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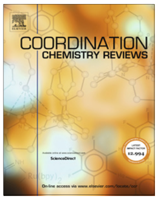

Review

Vanadium: History, chemistry, interactions with α-amino acids and potential therapeutic applications

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ABSTRACT

In the last 30 years, since the discovery that vanadium is a cofactor found in certain enzymes of tunicates and possibly in mammals, different vanadium-based drugs have been developed targeting to treat different pathologies. So far, the *in vitro* studies of the insulin mimetic, antitumor and antiparasitic activity of certain compounds of vanadium have resulted in a great boom of its inorganic and bioinorganic chemistry. Chemical speciation studies of vanadium with amino acids under controlled conditions or, even in blood plasma, are essential for the understanding of the biotransformation of e.g. vanadium antidiabetic complexes at the physiological level, providing clues of their mechanism of action. The present article carries out a bibliographical research emphaticizing the chemical speciation of the vanadium with different amino acids and reviewing also some other important aspects such as its chemistry and therapeutical applications of several vanadium complexes.

Contents

Abbreviations: 2,2′-bipy, 2,2-bipyridine; 6-mepic, 6-methylpicolinic acid; acac, acetylacetone; Ad, adenosine; Ala, alanine; Ala-Gly, alanylglycine; Ala-His, alanylhistidine; Ala-Ser, alanylserine; Asp, aspartic acid; BEOV, bis(ethylmaltolate)oxovanadium(IV); Cys, cysteine; Cyt, citrate; dhp, 1,2-dimethyl-3-hydroxy-4(1H)-pyridinone; dipic, dipicolinic acid; DMF, N,N-dimethylformamide; dmpp, 1,2-dimethyl-3-hydroxy-4-pyridinonate; DNA, deoxyribonucleic acid; EPR, Electron Paramagnetic Resonance; G, Gauss; Glu, glutamic acid; Gly, glycine; GlyAla, glycylalanine; GlyGly, glycylglycine; GlyGlyCys, glycylglycylcysteine; GlyGlyGly, glycylglycylglycine; GlyGlyHis, glycylglycylhistidine; GlyPhe, glycylphenylalanine; GlyTyr, glycyltyrosine; GlyVal, glycylvaline; Hb, hemoglobin; His, histidine; HisGlyGly, histidylglycylglycine; HIV, human immunodeficiency virus; hpno, 2-hydroxypyridine-N-oxide; HSA, albumin; hTf, transferring; Ig, immunoglobulins; Im, imidazole; Lac, lactate; LD_{50}, the amount of a toxic agent (such as a poison, virus, or radiation) that is sufficient to kill 50 percent of population of animals; L-Glu(γ)HXM, L-glutamic acid γ-monohydroxamate; l.m.m., low molecular mass; mal, maltol; MeCN, acetonitrile; NADH and NAD^+, nicotinamide adenine dinucleotide; NEP, neutral endopeptidas; NMR, Nuclear Magnetic Resonance; Ox, oxalate; PI3K, phosphoinositide 3-kinase; Pic, picolinic acid; Pro, proline; Pro-Ala, prolylalanine; PTP1B, protein tyrosine phosphatase 1B; py, pyridine; RNA, ribonucleic acid; Sal-Ala, N-salicylidene-L-alaninate; SalGly, salicylglycine; SalGlyAla, salicylglycylalanine; salGlyGly, N-salicylideneglycylglycinate; sal-L-Phe, N-salicylidene-L-tryptophanate; salophen, N,N′-bis(salicylidene)-o-phenylenediamine; salSer, N-salicylideneserinate; salTrp, *N*-salicylidene-L tryptophanate; saltrp, N-salicylidene-L-tryptophanate; salVal, N-salicylidene-L-valinate; SARS, severe acute respiratory syndrome; Ser, serine; T, Tesla; THF, tetrahydrofuran; Thr, threonine; VanSer, Schiff base formed from o-vanillin and L-serine; VBPO, vanadium bromoperoxidases; γ-PGA, poly-γ-glutamic acid.

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1. Introduction to vanadium: a general overview

Vanadium, is a gray metallic element (Z = 23) of centered cubic lattice, which due to its high melting point is considered as a refractory metal. This metal is located in the first transition series of the periodic table, specifically in the 5 group (group VB). In its metallic form, has an electronic configuration of $[Ar]3d^34s^2$, being V(II), V(III), V(IV) and V(V) the most common oxidation states [1]. Vanadium is considered a relatively abundant element, in fact, in soil, water deposits and in the atmosphere; its abundance is around 0.019% [2], representing an approximately concentration of 135 mg/kg in soil [3]. It is the 5th most abundant transition metal present in the soil, exceeding the vanadium contained in the Universe by a factor of 135 times [4]. In the ocean, its approximate concentration is around 30 –35 nM existing mainly as an ionic pair in the form of $M^{n+}H_2VO_4^-$ (M^{n+} represents the cations dissolved in seawater), and surpassed only by molybdates (MoO_4^{2-}) ions (around 100 nM) as the most abundant transition metal in the ocean [5]. In sweet water, for human consumption for example, the concentration of V is around 10 nM. However, in volcanic zones, the concentration of vanadium at water level is around 2.5 μM and frequently these high concentrations bring as consequence the contamination of aquifers [2]. The Geochemical characteristics of vanadium depends mainly on two factors: the oxidation state and pH. Hence, under reductive conditions the specie based on V(III) predominates, since higher oxidation states are more soluble [3]. In the human body, the concentration of vanadium is around to 0.3 μM and it remains in balance with the amount of vanadium excreted and consumed daily through food and drink intake [2].

Historically, the discovery of vanadium was done by Andrés Manuel del Río, while he was examining a lead mineral obtained from Zimapan, Mexico. Initially, Rio called it erythronium (redness), due to the red color imparted to its salts by the heating [3]. However, the French Chemical Society considered that Rio had not discovered a new chemical element, but instead, he had found impure chromium, so the identification of vanadium did not occur until 1830 by Sefstrom, who isolated it from a mineral extracted in the mines of Taberg, in Sweden [3]. Vanadium owes its name to Vanadis, the Scandinavian Goddess of love, beauty and fertility, because of its multicolored compounds [1,4].

In nature, vanadium can be found in 65 different minerals where the most common are: patronite ($V_2S{+}nS$), roscoelite ($2K_2O{\cdot}2Al_2O_3(Mg,Fe)O\text{-}3V_2O_5{\cdot}10SiO_2{\cdot}4H_2O$), bravonite ($(Fe,Ni,V)S_2$), davidite, (titanate of Fe,U,V,Cr and rare earths), sulvanite ($3Cu_2S{\cdot}V_2S_6$), vanadite ($Pb_5(VO_4)_3Cl$) and carnotite ($K_2O{\cdot}2U_2O_3$, $V_2O_5{\cdot}3H_2O$). It can be also found in porphyrins, present for example in Venezuelan heavy and extra heavy crude oil [6]. The concentrations range of vanadium in crude oils are shown in Table 1, where it is obtained as VO^{2+}-porphyrin, in its two isotopicforms ^{50}V (0.24%) and ^{51}V (99.76%), being the ^{50}V slightly radioactive with a half-life ($t_{1/2}$) >3.9 × 10^{17} years [1–7]. The vanadium-porphyrins are formed during early diagenesis of source rocks and the relative abundance of vanadium is related to the depositional environment [8]. Worldwide vanadium's main sources are located in Australia, Brazil, China, Finland, India, New Zealand, Russia, South Africa, Sweden, USA and Venezuela [4].

Table 1
Variation of vanadium abundance in oils [8]

Oil type	V (mg·kg^{-1})
Light oil (non-marine)	0.4
Crude oil (marine)	32
Heavy biodegraded oil	1200
Bitumen (marine)	2700

Vanadium, either as pure metal or in alloy form, do not show particular risk to the human health. However, vanadium reacts violently with certain materials such as BrF_3, chlorine, lithium and some strong acids [4,7]. Additionally, in powder form, it presents a moderate risk of fire. Nevertheless, certain vanadium compounds have been reported as irritating to mucosae and, in a prolonged exposure, may lead to complications at the pulmonary level. Generally, these pathologies do not tend to be chronic, for example, it has been reported that the LD_{50} of V_2O_5 in rats is about 23 mg kg^{-1} and vanadium-intoxication occurs particularly by the inhalation of vanadium-rich powders, where its symptoms are similar to those presented by influenza [4].

Many metal ions elements tend to interact with biomolecules, forming coordination bonds, which can be described by Pearson's theory of hard and soft acids and bases [9], so it is not surprising that natural evolution has incorporated certain metals ions to fulfill within essential biological processes at the physiological level [2]. The biological interest of vanadium lies, in its ability to participate in different processes. Mentioning a few examples, it has been found in the active site of haloperoxidases [10] and nitrogenases [11] as counter ion in DNA and RNA, in addition to the participation in the photocleavage of proteins and in insulin regulation process [12–14]. Whereas, certain vanadium compounds such as sodium vanadate and bis(maltolalo)oxovanadium (IV) have exhibited insulin-like activity [15]; other vanadium compounds have exhibited antiparasitic activity [16] and are potential antitumor agents [2,17]. Thus, the study of vanadium and its respective compounds are of great importance in the Bioinorganic and Medicinal Inorganic Chemistry, since they allow to obtain possible therapeutic treatment for different pathologies.

Hoping that this information will be useful to guide future research in this area of knowledge, the main goals of this review were two: 1) carry out a bibliographical research of the chemical speciation of binary and ternary complexes of vanadium with (non)essential α-amino acids and 2) collect information of prominent applications of vanadium compounds, especially vanadium complexes with (non)essential amino acids, in pharmacology and therapeutics applications, as well as their importance in bioinorganic chemistry.

2. Obtainment and industrial applications of vanadium

Vanadium as a metallic element is smooth and ductile [18]. The pure metal is relatively inert against oxygen, nitrogen and hydrogen at room temperature. It also has good resistance to corrosive processes by water, salts, dilute solutions of HCl, H_2SO_4 and alkaline solutions, but it can be easily oxidized at temperature above 660 °C. Vanadium is mainly obtained as a by-product of mining, or as a by-product in the production of the Uranium-Vanadium or in the production of phosphorus from ferrophosphorus [4]. While in oil-producer's countries such as Canada or Venezuela, vanadium is obtained from crude oil [4].