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Synthesis, structural and spectroscopic characterization of unusual ternary dinuclear tetraperoxo vanadium(V)-glycine complexes

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Abstract

Poised to understand the ternary V(V)-H_2O_2-amino acid interactions relevant to that metal ion's biological role, we have launched synthetic efforts involving the physiological ligands glycine and H_2O_2. In a pH-specific fashion, V_2O_5, glycine and H_2O_2 reacted and afforded the unusual complexes $(H_3O)_2[V_2(O)_2(\mu_2{:}\eta^2{:}\eta^1\text{-}O_2)_2(\eta^2\text{-}O_2)_2(C_2H_5NO_2)]\cdot 5/4H_2O$ (**1**) and $K_2[V_2(O)_2(\mu_2{:}\eta^2{:}\eta^1\text{-}O_2)_2(\eta^2\text{-}O_2)_2(C_2H_5NO_2)]\cdot H_2O$ (**2**). Both complexes **1** and **2** were characterized by UV/Visible, FT-IR, Raman, NMR spectroscopy, cyclic voltammetry, and X-ray crystallography. The structures of **1** and **2** reveal the presence of unusual ternary dinuclear vanadium-tetraperoxo-glycine complexes containing $[(V^V{=}O)(O_2)_2]$ units interacting through long V-O bonds and an effective glycinate bridge. The latter ligand is present in the dianionic assembly as a bidentate moiety spanning both V(V) centers in a zwitterionic form.

Keywords: vanadium, peroxo glycine structure, amino acids, zwitterions

1. Introduction

Participation of vanadium in abiotic and biological systems has been amply established in the past decades, with research activities aimed at clarifying its role and action [1-3]. Vanadium as an inorganic cofactor has been shown to participate in key metalloenzyme systems [4], such as nitrogenases [5] and haloperoxidases [6]. Concurrently, it has been shown to exhibit bioactivities including antitumorigenicity [7], mitogenicity [8], and inhibition of metabolic enzymes such as phosphoglucomutases and others [9]. Noteworthy, however, has been the association of vanadium with the heterogeneous syndrome of Diabetes mellitus by virtue of its insulin mimetic activity [10].

In its role as a metal ionic inducer of metabolic events in cellular physiology, vanadium reacts with physiological substrates of low as well as high molecular mass. Among the plethora of such potential ligands are small molecules including H_2O_2 and amino acids or amino acid macromolecules i.e. peptides and proteins. To this end, H_2O_2 reacts readily with V(V), forming a number of peroxo-vanadates, the nature of which depends on a) the pH of the reaction medium, and b) the relative molar concentrations of the involved reaction reagents.

The emerging compounds have been shown to exhibit a wide variety of activities *in vivo* and *in vitro*, including antitumorigenesis, catalysis and insulin mimesis. The extent to which these activities are promoted depends on the specific structural features of a) the peroxo moieties surrounding V(V), b) the structural properties of any potential heteroligands that seek V(V) binding, and c) the reaction conditions under which the synthesis of such species is achieved.

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Given that low molecular mass substrates available in biological fluids are potential targets for vanadium chemistry, amino acids are primary such ligands eliciting interactions from metal ions either in their free form or in the form of peptides, proteins and enzymes. The ultimate activity of vanadium bearing more than one peroxides and attracting aminoacids in its coordination sphere could be understood through detailed perusal of the arising ternary V(V)-peroxo-aminoacid interactions and the associated speciation as a function of pH and molecular stoichiometry of the participants. Given the paucity of well-defined structurally characterized V(V)-amino acid species bearing more than one peroxo moieties bound to them and exhibiting biological activity, research efforts were launched in our lab targeting the chemical reactivity in the ternary V(V)-H_2O_2-glycine system. Herein, we describe the synthesis, isolation, spectroscopic and structural characterization of unusual ternary dinuclear V(V) tetraperoxo species bearing the well established amino acid glycine in the zwitterionic form. The properties of such species are discussed in terms of its structural features potentially affecting the chemical reactivity of V(V) metal ion in a biologically relevant setting.

2. Materials and methods

All experiments were carried out under aerobic conditions. Nanopure quality water was used for all reactions. V_2O_5, glycine, and H_2O_2 30% were purchased from Aldrich. Ammonia and potassium hydroxide were supplied by Fluka.

3. Results and Discussion

The synthetic exploration of the ternary V(V)-peroxo-glycine system led to the $(H_3O)_2[V_2(O)_2(\mu_2{:}\eta^2{:}\eta^1\text{-}O_2)_2(\eta^2\text{-}O_2)_2(C_2H_5NO_2)]\cdot 5/4H_2O$ (**1**) complex through a facile reaction among simple reagents in aqueous solutions. In a typical reaction, V_2O_5 reacted with glycine in the presence of aqueous ammonia at pH 4.5. Addition of dilute hydrogen peroxide solution (vide infra) promoted efficiently the peroxidation reaction of vanadium. The overall stoichiometric reaction leading to complex **1** is shown schematically below:

$$V_2O_5 + C_2H_5NO_2 + 4\,H_2O_2 \xrightarrow[pH\sim4.5]{} (H_3O)_2[V_2(O)_2(\mu_2{:}n^2{:}n^1\text{-}O_2)_2(n^2\text{-}O_2)_2(C_2H_5NO_2)] + H_2O$$

In a similar reaction, V_2O_5 reacted initially with glycine in the presence of aqueous KOH, followed by addition of HCl and hydrogen peroxide at pH 5.5. Potassium hydroxide was important for two reasons. It helped adjust the pH of the reaction medium, at which the specific synthesis was carried out, and at the same time provided the cations necessary for balancing the negative charge on the derived anionic complex. The stoichiometric reaction leading to the formation of the compound $K_2[V_2(O)_2(\mu_2{:}\eta^2{:}\eta^1\text{-}O_2)_2(\eta^2\text{-}O_2)_2(C_2H_5NO_2)]\cdot H_2O$ (**2**) is shown below:

$$V_2O_5 + C_2H_5NO_2 + 4\,H_2O_2 + 2\,KOH \xrightarrow{pH\sim5.5} K_2[V_2(O)_2(\mu_2{:}n^2{:}n^1\text{-}O_2)_2(n^2\text{-}O_2)_2(C_2H_5NO_2)] + 5\,H_2O$$

Ethanol, added as a precipitating solvent to the reaction mixture in both reactions described above, afforded yellow crystalline compounds, the analytical composition of which was consistent with the formulation in **1** and **2** respectively (*vide supra*). Positive identification of the crystalline products was achieved by spectroscopic techniques and X-ray crystallography for one of the isolated single crystals from **1** and **2**. Both complexes are stable, in the crystalline form, in the air, for fairly long periods of time. Both species are readily dissolved in water and insoluble in dimethyl sulfoxide (DMSO), N,N'-dimethylformamide (DMF), acetonitrile, alcohols (CH_3OH, i-PrOH), and dichloromethane at room temperature even after heating up of the respective solutions. Aqueous solutions of both species are stable for over 24 hours, beyond which time the compounds start slowly to lose peroxide as that is confirmed by UV-Visible spectroscopy. The LC-MS spectrum of **2** showed the presence of the intact anionic complex, thus confirming its integrity in solution and consistence with the structure displayed in the solid state

The X-ray crystal structures of **1** and **2** consist of discrete anions and cations in the respective lattices. Both complexes **1** and **2** crystallize in the triclinic space group Pī with two molecules in the unit cell. The crystal structure diagram of the anion in **1** and **2** is shown in Figure 1.

The carboxylic group of the glycine ligand is deprotonated while the amine group is protonated. To this end, the glycine ligand acts as a zwitterion with an overall zero charge. The overall charge of the dinuclear complex assembly is 2-.

In the case of complex **1**, the counter ion for balancing the negative charge is the hydronium ion $[H_3O]^+$, whereas in the case of complex **2** the counter ion is K^+.

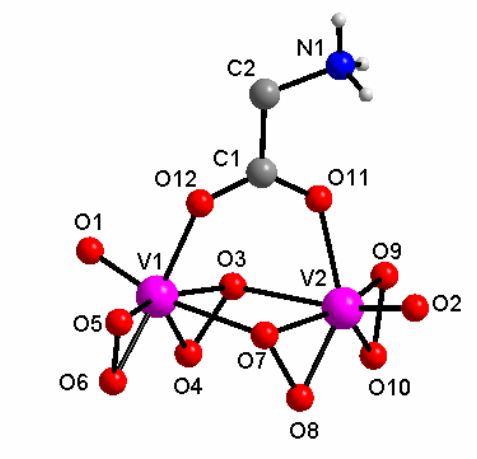

Figure 1. Crystal structure diagram of the $[V_2(O)_2(\mu_2{:}\eta^2{:}\eta^1\text{-}O_2)_2(\eta^2\text{-}O_2)_2(C_2H_5NO_2)]^{2-}$ anion with the atom labeling scheme in **1**.

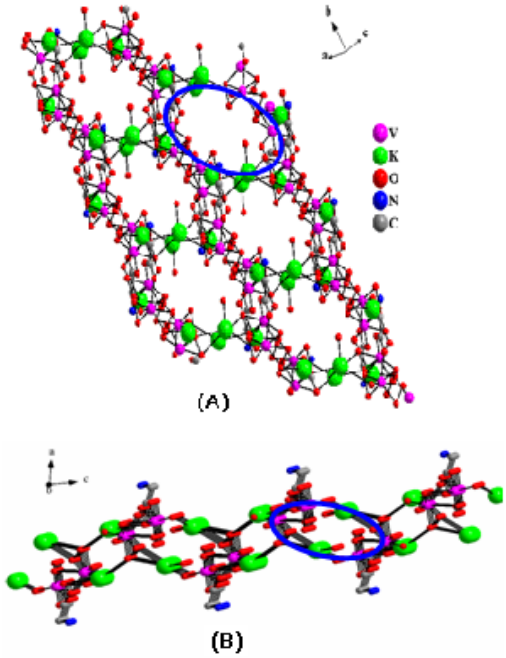

Figure 2. Packing diagram of **2**, along the *abc* diagonal (**A**) and in the *ac* plane (**B**)

4. Conclusion

An unusual family of ternary vanadium-(di)peroxo-glycine species was synthesized, isolated (in the presence of different cations) and characterized in the solid state and in solution. The structural features are distinct from those of simple vanadium-diperoxo species, which themselves are very few. The dinuclear nature of vanadium-diperoxo moieties does not deviate significantly from the one known thus far. The presence of amino acid glycinate as a zwitterion likely contributes to the solubility and stability of the existing species. Given that these species bear a physiologically important moiety present in human fluids, it'd be important to investigate whether glycinate-bearing V(V)-peroxo species exhibit biological activity, in line with previously observed activity shown by ternary V(V)-peroxo-L species. In view of this advancement in vanadium-peroxo chemistry, it'd be equally challenging to investigate amino acids, other than glycine, that may promote the same or similar chemistry to the one shown here with vanadium and hydrogen peroxide. In this regard, it would be important to see whether or not the physicochemical properties of binary vanadium-tetraperoxo species interacting with amino acids can be modulated (e.g. through pH-dependent synthesis) providing finely tuned soluble and potentially bioavailable forms of vanadium, capable of promoting further interactions with higher molecular mass biomolecules. Such ternary interactions, covering a wide spectrum of vanadium reactivity, could contribute to triggering critical events in signal transduction pathways linked to insulin mimesis or antitumorigenesis. The chemistries associated with such interactions are currently investigated in our lab.

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