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Synthesis and structural characterization of new oxovanadium(IV) complexes derived from azo-5-pyrazolone with prospective medical importance

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ABSTRACT

Four novel o-hydroxy substituted aryl-(m–H, –Cl, –Br, $-CH_3$) azo-5-pyrazolone compounds (***2a–d***, respectively) were synthesized as azo-group containing ligands by diazotization of aryl amines then coupled with 1-(4-chlorophenyl)-3-isopropyl-1*H*-pyrazol-5(4*H*)-one (**1**) and the structures were confirmed by FTIR, UV-Visible, GC-MS or ESI-LCMS and NMR spectroscopic techniques. As a result, the first synthesis of azo-5-pyrazolone based oxovanadium(IV) complexes (***3a–d***) was achieved by interaction of ***2a–d*** with half equivalent of vanadyl sulphate pentahydrate in a methanolic medium with moderate to high yields (67, 74, 60, 71 for ***3a–d***, respectively). The resulting complexes were characterized using FTIR, UV-Visible, ESI-LCMS and EPR spectroscopic techniques as well as with thermogravimetric (TG/DTG) analysis. They have the composition $[VO(L)_2]\cdot H_2O$; (***3a–c***) or $[VO(L)_2]\cdot CH_3OH$; (***3d***) where LH is an azo-5-pyrazolone compound as the ligand (***2a–d***). The electronic spectra of the complexes are typical of oxovanadium(IV) complexes showing a low intensity band near 500 nm. Spectroscopic results have shown that azo-5-pyrazolone compounds have acted bidendate and the coordination sites are hydroxyl-substituent on the -azo phenyl-aromatic ring and the pyrazolone carbonyl-moiety. The thermal data confirm that the complexes have methanol (***3a–c***) or water (***3d***) molecule outside the coordination sphere and the complexes show similar thermogravimetric decomposition fragments which are consistent with the proposed structures. A distorted octahedral geometry has been proposed for these complexes mainly with EPR and the other spectral techniques.

1. Introduction

Pyrazolone is a five membered derivative of pyrazole and has three possible isomers. Among them the 5-pyrazolones have been receiving increasing interest on account of their rich applications in different fields whether from polymers [1,2] to pharmaceutical chemistry [3,4] or from textiles [5] to agriculture [6,7]. They have a wide range of bioactivity (anti-inflammatory, antitumor, antifungal, anticancer, analgesic, antipyretic, antibacterial etc.) [8]. Even the simplest 5-pyrazolone derivatives, i.e. antipyrine and amidopyrine are among the most common analgesics [3,4].

Vanadium can be found in trace amounts in soil and water, also in the human body. Vanadium compounds have been found to be potentially active against some diseases such as diabetes type 2, endemic tropical and HIV infections and malign tumors [9]. Vanadium complexes are considered as a new class of non-platinum metal anti-tumor agent [10] and as a promising anti-diabetic [11] agent with low toxicity. Some researchers have investigated the anti-tumor properties of oxovanadium(IV) complexes working with mitocondria [12] or endoplasmic reticulum [13] targeted tumor selective photocytotoxicity of the complexes. Also they can be operative in cardio and neuro protection [9].

Aligned to the heightened interest in oxovanadium(IV) compounds, new researches have recently been published. Hassoon and co-workers [14] synthesized new polydentate ligand based complexes with anti-bacterial and anti-tumor activities and Somyajit and co-workers [15] developed the *trans*-dichlorooxovandium(IV) complex as a novel photoinducible DNA interstrand

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crosslinker for cancer therapy.

Vanadium oxide, vanadium dioxide and vanadate species have contributed to vanadium applications. Amorphous tungsten doped vanadium dioxide for smart window applications [16]; Zn-Sn-vanadium oxide nanocomposites for oxygen sensing applications [17]; and Ti, Zr, Nb and Mo-vanadium oxide thin films for uncoated infrared imaging [18] applications have been examined. Vanadate is an oxidised form of vanadium and has many examples: orthovanadate, hexavanadate, decavanadate and so on. This oxoanion has biological importance and is a potent inhibitor of certain plasma membrane ATPases [19,20]. There are also interesting applications such as new bismuth vanadate photocatalysts [21] and microwave dielectric ceramics [22]. It is also possible to follow many applications on vanadium redox flow batteries in the literature [23–25].

Some publications illustrate the catalytic activity of the complexes such as in the sodium borohydride reduction of aldehydes [26]; oxidative polymerization of diphenyl disulfide [27]; asymmetric synthesis [28]; electrochemical use such as in the non-enzymatic sensing of glucose and hydrogen peroxide [29]; and electrocatalytic oxidation and determination of cysteine [30].

It is known that long-term vanadium use can cause toxic side effects of tissue accumulation, diarrhea, abdominal cramps, bronchospasm, green tongue etc. in experimental diabetic rats [31,32]. On the other hand, after 12 weeks' administration of vanadyl sulphate on weight training athletes, it was shown that vanadium does not have any undesired effect on the blood cells, viscosity or biochemical parameters of liver or kidney function [31,33]. In a recent study on the effects of vanadium complexes with organic ligands, these species might decrease the side effect of vanadium without tissue accumulation [31,34].

Different research groups show the importance of the chemical structure of the ligands (especially the electron donating and withdrawing ability of the substituents) [35,36] and solvent used in the complexation for the stability of the complexes [37]. Wu and co-workers [38] synthesized new *N*-(2-hydroxyethyl)ethylenediamine-*N*,*N*′,*N*′-triacetic acid (HEDTA)-vanadium complexes and studied the effect of pH range for complex formation at a final concentration of 150 mM obtaining two structurally different complexes in the pH range of 3–11. In a recent study [39] ternary oxovanadium(IV) complexes with oxydiacetate and 1,10-phenanthroline or 2,2′-bipyridine were prepared and the researchers found by a potentiometric titration method that the ternary complexes are stable in the pH range of 3–6 (2 mM VO^{+2}) and, in the higher pH range, have a tendency to undergo hydrolysis.

Vanadium compounds, especially the coordination chemistry of oxovanadium(IV), have aroused significant interest for several main reasons. The vanadyl complexes are important for biological systems showing anticancer, DNA cleavage, DNA binding, insulin-mimetic, antidiabetic, antiinflammatory, antioxidant etc. activities [40]. The geometry and coordination number of oxovanadium(IV) depend on the ligand. It is also known that vanadyl is less toxic than the vanadate ion [41] and as shown above with all these characteristics the complexes exhibit pronounced applications.

Azo-5-pyrazolones have been used extensively as ligands in coordination compounds. However, to the best of our knowledge, there have not been any studies on oxovanadium(IV) metal with azo-5-pyrazolones in the literature although derivatives of oxovanadium(IV) and 5-pyrazolone compounds show unique bioactive properties. Spectroscopic research has shown the preference of this metal center for N and/or O atoms, as in 2-hydroxy aryl-substituted azo-5-pyrazolone moiety [42]. With this in mind and our continuing experience in pyrazolone chemistry [43–45], we would now like to report the synthesis of structurally characterized new oxovanadium(IV) complexes.

2. Results and discussion

2.1. Synthesis of the ligands and the complexes

Considering the pronounced biological activity of the pyrazolone structure, the azo-5-pyrazolone ligands (***2a***–***d***) were synthesized by the coupling reaction of 5-pyrazolone compound (***1***) [44] and the diazonium salt of 2-hydroxy- substituted aryl amines: 2-Aminophenol, 2-amino-4-chlorophenol; 2-amino-4-bromophenol and 2-amino-4-methylphenol in the presence of potassium hydroxide. Their structures were characterized on the basis of NMR techniques with FTIR, UV-Vis and GC-MS or ESI-LCMS analyses. The synthetic pathway to obtain the new azo-5 pyrazolones is described in Scheme 1. The resulting ligands can exist in two possible tautomeric forms, namely the azo-hydrazo and the azo keto-enol forms [45]. According to the spectroscopic results, all the ligands are dominantly of the azo-hydrazo tautomeric form in the solid as well as in the solution state.

For the synthesis of the complexes, half the equivalent of vanadyl sulphate pentahydrate was used with 2-hydroxy-aryl substituted azo-5-pyrazolones (***2a***–***d***). Approximately 4 h of reaction time is sufficient under reflux conditions in methanol (Scheme 2). The new complexes (***3a***–***d***) are commonly soluble in organic solvents: chloroform, dimethylsulphoxide and at a low concentration in methanol. They are all stable under room temperature conditions. They were prepared according to the following equation:

$$VOSO_4 \cdot 5H_2O + 2(2\boldsymbol{a}\text{–}\boldsymbol{d}) \rightarrow [VO(2\boldsymbol{a}\text{–}\boldsymbol{d})_2] \cdot CH_3OH \text{ or } H_2O + H_2SO_4$$

All the precipitated complexes were characterized structurally with the aid of spectral (FTIR, UV-Vis, LC-MS, ESR) and thermal techniques (TG/DTG-DSC) after purification. No crystalline compounds were obtained from any organic solvent, thus no definite structures can be described. The proposed structures of the complexes are presented in Scheme 2.

The synthesis, purification and detailed spectroscopic identification are listed for all the newly synthesized compounds in the experimental section.

2.2. Structural characterization of the complexes

2.2.1. FTIR spectral studies

The first basic information about the structures of the complexes was obtained from this spectral technique. All the complexes show significant differences from the starting compounds.

The ligands: 2-hydroxyaryl- substituted azo-5-pyrazolones have two important absorptions assigned to the carbonyl-and hydroxyl-groups. In the spectra of the complexes, it is possible to see the disappearance of the hydroxyl groups: (O–H) stretching of ***2a***–***d***: 3371; 3390; 3383 and 3336 cm^{-1}, respectively or carbonyl groups: (C=O) stretching of ***2a***–***d***: 1643, 1639; 1639 and 1639 cm^{-1}, respectively, showing the formation of a new bond between the oxgene of the hydroxyl-groups of ***2a***–***d*** or the oxgene of the carbonyl-groups of ***2a***–***d*** and the metal center.

With the aid of thermal techniques, the coordinated water and methanol molecules of the complexes were determined and this information was confirmed with IR spectral data of the complexes. The new oxovanadium(IV) complexes ***3a***–***c*** are all methanol coordinated except that ***3d*** is preferred to coordinate a water molecule. According to the spectra, ***3a***–***c*** have absorption bands corresponding to the O–H vibrations of methanol: 3360 (a broad band), 3603 and 3410 (a broad band), respectively and ***3d*** has an absorption band corresponding to the O–H vibration of water: 3545 cm^{-1}. All the metal complexes have absorption bands that can be