.6-1.0 ppm indicating non equivalence of the ring protons. The N-H proton gives a signal around 1.4 ppm. This signal appears doublet. This position is due to the electronegativity of nitrogen, the magnetic anisotropy of the neighboring carbonyl group and probably the presence of intermolecular hydrogen bonding. The O-H proton of the ligand gives a doublet appearing around ∂1.3 ppm Fig. 3.

Magnetic Moment

The room temperature magnetic moment data for the complex is as shown in Table 1.

The molybdenum (VI) complex has magnetic moment of 1.90B.M in the absence of higher region between 1.90-2.2 B.M are however, characteristics of four-coordinate complex suggest square pyramidal geometry (Craig, 2004; Nwabueze and Aliyu, 2007).

Microbial Sensitivity

The microbial sensitivity test carried out on the ligand and its isolated Molybdenum (VI) complex exhibit moderate activity against the entire microorganism tested (Table 5, 6).

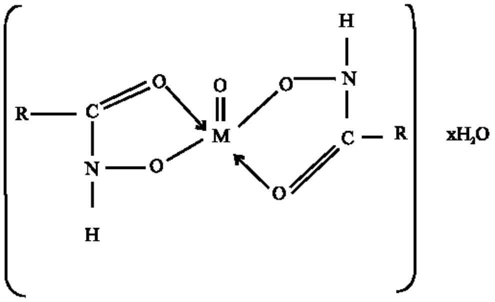
Table 5: Diameter of zone of symbol comment (inhibition)

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

+: Indicates activity

Table 6: Diameter of zone of inhibition of the ligand and its isolated complex

		Zone of inhibition				
Compound	Symbol	*S. aureus*	*Candida*	*B. subtillis*	*E. coli*	Comment
CPAH	++	18	19	18	19	Minimum
$Mo(CPAH)_6 \cdot 2H_20$	+++	22	24	23	25	Moderate activity



Scheme: 1: M = Molybdenum (VI) ion. Where X = 0

CONCLUSION

Based on the above discussion, the structure shown in scheme 1 is proposed for the complex. Proposed structure for (O,O) bonding mode in square pyramidal complex of oxomolybdenum (VI) hydroxamate. The major difference in this research work is in the area of its microbial activities wherein it shows significant activities.

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