JAP&T
TPA-Timişoara

Available online at http://journal-of-agroalimentary.ro

Journal of Agroalimentary Processes and Technologies 2011, *17*(2), 130-133

*Journal of Agroalimentary Processes and Technologies*

# The chemistry of vanadium with amino acids and their derivatives. Relevance to health and disease

**Athanasios Salifoglou**

*Department of Chemical Engineering, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece*

**Received: 01 April 2011; Accepted: 25 May 2011**

***Abstract***

Vanadium is a highly acclaimed chemical element in the chemistry and biology of eukaryotic organisms. Outstanding among the various functions of that elements at different oxidation states stand the antitumorigenic and insulin mimetic activities. The latter reactivity acquires special interest in the case of the human disease of *Diabetes mellitus II*. IN an effort to explore the potential chemical reactivity of vanadium in the presence of physiological amino acids and the biologically important hydrogen peroxide, research efforts were launched to investigate the potential structural speciation of ternary systems of that element with the aforementioned reagents. The emerging ternary species exhibit unique composition and structures, the physicochecmial properties of which suggest a diverse chemistry in the framework of biological insulin mimetic activity.

***Keywords***: vanadium, insulin mimesis, structural speciation, hydrogen peroxide, amino acid

## 1. Introduction

Vanadium is a chemical element with a very broad presence in the abiotic and biological world. Numerous applications in abiotic systems stem from the employment of vanadium in industrial processes and materials development. In the biological world, a plethora of vanadium enzymes exist, in which vanadium has the role of the inorganic cofactor of the active site, with the metal ion serving as the site of catalytic reactions for halide insertion into organic substrates, nitrogen fixation, and others [1]. Beyond the direct involvement of vanadium in transformation biosystems, that inorganic element stands as a carrier of chemical reactivity related to vital cellular processes linked to the physiology of cells and the prevention of pathophysiological events or potential therapeutics. In such a capacity, vanadium exerts among others antitumorigenic and mitogenic acitivity in a cellular environment.

Outstanding, however, among the diverse array of activities is the insulin mimetic ability displayed by vanadium in the case of Diabetes mellitus. In this case, the form of vanadium as well as its chemical reactivity in a cellular environment appears to be crucial. In this respect, it emerges as a need to understand the interactions of vanadium at various oxidation states with cellular components (of low as well as high molecular mass) in aqueous media. In binary or ternary systems, intricate and quite complex species arise as a result of which soluble and potentially bioavailable species exert their influence on insulin mimesis with variable results. Given the fact that cytotoxicity appears to play a crucial role in the development of such metallodrugs, the composition and structure of vanadium species in aqueous media would be essential in further determining the potential for biological activity.

Corresponding author: *e-mail:* salif@auth.gr

Poised to a) understand the nature of interactions developing with vanadium (at various oxidation states of biological relevance) and low molecular mass targets in cellular media, and b) synthesize, isolate and characterize binary and ternary vanadium species bearing physiological ligands, research efforts were launched in our labs to investigate the ternary systems of V(V)-amino acid(s)-hydrogen peroxide. To this end, the work carried out focuses on such systems with emphasis given in the simplest of amino acids, namely glycine, reacting in aqueous media in the presence of hydrogen peroxide.

Driven by the existing solution speciation studies with other low molecular mass physiological ligands, synthetic efforts targeted the structural speciation of the aforementioned system(s) in aqueous media. The strategy employed was the pH-dependent synthesis of discrete V(V)-amino acid-peroxo complexes, with the latter exhibiting structural and chemical reactivity properties commensurate with the demands for a well-defined potential insulin mimetic agent.

## 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.

The synthesis of new ternary species of vanadium at the oxidation V(V) with the simple amino acid glycine and hydrogen peroxide was pursued under pH specific conditions. The synthetic process n the presence of a base is described in detail.

## 3. Results and Discussion

The principal strategy in the structural speciation of the ternary system under investigation stems from the affinity of peroxide ligands to stabilize vanadium at the oxidation state V(V). To this end, the synthetic exploration of the ternary V(V)-peroxo-glycine system took place in an aqueous system. Ammonia was used as the base responsible for adjusting the pH of the reaction mixture to a specific value. The synthetic process led to the isolation of $(H_3O)_2[V_2(O)_2(\mu_2{:}\eta^2{:}\eta^1\text{-}O_2)_2(\eta^2\text{-}O_2)_2(C_2H_5NO_2)]\bullet 5/4\ H_2O$ (**1**) complex through a facile reaction among the previously mentioned 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 promoted efficiently the peroxidation reaction of vanadium. The overall stoichiometric reaction leading to the isolation of complex **1** is shown schematically below:

$$V_2O_5 + C_2H_5NO_2 + H_2O_2 \xrightarrow[pH\sim 4.5]{} (H_3O)_2[V_2(O)_2(\mu_2{:}n^2{:}n^1\text{-}O_2)_2(n^2\text{-}O_2)_2(C_2H_5NO_2)] + H_2O$$

In a similar reaction mixture, $V_2O_5$ 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. As a base, 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 and ultimate isolation of the compound $K_2[V_2(O)_2(\mu_2{:}\eta^2{:}\eta^1\text{-}O_2)_2(\eta^2\text{-}O_2)_2(C_2H_5NO_2)]\bullet H_2O$ (**2**) is shown below:

$$V_2O_5 + C_2H_5NO_2 + 4\,H_2O_2 + 2\,KOH \xrightarrow{pH\sim 5.5} K_2[V_2(O)_2(\mu_2{:}n^2{:}n^1\text{-}O_2)_2(n^2\text{-}O_2)_2(C_2H_5NO_2)] + 5\,H_2O$$

Analogous reactions were explored with other amino acids as well. So far, however, no crystalline products have been isolated.

Vanadium(V)-peroxo complexes of the type $M_x[V(=O)(O_2)L]$ and $M_x[V(=O)(O_2)_2L]$ (where L is appropriate organic vanadium binder and x is a function of the charge of L) have been shown to exert insulin mimetic activity in *in vitro* and *in vivo* experiments [2]. In fact, the triggering and often stimulating activity of peroxo vanadates toward biochemical processes such as protein tyrosine phosphorylation and protein tyrosyl phosphatase activity related to insulin mimesis has been shown to be more potent (at least four fold) than that exhibited by the non-peroxo vanadates compounds.

In the present case, the title complexes **1** and **2** bear the fundamental characteristics of the species shown to exhibit such activity, i.e. diperoxo vanadium units, in a tetraperoxo assembly.

As a matter of fact, in line with previously mentioned characteristic features of anitumor displaying activity V(V)-peroxo species vs. non-peroxo vanadium species in biologically relevant media, complexes **1** and **2** possess among others a) a seven-coordinate V(V) in a pentagonal bipyramidal geometry, the peroxo groups in a position *cis* to the V=O moiety, c) a long V-O bond *trans* to the V=O moiety (2.330(5) vs 1.609(5) Å and 2.352(2) vs 1.616(7) Å in **1**, and 1.611(3) vs 2.378(3) Å and 1.610(4) vs 2.344(3) Å in **2**).These striking characteristics denote the chemical propensity of V(V) for peroxo moieties concurrently supported by the bidentate mode of binding of the zwitterionic ligand glycinate. What stands out in the structure of 1 and 2 (Figure 1) is a) the load of peroxo moieties (two peroxide ligands) on each vanadium center, thereby rendering its coordination geometry pentagonal bipyramid, b) the interconnection of the two fundamental $[V(=O)(O_2)_2]$ units through ligation of the peroxide anchors to adjacently located V(V) centers, and c) the acetate-like binding of the glycinate moiety to the divanadium core, thereby enhancing its stability, and d) the zwitterionic nature of the glycinate ligand, with the zero charge, thereby not contributing to the overall charge of the complex, which stands at 2-.

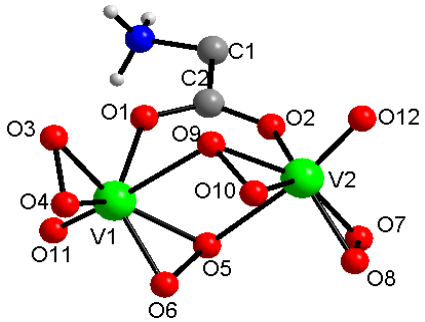


***Figure 1***. Structure of the $[V_2(O)_2(\mu_2{:}\eta^2{:}\eta^1\text{-}O_2)_2(\eta^2\text{-}O_2)_2(C_2H_5NO_2)]^{2-}$ anion in **1** and **2**.

The structural composition of **1** and **2** are substantially different form those previously encountred with hydroxycarboxylic acids and hydrogen peroxide [3,4].

In view of the pluripotent chemical reactivity of vanadium peroxides, the fundamental $[V(=O)(O_2)_2]$ units a) are generated in aqueous media, b) persist in aqueous media, c) bear bound physiological hetero-ligands such as amino acids (i.e. glycinate) in a zwitterionic form, d) are poised to reflect a chemical propensity toward cellular targets and processes influencing the physiology/pathology of cells. It remains to be seen whether the herein unusual dinuclear V(V)-tetraperoxo species will exhibit insulin mimetic effects in vitro.

## 4. Conclusions

Expedient synthetic approaches in the ternary V(V)-amino acid-hydrogen peroxide systems led t the isolation of discrete complexes bearing two V(V) centers loaded with two peroxide ligands each and bridged through the amino acid glycine carboxylate ligand. The presence of base in the reaction medium was useful only in the case of potassium hydroxide with ammonia acting only as a pH adjuster, with no ostensible incorporation of the arising ammonium cation in the respective lattice. The structural assembly revealed in compounds **1** and **2** are but a first glimpse into the structural speciation of V(V) with amino acids in the presence of hydrogen peroxide. It'd be worth synthesizing and structurally characterizing other species similar or congener to **1** and **2** in hopes of gaining insight into the chemical reactivity of V(V) with low molecular mass amino acids or (oligo) peptides. Such knowledge would be useful in understanding how such binary species or ternary assemblies containing peroxo moieties interact with cellular targets and in so doing the induce insulin mimetic effects consistent with the so far observations about vanadium as a potential metallopharmaceutical in *Diabetes mellitus II.*

## Acknowledgements

The financial support of the Greek Ministry of Education, Life Long Learning & Religious Affairs, through a Heraklitos II grant, is gratefully acknowledged.

## References

1. (a) Rehder, D. *Bioinorganic Vanadium Chemistry*; Wiley: New York, 2008. (b) Rehder, D., Is vanadium a more versatile target in the activity of primordial life forms than hitherto anticipated?, *Org. Biomol. Chem.* **2008**, *6*, 957–964, doi: 10.1039/B717565P (c) Baran, E. J., Oxovanadium(IV) and oxovanadium(V) complexes relevant to biological systems, *J. Inorg. Biochem.* **2000**, *80*(1-2), 1–10, doi:10.1016/S0162-0134(00)00032-5

2. Shaver, A.; Ng, J. B.; Hall, D. A.; Loon, B. S.; Posner, B. I., Insulin mimetic peroxovanadium complexes: preparation and structure of potassium oxodiperoxo(pyridine-2-carboxylato) vanadate (V), $K_2[VO(O_2)_2(C_5H_4NCOO)].2H_2O$, and potassium oxodiperoxo( 3-hydroxypyridine-2-carboxylato) vanadate (V), $K_2[VO(O_2)_2(OHC_5H_3NCOO)]$ $.3H_2O$, and their reactions with cysteine *Inorg. Chem.* **1993**, *32*(14), 3109-3113, doi: 10.1021/ic00066a024
3. Kaliva, M.; Giannadaki, T.; Raptopoulou, C. P.; Tangoulis, V.; Terzis, A.; Salifoglou, A., pH-dependent investigations of vanadium(V)-peroxo-malate complexes from aqueous solutions. In search of biologically relevant vanadium(V)-peroxo species, *Inorg. Chem.* **2001**, *40*(15), 3711–3718, PubMed: 11442368
4. (a) Kaliva, M.; Gabriel, C.; Raptopoulou, C. P.; Terzis, A.; Salifoglou, A., pH-specific synthesis, isolation, spectroscopic and structural characterization of a new dimeric assembly of dinuclear vanadium(V)–citrate–peroxo species from aqueous solutions *Inorg. Chim. Acta* **2008**, *361(9-10)*, 2631–2640, doi:10.1016/j.ica.2007.11.014 (b) Kaliva, M.; Kyriakakis, E.; Gabriel, C.; Raptopoulou, C. P.; Terzis, A.; Tuchagues, J.-P.; Salifoglou, A., Synthesis, isolation, spectroscopic and structural characterization of a new pH complex structural variant from the aqueous vanadium(V)-peroxo-citrate ternary system, *Inorg. Chim. Acta* **2006**, *359*(14), 4535–4548, doi:10.1016/j.ica.2006.07.011