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Synthesis, Characterization and Antimicrobial activity of bis(γ-aminobutyrohydroxamate)oxovanadium(IV)

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ABSTRACT: The complex $[VO(\gamma\text{-}C_3H_8NCONHO)_2]$ (I) has been synthesized by the reaction of $VOSO_4.5H_2O$ with bimolar amounts of potassium-γ-aminobutyrohydroxamate (Kγ-ABH) in methanol and characterized by elemental analyses, molar conductance and IR and ESR spectral. The molecular modeling dynamics of the complex suggest a square pyramidal geometry around vanadium. The antimicrobial activities of the newly synthesized complex and respective potassium hydroxamate ligand have been screened *in vitro* against six bacterial strains *viz. Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Klebsiella pneumoniae Salmonella typhi.* and *S. paratyphi* and three fungal strains viz. *A. niger, B. fulva* and *M. circinelloides* has been assayed by MIC method. The complex has improved antimicrobial activity compared to free ligand.

Keywords: Potassium-γ-aminobutyrohydroxamate; bis(γ-aminobutyrohydroxamate) oxovanadium(IV); spectroscopic studies; antimicrobial activity.

INTRODUCTION

There has been an intense increase of research activity in the broad domain of vanadium chemistry during the past few years. Much of the interest stems from the potential of vanadium complexes as its catalytic [1-3], industrial and immense pharmacological activities [4-10]. Oxovanadium(IV) complexes derived from a variety of ligands [11-13] are well studied as compared to oxovanadium(IV) and (V) complexes of hydroxamate ligands [14-17] which have only a few scattered reports. The synthetic significance of hydroxamate derivatives essentially stems from the broad spectrum of biological activities associated with hydroxamic acids, an important family of organic bioligands and strong chelators [18-20]. Vanadium-hydroxamate interactions has gained a special interest owing to their use as bioinorganic model compounds to study their enzymatic interactions, growth inhibiting and insulin-mimetic properties [21-27]. As part of our research interest on the synthesis of biologically important hydroxamatovanadium(IV)complexes [28-30], we have synthesized new oxovanadium(IV) complex incorporating γ-aminobutyrohydroxamate ligand (Fig.1), which has been assayed *in vitro* against six bacterial strains *viz. Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Klebsiella pneumoniae, Salmonella typhi.* and *S. paratyphi* and three fungal strains viz. *A. niger, B. fulva* and *M. circinelloides* by MIC method.

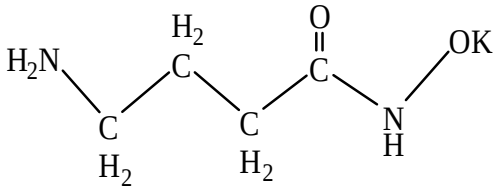


Fig.1 Potassium-γ-aminobutyrohydroxamate;K-γ-ABH ($C_3H_8NCONHOK$)

MATERIAL AND METHODS

All the solvents used were of A.R. grade and were dried by standard methods. The potassium γ-aminobutyrohydroxamate was synthesized by method reported earlier [31]. The vanadium content in complexes was determined as V_2O_5.[32]. The carbon, hydrogen and nitrogen analysis were obtained on Eager 300 NCH System Elemental Analyzer. The molar conductances (10^{-3} M solutions in methanol) were obtained at 25} 0.1oC on Elico Conductivity Bridge Type CM-82T. The room temperature magnetic susceptibilities were measured by Guoy's method using $Hg[Co(NCS)_4]$ as calibrant [33]. IR spectra of compounds were recorded as KBr pellets on Nicolet-5700 FTIR spectrophotometer. The pellets were prepared in a dry box to avoid the action of moisture. X-band ESR spectra were recorded on Varian E-112 ESR Spectrometer with X-band microwave frequency (9.5 GHz) with sensitivity of 5 x 1010 Δ H spins using powdered sample.

1. Synthesis: Preparation of Bis(γ-aminobutyrohydroxamate)oxovanadium(IV):

To a stirred solution of potassium γ-aminobutyrohydroxamate (1.47g, 9.48mmol) in methanol (10mL), a solution of VO^{2+} prepared by dissolving $VOSO_4.5H_2O$ (1.20g, 4.74mmol) in 5mL of methanol. The reactants were stirred at room temperature, whereupon the formation of green precipitate was observed. After filtration the precipitate was washed with methanol and dried in air (yield 72%).

Anal. Calcd. For **[$VO(ONHOCNH_8C_3)_2$] ($VC_8H_{18}O_5N_4$) (301)** (%): C, **31.89**; H, **5.98**; N, **18.60**; V, **16.94**. Found: C, **31.45**; H, **5.68**; N, **18.25**; V, **17.12**.

2. Antimicrobial activity test: The ligand potassium γ-aminobutyrohydroxamate and newly synthesized complex $[VO(\gamma\text{-}C_3H_8NCONHO)_2]$ were screened *in vitro* for their antibacterial activity against different bacteria Gram +ve *Staphylococcus aureus, Staphylococcus epidermidis* and Gram –ve *Escherichia coli, Salmonela typhi, Salmonella paratyphi and Klebsiella pneumoniae* and were also screened for antifungal activity against *Aspergillus niger, B. fulva* and *M. circinelloides* to obtain MIC's at different concentrations in DMSO (1mg/mL) employing the standard method as recommended by National Committee for Clinical Laboratory Standard (NCCLS). MIC is the lowest concentration of the antimicrobial agents that prevents the development of visible growth after overnight incubation. All the samples were tested in triplicate. The results were compared with standard antibacterial and antifungal drugs *viz*. tetracycline hydrochloride and fluconazole (treated control), untreated control containing both broth and fungi and the control containing only broth (blank).

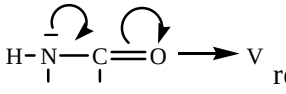
3. MIC determination by two-fold serial dilution: The MIC assay [34] was performed in a 96-well micro-titre plate. For MIC assay of each test drug; a stock solution of 1mg/mL of each drug was prepared in DMSO and a row of twelve wells was used out of which last two wells were taken as untreated control (no drug added). Each of the ten wells received 100 µL of the Muller-Hinton broth, except the first well that received 200 µL of broth containing 500 µg / mL concentration of the test drug. From the first well (containing test drug), 100 µL broth was withdrawn with a sterile tip, and same was added to the 100 µL of the broth in the second well; contents were mixed four times. Then 100 µL was withdrawn from 2nd well and was added to the third well. This way a range of two-fold serial dilution were prepared (500 – 0.98 µg / mL) by performing two-fold serial dilution. The broth in each of the wells was inoculated with 2 µL of the bacterial culture (*K. pneumoniae, S. epidermidis, S. aureus, E. coli, S. typhi, S. paratyphi*) and 5 µL of the fungal culture *(Aspergillus niger, B. fulva* and *M. circinelloides)* the contents were mixed by ten clockwise and ten anticlockwise rotation on a flat surface. The plate was incubated at 35°C and 30°C for bacteria and fungi respectively thereafter. The observations for growth of bacteria were recorded after 24 h and five days for bacteria and fungi respectively.

RESULTS AND DISCUSSION

The reaction of $VOSO_4.5H_2O$ with bimolar amounts of potassium-γ-aminobutyrohydroxamate in methanol afforded the quantitative formation of $[VO(\gamma\text{-}C_3H_8NCONHO)_2]$ in confirmity with elemental analyses according to the following equation:

$$VOSO_4.5H_2O \xrightarrow{2C_3H_8NCONHOK} [VO(ONHOCNH_8C_3)_2] + K_2SO_4 + 5H_2O$$

The complex is green in color, soluble in most of the common organic solvents as well as in methanol and dimethylsulphoxide. The molar conductance value of the millimolar solution of the complex in methanol (3.78 Scm^2mol^{-1}) suggested its non–electrolytic nature. The room temperature magnetic moment value of the complex is 1.72 B.M. which suggest its paramagnetic nature and +4 oxidation state for vanadium.

1. IR Spectra: The formation of complex has been inferred from a comparison of their IR spectra with those of the free ligand potassium-γ-aminobutyrohydroxamate scanned in 4000–250 cm^{-1} region. The absorption bands due to υ(C=O) mode in potassium appeared in 1680-1559 cm^{-1} regions in potassium γ-aminobutyrohydroxamate. The occurrence of sharp absorption bands due to υ(C=O) mode in 1660-1560 cm^{-1} regions in oxovanadium(IV) complex derived from hydroxamate ligand suggested bonding through carbonyl oxygen to vanadium. The absorption band due to υ(C–N) mode occurring in 1380-1338 cm^{-1} region in free hydroxamate ligand has been found to appear in 1390-1348 cm^{-1} region in newly synthesized oxovanadium(IV) complex. The lowering in ν(C=O) and the shift of ν(C-N) to higher wave number is in agreement with the electron shift  resulting from the donation of electrons from the carbonyl oxygen to the metal atom accompanied by the strengthening of the C-N bond thereby suggesting the coordination trough the carbonyl oxygen. The sharp bands observed at 927 cm^{-1} in K(γ-ABH) respectively ascribed to υ(N–O) mode have been found to occur in 940 cm^{-1} region in respective oxovanadium (IV) hydroxamate derivatives indicating thereby bonding through oxygen atom of −NHO group [35]. The band observed in 969 cm^{-1} region in complex under study has been ascribed to υ(V=O) mode.

2. ESR Spectra: The room temperature X-band ESR spectra of [VO(γ-$C_3H_8NCONHO)_2$] (Fig. 2) displayed well resolved typical eight lines due to the interaction of an unpaired electron of vanadium(IV) center with its own nucleus, I=7/2 consistent with a single paramagnetic species of vanadium(IV). The g average values determined from the spectra are ≈ 1.98 similar to the spin only values (free electro value of 2.00) suggesting little spin orbit coupling.

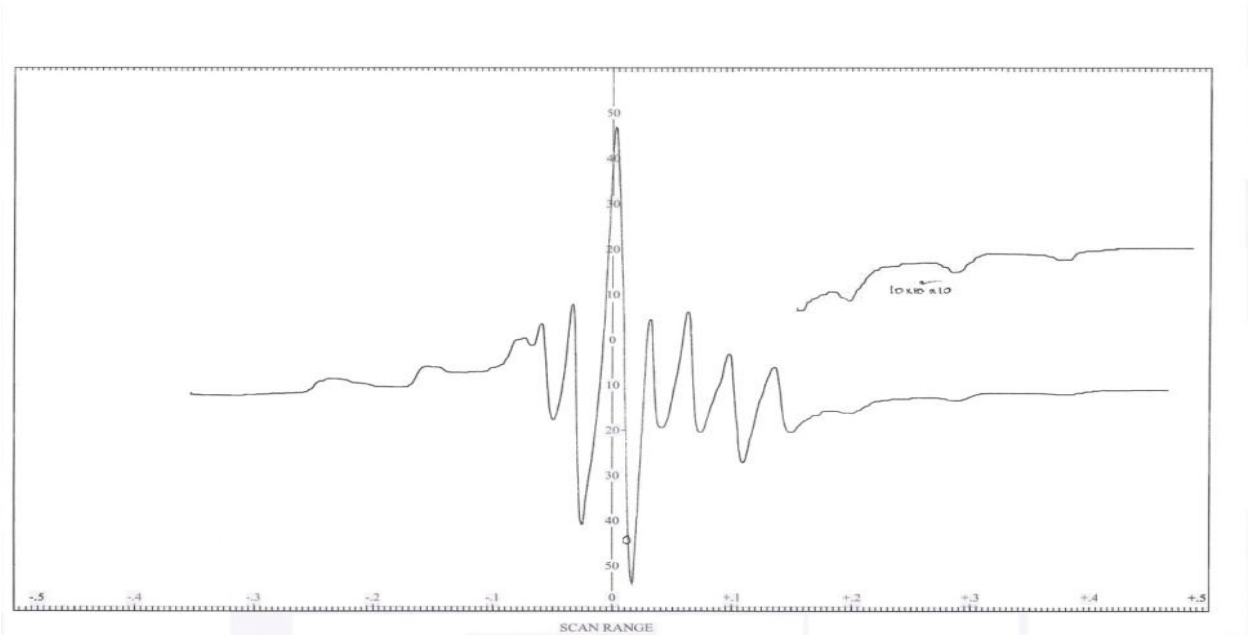


Fig. 2. ESR spectrum of [VO(γ-$C_3H_8NCONHO)_2$]

3. Molecular Modelling: The molecular mechanical adjustments for energy optimization from strained structures to the likely geometry of parent complex were made. The molecular mechanics were repeated

five to six times to ensure that the structure with minimized energy has been attained. The structure with minimized energy is assumed to be closer to the stable geometry and is in conformity with physicochemical and spectral data. On the basis of molecular modelling calculations for [VO(γ-$C_3H_8NCONHO)_2$] a probable square pyramidal geometry around vanadium may tentatively be proposed (Fig. 3).

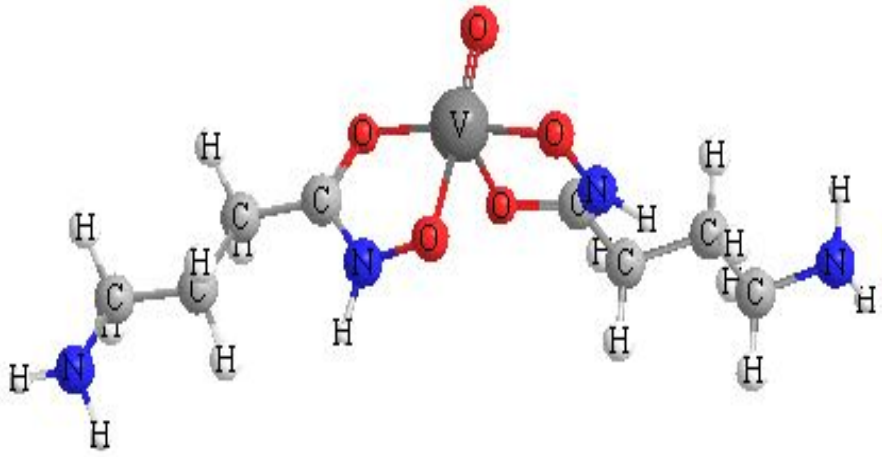


Fig. 3 Proposed structure of [VO(γ-$C_3H_8NCONHO)_2$]

4. Antimicrobial activity: Literature contains reports that metal salts do not exhibit antimicrobial activity but complexation leads to show significant activity [36, 37]. The antimicrobial activity (antibacterial and antifungal activity) of potassium γ-aminobutyrohydroxamate (Kγ-ABH) and complex [VO(γ-$ABH)_2$] has been assayed.

5. Antibacterial activity test: The hydroxamate ligands viz. potassium γ-aminobutyrohydroxamate (Kγ-ABH) has been assayed for their antibacterial activity which inhibited the bacterial growth of *E. coli* at concentration 62.5 µg/mL and *S. aureus, S. epidermidis, K. pneumoniae, S. typhi.* and *S. paratyphi at* 125 µg/mL. The complex [VO(γ-$ABH)_2$] inhibited the growth of all bacteria at MIC 62.5 µg/mL.

6. Antifungal activity: The ligand potassium γ-aminobutyrohydroxamate, vanadyl sulphate and newly synthesized complex [VO(γ- $C_3H_8NCONHO)_2$] were screened *in vitro* for their antifungal activity on selected fungi *A. niger, B. fulva,* and *M. circinelloides* using the minimum inhibitory concentration (MIC) method. A perusal of data has shown that the ligand inhibits the fungal growth at 125 µg / mL and complex [VO(γ-$C_3H_8NCONHO)_2$] at 62.5 µg / mL. The results were compared with standard antifungal drug fluconazole (treated control) and have been found to be satisfactory.

The increase in activities of complex may be explained on the basis of chelation theory; chelation reduced the polarity of the metal atom mainly because of partial sharing of its positive charge with the donor groups and possible electron delocalization within the whole chelate ring. Also, chelation increased the lipophilic nature of the central atom which subsequently favoured its permeation through the lipid layer of the cell membrane [38, 39].

CONCLUSION

The title complex of composition [VO(γ-$C_3H_8NCONHO)_2$] has been synthesized and thoroughly characterized by various physicochemical and spectral techniques and a square pyramidal geometry around vanadium in this coordination complex has been inferred. The antimicrobial screening of complexes has depicted moderate to significant inhibitory effect compared to free ligand.

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