Report of dioxidovanadium complexes of bioactive heterocycles: Synthesis, characterization and study of biological activity

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By

Parbati Tudu

Roll No. 412CY2030

Under the esteemed guidance of

Dr. Rupam Dinda

Department of Chemistry

National Institute of Technology, Rourkela-769008, Odisha

NATIONAL INSTITUTE OF TECHNOLOGY

ROURKELA

CERTIFICATE

This is to certify that the dissertation entitled **"*Report of dioxidovanadium complexes of bioactive heterocycles: Synthesis, characterization and study of biological activity* "** submitted by ***Ms Parbati Tudu*** of Department of Chemistry, National Institute of Technology, Rourkela for the degree of Master of Science in Chemistry is based on the result obtain in the bonafide project work carried out by her under my guidance and supervision. To the best of my knowledge, the matter embodied in the thesis has not been submitted to any other University/Institute for the award of any degree or diploma.

I further certify that to the best of my knowledge she bears a good moral character.

Date:6.05.2014

Dr. Rupam Dinda.

Department of Chemistry

National Institute of Technology

Rourkela- 769008

ABSTRACT

A series of new dioxidovanadium(V) complexes [VO_2L^{1-4}] (**1**-**4**) have been reported. The complexes are obtained from the reaction of the HL^{1-4} with $VO(acac)_2$ in 1:1 molar ratio in different solvent medium. All the synthesized ligands and the metal complex are successfully characterized by elemental analysis, IR and UV-vis spectroscopy. From various studies it is indicated that all the complexes possess square pyramidal structure.

1. INTRODUCTION

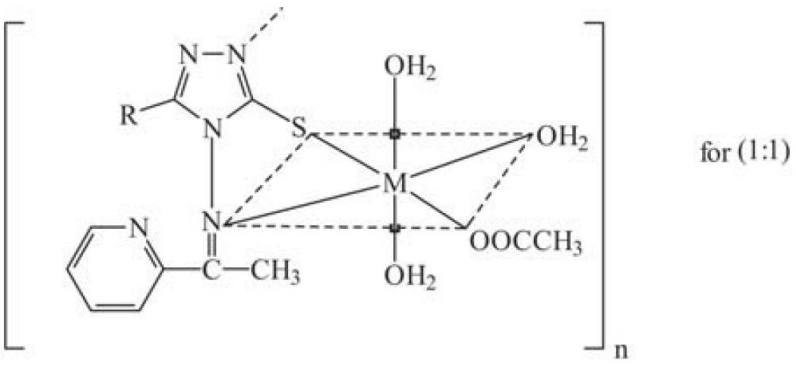
In past few years metal complexes of biologically active ligands has gain much interest in the field of coordination chemistry,[1-3] it may be due to the fact that, chelation has much effect in biological properties of ligands as well as metal involved. It is well reported in the literature that chelation is the cause and cure of many diseases including the disease like cancer.

Vanadium being a versatile metal with variable oxidation state has explored much in coordination chemistry in past few decades. Synthesis, characterization, properties and application of vanadium complexes in diverse fields have a widespread interest. This metal act as active site in various enzymes such as vanadium-dependent nitrogenases, haloperoxidase,[4–10] which stimulated the research for functional model. Due to the discovery of Amarnita muscaria, which contains vanadium in the form of vanadate ion (VO^{3+}) in a nonporphyrinic O/N donor environment,[11-12] interest in this field has been increased. Vanadium compounds found to show activity like anti-carcinogenic,[13] anti-leishmanial[14] etc. which, enhances its biological importance. Moreover, inorganic vanadyl and vanadate, as well as some vanadium (IV) and (V) complexes, are potent insulin mimics and as such may find use as alternatives to insulin in the treatment of diabetes.[15]

On the other hand, hydrazones, –NH–N=CRR' (R and R′ = H, alkyl, aryl), are versatile ligands due to their applications in the field of analytical[16] and medicinal chemistry.[17] Hydrazone moieties are the most important pharmacophoric cores of several anticancer, antiinflammatory, antinociceptive, and antiplatelet drugs.[18]

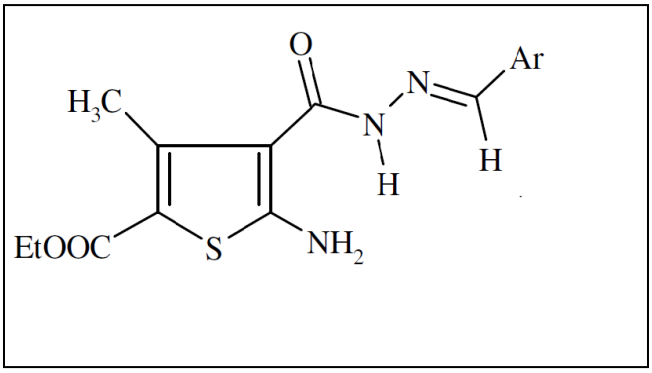
Kiran Singh and group[19] have reported the a series of metal complexes of Co(II), Ni(II), Cu(II) and Zn(II) (**Figure-1**) prepared from biologically active ligands. These ligands were prepared by the condensation of 4-amino-5-mercapto-3-methyl-s-triazole (AMMT), 4-Amino-3-ethyl-5-

mercapto-s-triazole (AEMT) with 2-acetylpyridine. Antibacterial activities of 10 complexes have been studied *in vitro*. It was observed that heterocyclic bidentate Schiff bases were associated with substantially higher antibacterial activities than some commercial antibiotics.



(Figure-1)

Hafez et. al[20] have reported the synthesis of two series of 5-ethyl-2-amino-3-pyrazolyl-4-methyl thiophenecarboxylated and 2-thioxo-N^3-aminothieno[2,3-d] pyrimidines from 3,5-diethyl-2-amino-4-methylthio-phenecarboxylate and evaluated as anti-inflammatoryanalgesic and ulcerogenic activities **(Figure-2)**. Some of the compounds containing the substituted hydrazide showed more potent anti-inflammatory activity and analgesic activities than the than the standard drug (Indomethanic and aspirin) along without ulcerogenity.



(Figure-2)

Cheng et. al.[21] have been reported the synthesized and characterized of two trinuclear complexes, $Cu_3L_2(py)_2$ (1) and $Ni_3L_2(py)_4$(2) **(Figure-3)**,where central metal ion and two trinuclear metal ions in the two complexes are combined by two bridging deprotonated L^{3-} ligand forming a bent trinuclear structure. Antibacterial screening data indicate all compounds have stronger antimicrobial activities against the tested microorganisms than ligand.

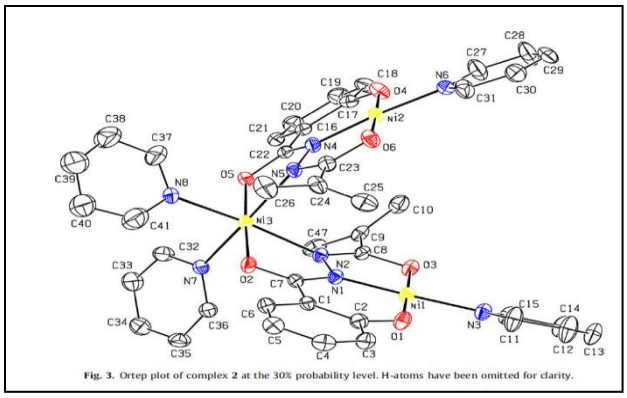


Fig. 3. Ortep plot of complex 2 at the 30% probability level. H-atoms have been omitted for clarity.

(Figure-3).

Patel and coworkers[22] have reported the superoxide dismutase (SOD) and antimicrobial properties of copper (II) complexes complexes of the type [Cu(L)X_2)], where L = (E)-N-phenyl-2-[phenyl (pyridine-2-yl)methylene]hydrazinecarboxamide X =Cl/Br **(Figure-4**). The superoxide dismutase activity reveals that these two complexes catalyze the fast disproportionationof superoxide in DMSO solution.

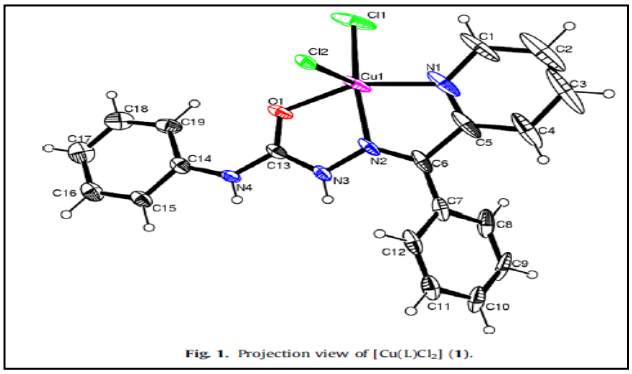
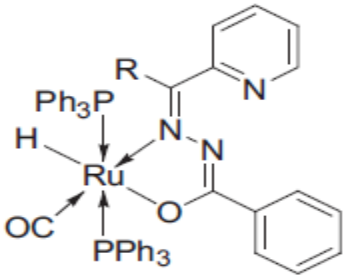


Fig. 1. Projection view of [Cu(L)Cl_2] (1).

(Figure-4).

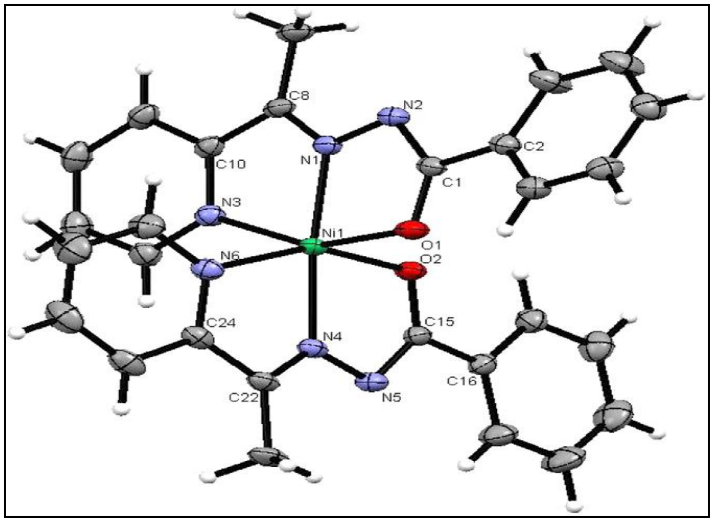
Dharmaraj et. al[23] have reported synthesised of bivalent, ruthenium organometallics containing hydrazone ligands with the composition [RuH(-CO)(PPh_3)$_2$(L^{1-3})] **(Figure-5**), from the reactions of [$RuH_2(CO)(PPh_3)_3$] and benzoic acid pyridine-2-ylmethylene-hydrazide (HL_1) (1) /benzoic acid (1-pyridin-2-yl-ethylidene)-hydrazide (HL_2)(2)/benzoic acid (phenyl-pyridin-2-yl-methylene)-hydrazide (HL_3) (3) and characterised by variousphysicoechemical techniques. Here it is reported that substitution (H or CH_3 or C_6H_5) at the azomethine carbon of coordinated hydrazones in these ruthenium has marked effect on the potential binding with DNA/BSA, free radical scavenging and cytotoxicity.



Ligand	R
HL^1	H
HL^2	CH_3
HL^3	C_6H_5

(Figure-5)

N. Dharmaraj and group[24] have also reported the synthesis of bivalent transition metal hydrazone complexes of Ni (II)and Co(II) derived from 2-acetyl pyridine and carboxylic acid hydrazides of benzhydrazide or thiophene-2-carboxylic acid hydrazide **(Figure-6**). To explore the potential medicinal value of the complexes, binding interaction of all the complexes with bovine serum albumin (BSA) was studied at normal physiological conditions using fluorescence and UV–Vis spectral techniques.



(Figure-6)

Cai-feng Bi[25] have been reported the synthesis and characterization of several transition metal coordination complexes of Cu, Zn, Cd by taking 2-acetyl pyridine derivative as ligand systems. These compounds are screened for anticancer activities of these three complexes on MDA-MB-231 breast cancer cells and was found that all the three complexes can inhibit the cellular proliferation. In addition, the cadmium complex, can inhibit proteasomal chymotrypsin-like activity and also can induce apoptosis on human breast cancer.

From the literature survey it is obvious that, though the chemistry of metal complex having bioactive heterocycles is quite developed, but that of with vanadium is less well known and are need to be explored. Keeping this observation in mind and in continuation of our studies on dioxidovanadium complexes of hydrazone Schiff base ligands, in this dissertation, I have reported the synthesis, full characterizations of four new tridentate ligands containing heterocyclic group and corresponding dioxidovanadium(V) complexes. All the synthesized ligands and corresponding metal complex have been characterized by several spectroscopic techniques. The X-ray study of one of the complex is reported and others are under process.

2. EXPERIMENTAL

2.1. Physical Measurements:

Elemental analyses (C, H, N) were performed by Vario ELcube CHNS Elemental analyzer. FTIR spectra (4000-400 cm^{-1}) as KBr discs of the samples were recorded on a Perkin Elmer spectrum RXI. Electronic spectra were obtained using a Perkin Elmer Lambda 35 UV/VIS spectrophotometer.

2.2. Chemicals and solvents:

Chemicals were procured from companies like Aldrich, E. Merck and Fluka and used without further purification. HPLC grade acetonitrile, dichloromethane and chloroform were used for spectroscopic studies. All other solvents were A.R. grade and used as received for synthetic work. NH_4VO_3 and $VOSO_4$ were procured from Loba Chemie. $[VO(acac)_2]$ was synthesized in the laboratory by following the procedure which has been described in the literature.[26]

2.3. Work plan:

This proposal is concerned with the design of various tridentate ligands (NNO) having pyridine derivatives and synthesis of the corresponding dioxidovanadium complexes by the reaction of tridentate ligands with various metal precursor of vanadium. The different steps of the methodology are given below.

2.4. Synthesis of the Ligands:

Schiff base ligands, (HL^{1-3}) were prepared by condensation of acidhydrazides and the corresponding ketone of pyridine derivative in stirring ethanol medium by following a standard procedure.[27] Whereas ligand HL^4 is prepared by condensation of 2-amino benzohydrazide with

2-benzoyl pyridine in refluxing methanol medium. The resulting white compound was filtered, washed with ethanol and dried over fused $CaCl_2$.

2.5. Synthesis of complexes $[VO_2L^{1-3}]$(1-3):

To the hot solution of ligand, HL^{1-3} in refluxing methanol medium, $[VO(acac)_2]$ in DMF was added the color changed instantly to greenish brown. It was cooled, filtered off and kept for crystallization. Slow evaporation of the filtrate over 4 days produced yellow crystalline compounds. The characterizations of the complexes were done systematically. Yield: ~ 60%.

2.6 Synthesis of complex $[VO_2L^4]$(4):

To the hot solution of ligand, HL^4 in methanol medium, $[VO(acac)_2]$ was added, the color changed instantly to orange. After reflux, it was cooled, filtered off and kept for crystallization. Slow evaporation of the filtrate produced orange crystals. Some crystals are of diffraction quality and were used directly for X-ray structure determination using single crystal X-ray diffractometer. Yield: 64%.

3. RESULTS AND DISCUSSION

The spectral (IR, UV-Vis) data of the ligand, H_2L^1 and their corresponding dioxidovanadium (V) complex, $[VO_2L^1]$(**1**) are given in below. The infrared spectra of the complex display characteristics similar to a dioxidovanadium complex. The disappearance of characteristic bands due –NH and –C=O in the ligand spectra, and the appearance of new bands in the range 1253 cm^{-1} in the complex indicates the enolization of these two groups forming a –N=C–O bond sequence. The strong and sharp peak displayed by the complexes in the range 1595 cm^{-1} is likely to be associated with the –C=N–N=C– moiety.[28,29] The presence of two strong bands in the range

956, 941 cm^{-1} is assigned to V=O stretching,[30] which clearly indicates the dioxido nature of the complex shown in (**Figure** 7-**8).**

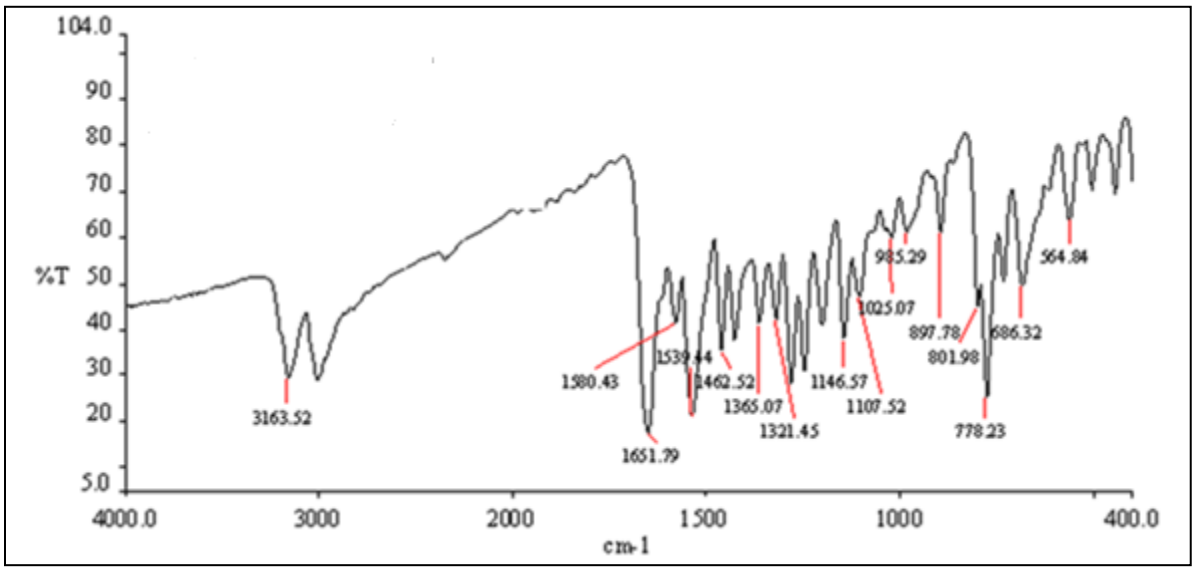


Figure-7 FTIR Spectrum of (E)-N-(1-pryidin-2-yl)ethylidene)-1-naphthohydrazide (HL^1)

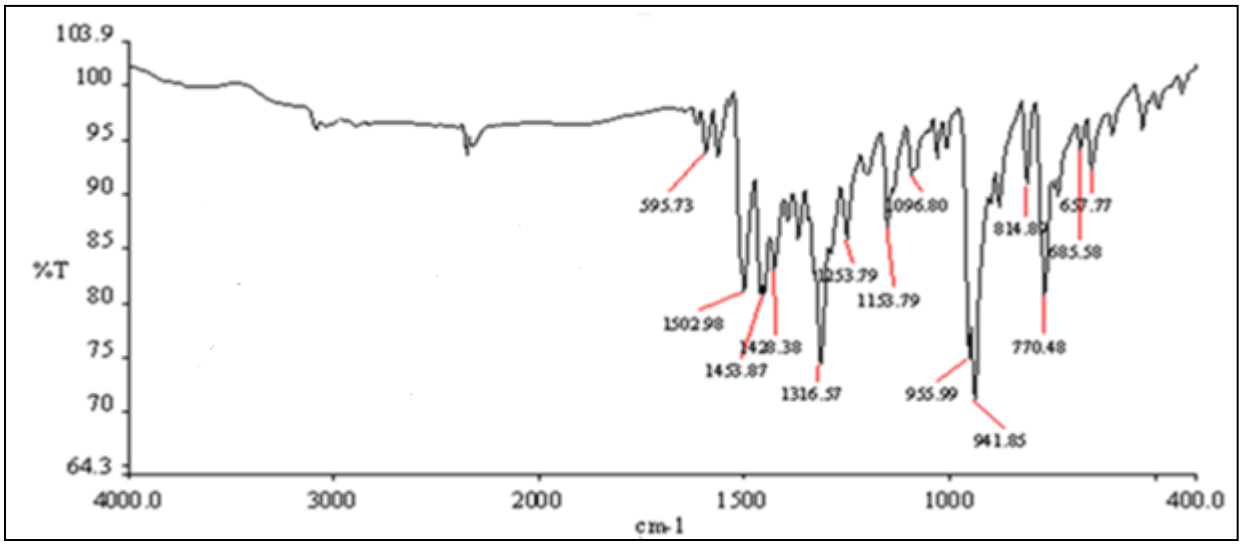


Figure-8 FTIR Spectrum of complex (VO_2L^1)(1)

The electronic spectrum of the complex 1 was recorded in DMF. The strong absorption observed at the wavelength 397nm is assignable to the ligand-to-metal charge transfer transitions

whereas the other bands in the higher energy region (286–263 nm) are likely to be due to ligand centred transitions.[28] shown in (**Figure 9)**.

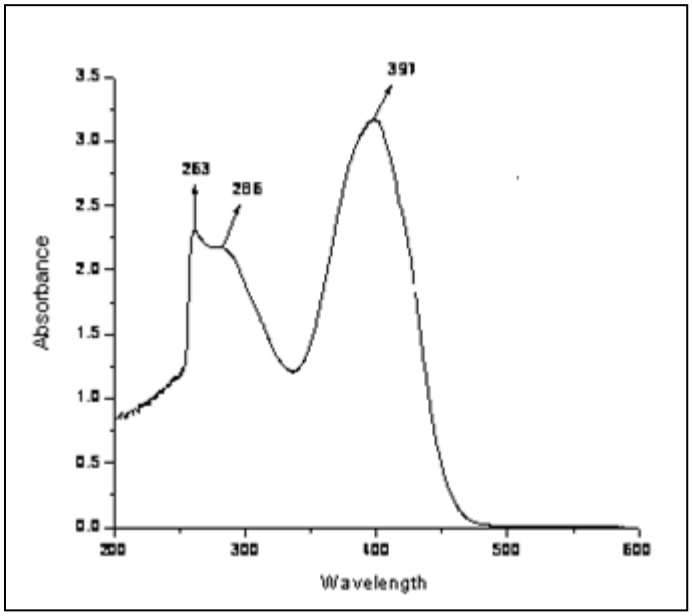


Figure-9 UV-vis Spectrum of complex (VO_2L^1)(1)

4. CONCLUSION

Four Schiff's base hydrazone ligands were synthesized and successfully characterized by IR and elemental (C, H, N) analyzer. The basic and electronic property of these ligands has been nicely explored in the syntheses of corresponding dioxidovanadium(V) complexes. All the four complexes reported here, has been fully characterized by IR and UV-visible spectroscopy. Biological studies are under process.

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