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Coordination Chemistry Reviews 372 (2018) 117–140

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

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

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ARTICLE INFO

Article history:
Received 21 July 2017
Accepted 3 June 2018
Available online 21 June 2018

Keywords:
Vanadium complexes
Amino acids
Antidiabetics
Antitumors
Chemical speciation

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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https://doi.org/10.1016/j.ccr.2018.06.002
0010-8545/

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 ($2K_2O{\cdot}2Al_2O_3(Mg,Fe)O{-}3V_2O_5{\cdot}10SiO_2{\cdot}4H_2O$), 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 ($t_{1/2}$) $>3.9 \times 10^{17}$ 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 ($mg{\cdot}kg^{-1}$)
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].

Roscoe was the first one to isolate vanadium in almost pure form in 1867 by hydrogen reduction of vanadium dichloride, VCl_2 [7,18]. Currently, vanadium can be obtained by the reduction of vanadium trichloride with magnesium or with a magnesium-sodium mixture. Vanadium can also be extracted by leaching with water and precipitating at pH 2–3 as sodium hexavanadate ($Na_4V_6O_{17}$), obtaining a red precipitate by the addition of sulfuric acid [4]. However, most of the vanadium produced at industrial level is obtained by a modification of the McKechnie-Seybair process, it consists in reducing the V_2O_5 with calcium under pressure [7]. The purification of vanadium tends to be difficult since it is easily contaminated by other elements [7,19], this process can be carried out by either calcium reduction, by iodide refining (via van Arkel-deBoer process), by thermal decomposition, by solvent extraction or by electrolytic refining of molten salts, achieving a purity of 99.95% [4,19].

One of the most important developments in the 1960s, by the U. S. Bureau of Mines, is the extraction of vanadium from heavy and extra-heavy crude oil by an electrodeposition process. It consists on the cathodic deposition of vanadium in a solution of VCl_2 in a eutectic mixture of KCl-LiCl fused salts at a temperature of about 650 °C. By means of this method, it is possible to obtain vanadium with a degree of purity of up to 99.995% [4].

Vanadium can also be used in nuclear applications, when it is used as an alloy of $(Fe,Co,Ni)_3V$ for the coating of fuel elements of reactors, provides a good structural strength at high temperatures and resistant to the corrosive action by liquid sodium and, has furthermore, a small cross section of neutron fission [4,7]. In addition, with the development of intermetallic compounds, vanadium is used to construct superconducting magnets, presenting a critical current of 20 T, which is the highest value obtained for any known material, providing a magnetic field of 175,000 G [4,7]. One of the most important vanadium-compound for industrial applications is vanadium pentoxide (V_2O_5). It is used as a catalyst in many industrial processes, such as in the manufacture of ceramics, in the production of maleic anhydride by catalyzing the oxidation of butane with air, in the production of phthalic anhydride by the oxidation of o-xylene or naphthalene, and in the production of adipic acid, oxalic acid and anthraquinone [7]. V_2O_5 is also used in the production of sulfuric acid, due to its efficiency to convert SO_2 into SO_3, it is also used as catalyst component in the selective heterogeneous catalytic reduction of NO_X emanations in many industrial plants [7,20–22].

3. Chemical speciation with (non)essential aminoacids

Vanadium complexes are present in different biological systems, and on many occasions, can form complexes with proteins (such as transferrin, albumin and hemoglobin) and α-amino acids. The importance of these complexes, their identification and characterization is given by the chemical speciation of possible binary and ternary vanadium complexes that can be formed with different α-amino acids [23–25]. In fact, since the late 1980s, there has been a great interest in the metabolic reactions of vanadium-amino acid compounds, thus, different amino acid reactions in biological systems have been catalyzed by enzymes containing pyridoxal phosphate. These enzymatic reactions have been modeled by the formation of Schiff bases, produced by the condensation between an aromatic aldehyde and the α-amino acid. On the other hand, the vanadium N-salicylidene-amino acid complexes have been used as model systems for the study of enzyme-catalyzed reactions containing pyridoxal [24,26]. Fig. 1 shows the formation of a Schiff base between the pyridoxal-derivative and α-amino acid.

Regarding to the vanadium-amino acid systems, throughout the literature, have been found several studies of chemical speciation of binary and ternary complexes. These studies were mainly carried out by potentiometric techniques, EPR (Electron Paramagnetic Resonance) for V(IV) compounds, NMR (Nuclear Magnetic Resonance) for V(V) compounds, UV/Visible molecular absorption and by circular dichroism to different concentrations and using different ionic media.

Vanadium can form a divalent cation, but these studies lack of interest in biological systems because this ion oxidizes faster to higher oxidation states, in fact, in aqueous solution V(II) reduces water to hydrogen [27]. Nevertheless, the V(II) complexes with saccharin as ligand were successfully characterized by the Cotton group, highlighting the stability of the complexes $[V(C_7H_4NO_3S)_2(H_2O)_4]\cdot 2H_2O$ and $[V(C_7H_4NOS)_2(py)_4]\cdot 2py$ [28–30]. In both cases, the complexes presented an octahedral geometry, where four molecules of water or pyridine, depending on the study, surrounded the vanadium atom and protected the metallic center providing enough stability to obtain the XRD (X-ray diffraction) structures [29,30].

V(III) ions, on one hand, hydrolyze in aqueous solution forming mononuclear and polynuclear species, where at pH close to neutrality, the trimer $V_3(OH)_8^+$ becomes predominant [15,31–33]. V(III) complexes with biogenic ligands that possess donor sulfur atoms in aqueous solution are hydrolysable at high pH values, and may form polynuclear species [24]. V(III) complexes with L-cysteine [24,34–36], L-alanine [24,37–39], L-aspartic acid [40,41], L-glutamic acid [41–43], L-histidine [35,40], among other amino acids and small blood serum bioligands have been studied [43–45], evidencing a concentration and pH dependence in solution as shown in Fig. 2.

A speciation study of V(III)-glycine and V(III)-cysteine systems reported the formation of the species $V(III)L_3$, VL'_3 and VL'_2; where L and L′ correspond to the glycine and cysteine, respectively [34]. Note that, in the VL'_2 and VL'_3 complexes, two molecules of L-cysteine are coordinated to the V(III) through the amino, carboxylic and thiolate groups [34,46,47]. Solution of vanadium(III) with L-cysteine (pH ≃ 7, L/M = 20) was administrated to culture medium of hepatoma Morris 5123 growing cells showing cytotoxic effect of this solution towards tumor cells. The viability of these cells was reduced by 70% at 100 μM of the vanadium species

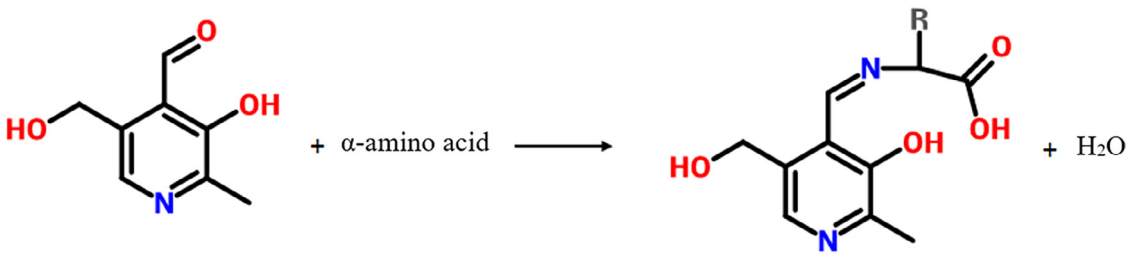


Fig. 1. Formation reaction of a Schiff base that acts as an intermediary species in reactions catalyzed by enzymes containing pyridoxal. Modified from Ref. [24].

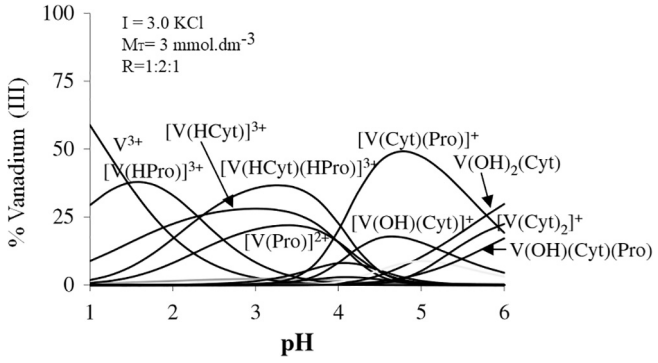


Fig. 2. Species distribution diagram for the system V(III)-H_2Cyt-HPro in 3.0 mol·dm^{-3} KCl at 25 °C using the molar ratio (R = 1:2:1) at metal concentration of 3 mmol·dm^{-3}. Modified from Ref. [37]. H_2Cyt and HPro represents, citric acid and proline respectively.

concentration in the culture medium [47]. Further studies showed that V(III)-cysteine complexes also exhibit significantly greater total antioxidant capacity, high inhibition of neutral endopeptidase (NEP) at a concentration of 10^{-3} M, and high lung prevention of lung metastasis tested in Wistar rats [48]. In Section 4, will be describe the mechanism of action for the antitumor activity of vanadium(III)-L-cysteine complexes.

The study of ternary complex formation between vanadium (III)-cysteine and small blood serum bioligands (e.g. lactic, oxalic, phosphoric and citric acids) showed that, for example, in presence of lactate, only two complexes are formed V(Cys)(Lac) and [V(Cys)(Lac)(OH)]$^-$ being the last one the most important at pH > 4. In combination with citrate and oxalate, the only complex detected at pH > 4 are the [V(Cys)(Cit)]$^{2-}$ and [V(Cys)(Ox)]$^-$, respectively. While in vanadium(III)-H_2Cys-H_3PO_4 system, only two complexes were detected: V(Cys)(H_2PO_4) and [V(Cys)(HPO_4)]$^-$ being the second one more abundant at pH > 4. This study also showed that the system V(III)(Cys)-(Lac/Cit) ternary complexes were more stable than the binary ones in detriment with the system V(III)(Cys)-$(HPO_4)^-$/(Ox) where binary complexes are more stable than the ternary one [41]. Further modeling studies in aqueous solutions with dipicolinic acid (dipic) and L-cysteine (Cys), L-histidine (His), L-aspartic (Asp) and L-glutamic (Glu) acids [43], showed that the species presented in Table 2 are those with the best experimental and theoretical fitting of emf(H) data, while Fig. 3 represents the distribution species diagram for V(III)-dipic-Cys and V(III)-dipic-His systems.

The chemical equilibria of the complexation processes between V(III) with L-alanine (Ala) and L-aspartic acid (Asp) in aqueous solution showed that L-alanine forms mononuclear species only. In ML_2 species, (where M and L represents V(III) and a α-amino acid respectively), which are predominant between pH 4 and 8, L-alanine acts as a bidendate ligand through O and N atoms. With L-aspartic acid, the complexation processes showed to be more complicated. For example, up to pH ≃ 4 they are similar to those for L-alanine, but in the higher pH region, it forms mono and various dinuclear species of carboxylic or μ-oxo bridges differing from each other by the number of coordinated ligands and OH^- groups. Nevertheless, both V(III)-L-aspartic acid and V(III)-L-alanine complexes, have a significant apoptotic effect on Hepatoma Morris 5123 cells [49]. Complex compounds of vanadium(III) with L-histidine (His) instead, showed that solutions at pH 2–4.5, consecutive mononuclear species MLH, ML_2H_2, MLH_2, ML_2H_4 and ML are formed, but at higher pH, mixed hydroxy- and/or oxo-species appeared in solution. At pH range of 6–8.5, V_2OL_4 species predominantly exists in solution [50]. It is important to note that, ML_nH_m represents different binary complexes where M is the metallic center, L_n is the n α-amino acids coordinated to vanadium and H_m is the *m* acidic protons of the α-amino acids which acts as a ligand.

As V(III) complexes are very susceptible to be oxidated to V(IV) (which it is also easily oxidaze to V(V) after some time) it is important to highlight that the speciation studies of V(III) described so far were done in strict absence of oxygen, and that speciations done up to pH = 7 or 10 (as in Fig. 3) should be considered as approximate. For the same reason, the biological effects observed on *in vitro* studies evaluating the effect of V(III) complexes on Hepatoma Morris 5123 cells [49] may be due to V(IV) and/or V(V) complexes obtained by oxidation of the initial compounds.

In the present review, we had pointed out those studies where vanadium interacts with amino acids such as L-cysteine, L-histidine and L-glycine among other blood serum component such as phosphate, lactate, oxalate and citrate, because they are the most

Table 2
Ternary species that presented the best experimental and theoretical fitting of emf(H) data for the studied systems [40].

V(III)-dipic-His	V(III)-dipic-Cys	V(III)-dipic-Asp	V(III)-dipic-Glu
[V(Hdipic)(HHis)]$^{2+}$	[V(dipic)(H_2Cys)]$^+$	[V(dipic)(H_2Asp)]$^+$	[V(Hdipic)(H_2Glu)]$^{2+}$
[V(dipic)(HHis)]$^+$	V(dipic)(HCys)	[V(dipic)(Asp)]$^-$	[V(dipic)(H_2Glu)]$^+$
V(dipic)(His)	[V(dipic)(Cys)]$^-$	[V(dipic)(Asp)(OH)]$^{2-}$	V(dipic)(HGlu)
[V(dipic)(His)(OH)]$^-$	[V(dipic)(Cys)(OH)]$^{2-}$	[V(dipic)(Asp)$(OH)_2$]$^{3-}$	[V(dipic)(HGlu)(OH)]$^-$
[V(dipic)(His)$(OH)_2$]$^{2-}$			[V(dipic)(HGlu)$(OH)_2$]$^{2-}$

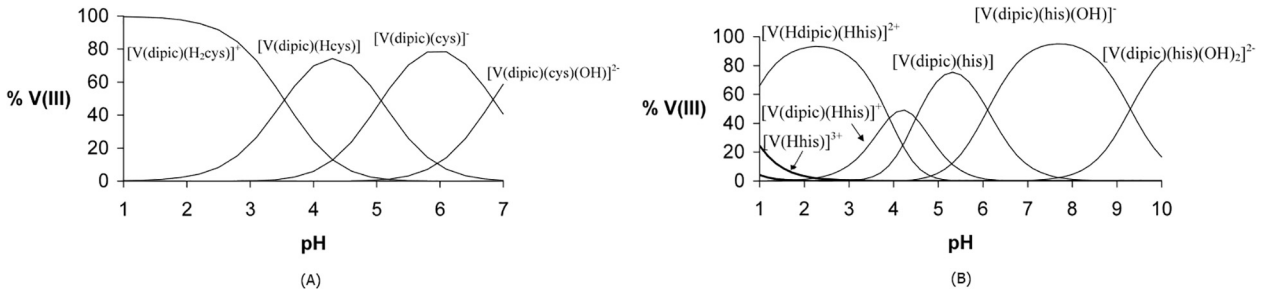


Fig. 3. A) Species distribution diagram for the system V(III)-H_2dipic-H_2cys in KCl 3.0 mol·dm^{-3}at 25 °C. B) Species distribution diagram for the system V(III)-H_2dipic-HHis in KCl 3.0 mol·dm^{-3} at 25 °C. In both cases the molar ratio (R = 1:1:1) was used and the V(III) concentration in the medium was 3 mmol·dm^{-3}. Modified from Ref. [40].

important bioligand in the media. However, it would be also important for further studies, to know the complexation system between V ions and other reductants components present in the blood serum such as glutathione, thiols and ascorbate, and some other oxidants component such as molecular oxygen and hydrogen peroxide [51–53].

V(IV) ion, on the other hand, does not exist as a pure ion in aqueous solution. In this media, it is much more stable as oxidovanadium(V) (VO^{2+}), which after some time (longer than V (III)), it is oxidized into V(V) (VO_2^+) [24]. The different species depended, as expected, on the pH of the solution and the total concentration of V(IV)O, as can be seen in Fig. 4. At pH lower than 6, the main species present are $[V^{IV}O(H_2O)_5]^{2+}$ and $[V^{IV}O(OH)]^+$, at pH higher than 6, the precipitate of $V^{IV}O(OH)_2$ is formed except at low V(IV)O concentration. A water-soluble specie $[V^{IV}O(OH)_3]^-$ is also formed at pH values from 6 to 11 [51]. However, circular dichroism, UV and EPR spectroscopy studies with solutions containing amino acids, have shown that the most predominant species between $5 \leq pH \leq 12$ is $[(V^{IV}O)_2(OH)_5]_n^-$, where *n* will depend on the total concentration of vanadium(IV), it is important to mention that, the relative abundances of the species $[V^{IV}O(OH)_3]^-$ and $[(V^{IV}O)_2(OH)_5]_n^-$ will also depend on the total V(IV) oxide concentration. Nevertheless, the stability constant of the $[(V^{IV}O)_2(OH)_5]_n^-$ has been difficult to determine [24,55]. At pH > 12, the predominant species is $[V^{IV}O(OH)_3]^-$ [54], corroborated through Optical, Raman and EPR spectroscopy. Different studies showed that the stability constant of the vanadium(IV) complexes at pH >5 is about $\log\beta_{20\text{-}5} \approx -22.3 \pm 0.2$, and the hydrolytic process are extensive and important even in presence of high molar ratios of the amino acid [24,33,55,56].

VOL_2 complexes, where L is a bidentate monoanionic ligand, are strongly influenced by the nature of the linking atoms and the size of the metallacycle that are formed [57]. Many studies can be found in the literature on the system V(IV)O with amino acids, and despite their complexity produced by the hydrolysis reaction with the metal, their equilibrium models have been established through potentiometric data, visible absorption, EPR and circular dichroism [56,58]. The modeling studies in aqueous solutions with V(IV)O and the amino acids L-alanine (Ala) [56], L-serine (Ser) [58], L-threonine (Thr) [58], L-glycine (Gly) [59], L-histidine (His) [60,61], L-aspartic (Asp) [62], L-glutamic (Glu) [63] acids and L-cysteine (Cys) [64,65], showed that the species presented in Tables 3 and 4 are those that gave the best fitting of the experimental data.

The most important application of V compounds in medicine is their use as anti-diabetic drugs. In the bloodstream, V species can undergo manifold processes, such as ligand exchange, redox and

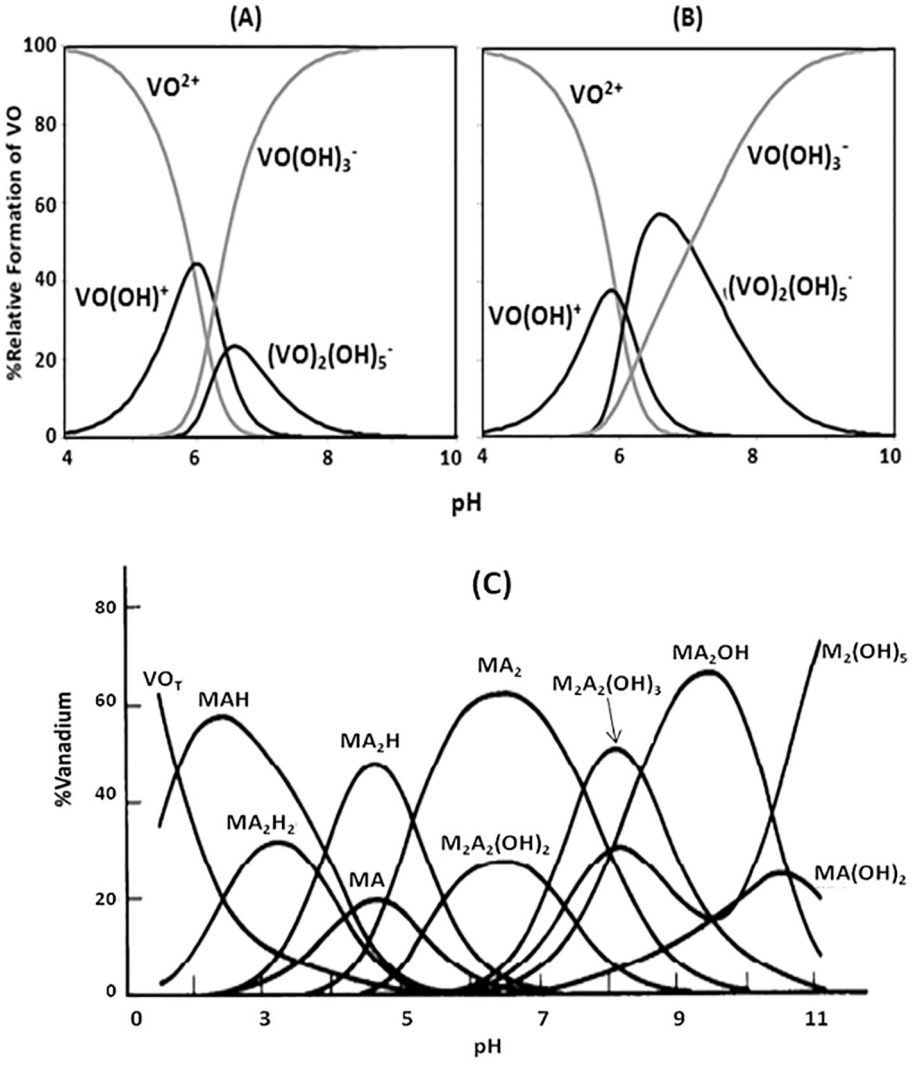


Fig. 4. Species distribution diagram for the hydrolysis of vanadium(IV) oxide A) 10 nM of concentration V(IV)O, B) 100 nM of concentration V(IV)O (Modified from Ref. [24]). C) Species distribution diagram for the system VO′-L-Ala considering the conditions $[V(IV)O] = 8{\cdot}10^{-3}$ mol·dm^{-3} and L/M = 53.9. Modified from Ref. [56].

Table 3
Ternary species that gave the best fitting of the experimental data for the systems V(IV)O–Ala, V(IV)O–Ser, V(IV)O–Thr, and V(IV)O–Gly.

V(IV)O–Ala [56]	V(IV)O–Ser [58]	V(IV)O–Thr [58]	V(IV)O–Gly [59]
MLH	MLH	MLH	MH
ML	ML	ML	ML
MLOH	MLOH	MLOH	MLOH
ML_2H_2	ML_2H_2	ML_2H_2	ML_2H
ML_2H	ML_2H	ML_2H	ML_2
ML_2	ML_2	ML_2	ML_2OH
ML_2OH	ML_2OH	ML_2OH	$ML(OH)_2$
$M_2L_2(OH)_2$	$M_2L_2(OH)_2$	$M_2L_2(OH)_2$	$M_2L_2(OH)_2$
$M_2L_2(OH)_3$	$M_2L_2(OH)_3$	$M_2L_2(OH)_3$	
	$ML(OH)_3$	$ML(OH)_3$	
	$M_2L_2(OH)_2$	$M_2L_2(OH)_2$	
	$M_2L_2(OH)_3$	$M_2L_2(OH)_3$	

Note: HL denotes the amino acid (H_2L in the case of cysteine, this applies also to Cys, His, Glu and Asp), $ML_nH_m(OH)_r$ denotes the different binary complexes, where M is the metal nucleus V(IV)O, L_n represent the α-amino acid in its total deprotonated forming this case coordinated to vanadium, $(OH)_r$ are hydroxy substituents, which came from the hydrolysis of H_2O molecules coordinated to metal center and H_m are the *m* protons acidic of the α-amino acids which acts as ligands.

Table 4
Ternary species that gave the best fitting of the experimental data for the V(IV)O–amino acid systems V(IV)O–His, V(IV)O–Asp, V(IV)O–glu and V(IV)O–Cys.

V(IV)O–His [60,61]	V(IV)O–Asp [62]	V(IV)O–Glu [63]	V(IV)O–Cys [64,65]
MLH_2	MLH_2	MLH_2	MLH_2
MLH	MLH	MLH	MLH
$ML(OH)_2$	ML	$ML(OH)_3$	ML_2H_4
ML_2H_4	ML_2H_3	ML_2H_4	ML_2H_3
ML_2H_3	ML_2H	ML_2H_2	ML_2H_2
ML_2H_2	ML_2	ML_2H	ML_2H
ML_2H		ML_2OH	ML_2
ML_2		$M_2L_2(OH)_5$	M_2L_2
ML_2OH		$M_2L_2(OH)_6$	
$M_2L_2(OH)_4$			

Note: HL denotes the amino acid (H_2L in the case of cysteine, this applies also to Cys, His, Glu and Asp), $ML_nH_m(OH)_r$ denotes the different binary complexes, where M is the metal nucleus V(IV)O, L_n represent the α-amino acid in its total deprotonated forming this case coordinated to vanadium, $(OH)_r$ re hydroxy substituents, which came from the hydrolysis of H_2O molecules coordinated to metal center and H_m are the *m* protons acidic of the α-amino acids which acts as ligands.

complexation reactions. When a V(IV)O species is absorbed in the gastrointestinal tract and moves into the serum, it encounters many low molecular mass (l.m.m.) bioligands such as citrate, lactate, phosphates, amino acids, etc, and proteins such as transferrin (hTf), albumin (HSA) and immunoglobulins (Ig). Its final form depends on the affinity for the various bioligands and on their relative concentrations [51].

Garribba et al. [66] by means of EPR spectroscopy, studied the complexation of the V(IV)O ion in several systems, as well as the ion transport in blood serum at physiological conditions. In this study, were considered the ternary systems formed by (1) V(IV)O-serum apo-transferrin (hTf)-human serum albumin (HSA); (2) V(IV)O-hTf-L; and (3) V(IV)O-HSA-L, where L represent one of the ligands lactate, citrate, oxalate, phosphate, L-glycine and L-histidine, which are the six most important low-molecular-mass bioligands of the blood serum. The experimental data indicates a small amount of $(V^{IV}O)_2$HSA in aqueous solution, while the most abundant species was the $(V^{IV}O)_2$hTf, it means that transferrin is a stronger binder than albumin at a physiological ratio. Among the L ligands, only lactate and citrate were able to bind V(IV)O in the presence of transferrin or albumin, the others did not interact at all. From these results, it was also studied the quaternary systems (4) V(IV)O-hTf-HSA-lactate and (5) $V^{IV}O_2$-hTf-HAS-citrate. The results revealed that the predominant species was $(V^{IV}O)_2$hTf, followed by the mixed complexes V(IV)O-hTf-lactate or V(IV)O-hTf-citrate, whereas $(V^{IV}O)_2$HSA and $[(V^{IV}O)_2(cytH_{-1})_2]^{4-}$ are minor components at physiological pH.

Another research based in blood serum system [67], studied the biotransformations of four insulin-enhancing vanadium compounds: $[V^{IV}O(6\text{-mepic})_2]$, cis-$[V^{IV}O(Pic)_2(H_2O)]$, $[V^{IV}O(acac)_2]$ and $[V^{IV}O(dhp)_2]$; where 6-mepic, Pic, acac, and dhp represents the deprotonated forms of the carriers ligand: 6-methylpicolinic and picolinic acids, acetylacetone and 1,2-dimethyl-3-hydroxy-4(1H)-pyridinone, respectively. It was also studied the behavior of the insulin-enhancing species: human serum apo-transferrin (hTf), human serum albumin (HSA), lactate (lact) or citrate (cyt) at physiological pH [68]. The results indicated that, ligands that coordinates weakly to the metal center such as 6-mepic, the carrier ligand can interact in some way with V(IV)O ion, until it is intaked into the cell. But when V(IV)O interacts with strongly coordinating ligands such as Pic, acac, and dhp, V(IV)O is transported not only by transferrin, but also as $[V^{IV}O(carrier)_2]$ and as mixed species V(IV)O-hTF-carrier. The albumin, can participate in the transport of an insulin-enhancing compound forming a mixed speciescis-$V^{IV}O(carrier)_2$(HSA) [67].

Kiss et al. [68], have also studied the interaction of V(IV)O ion with human serum albumin (HSA) through EPR, circular dichroism (CD) and UV/Visible spectroscopy. The experimental results revealed that V(IV)O occupies two types of binding sites in albumin, which compete not only with each other, but also with hydrolysis of the metal ion. The studies of ternary systems V(IV)O-HSA-L, where L represents the ligands drug candidate, maltol (mal), picolinic acid (Pic), 2-hydroxypyridine-N-oxide (hpno) and 1,2-dimethyl-3-hydroxy-4(1H)-pyridinone (dhp), indicates that the systems with mal, pic, hpno, and dhp, ternary species $(V^{IV}OL_2)_n$(HSA) are formed, being 6 the maximum value for *n* (mal, pic) and the species $(V^{IV}OL)_n$(HSA) was exclusively detected only with pic. Based on the spectroscopic studies, is proposed that in the species $(V^{IV}OL_2)_n$(HSA), the protein is bound to vanadium through the histidine side chains. The degree of formation of the ternary species, corresponding to the reaction $V^{IV}OL_2$ + HSA ⇆ $V^{IV}OL_2$(HSA) is hpno > Pic ≥ mal > dhp.

Garribba et al. [69] also studied the interaction of V(IV)O ion with hemoglobin (Hb) using EPR, UV/Vis and computational DFT methods. The *in vitro* results revealed that, Hb binds to V(IV)O by three unspecific sites (named α, β, and γ) and the strength of the bound VO^{2+}-Hb is lower than V(IV)O-hTf. In this study, the systems with V(IV)O potential antidiabetic compounds $[V^{IV}O(6\text{-mepic})_2]$, cis-$[V^{IV}O(Pic)_2(H_2O)]$, $[V^{IV}O(acac)_2]$ and $[V^{IV}O(dhp)_2]$, the formation of the mixed species *cis*-VOL_2(Hb) was detected with equatorial binding of an accessible histidine residue (when L = maltolate (maL) or 1,2-dimethyl-3-hydroxy-4(1H)-pyridinonate (dhp)). Instead, with acetylacetonate (acac) the presence of ternary complexes were not observed. Experimental evidence of the uptake of $[V^{IV}O(mal)_2]$, $[V^{IV}O(dhp)_2]$ and $[V^{IV}O(acac)_2]$, by red blood cells,

indicates that the neutral compounds penetrate the erythrocyte membrane through passive diffusion, being found in the intracellular medium in amounts higher than 50%. Alternatively, inside the red blood cells, the compounds $[V^{IV}O(mal)_2]$, $[V^{IV}O(dhp)_2]$ and $[V^{IV}O(acac)_2]$, are quantitatively transformed into *cis*-$V^{IV}O(dhp)_2$(Hb), *cis*-$V^{IV}O(mal)_2$(Hb) and *cis*-$V^{IV}O(mal)_2$(Cys-S-), with the equatorial coordination of a thiolate-S- of glutathione. $[V^{IV}O(acac)_2]$ can be also biotransformed in the binary species $(V^{IV}O)_xHb$, $V^{IV}O(L_1,L_2)$ and $V^{IV}O(L_3,L_4)$, where L_1, L_2, L_3, and L_4 are red blood cell bioligands.

Finally, studies concerning to the transport of vanadium complexes in blood, concluded that vanadium complexes are mostly transported by transferrin (hTf) [69–73]. At low micromolar concentrations, assuming that V(IV) maintains its oxidation state, most of the complexes hydrolyse and vanadium(IV) is transported as (VO)hTf, with V(IV)O bound at one of the iron sites [69–73].

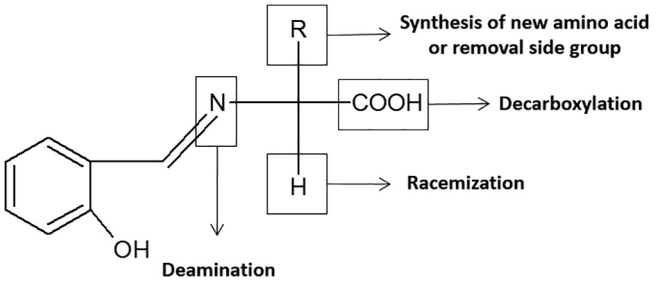


Fig. 5. Schematic diagram of possible reactions for the ligand N-salicylideneamino acidato. Modified from Ref. [24].

On the other hand, vanadium-pyridoxal complexes seek to mimic biological systems that are catalyzed by pyrodoxal phosphate enzymes, among others. These emulated systems, through the formation of a Schiff base by the condensation of the appropriate aromatic aldehyde and the amino acid, are favored by the presence of the metal, and in the case of pyridoxal, it acts as a bidentate ligand maintaining the planarity of the system [74]. Additionally, Pessoa et al. proposes a series of possible reactions that can be activated by vanadium O-N-salicylideneimine acidate complexes in reactions that are catalyzed by pyridoxal enzymes. Fig. 5 shows this series of reactions [24].

The system V(IV)O-sal-cys is a good example of how vanadium O-N-salicylideneimine acidate complexes activate two of the reactions side group removal (desulphydration of cysteine) and deamination [24,75]. In this system, the complex $[VO(salCys)(H_2O)]$ is formed (A complex in Fig. 6) which suffers a desulphydration step producing H_2S and the dehydroalanine complex (B complex in Fig. 6), then the reaction proceeds by the decomposition of the Schiff base ligand and the amino acid producing e.g. NH_3 and pyruvic acid.

In the system V(IV)O-sal-trp, the complex $[V^{IV}O(saltrp)(H_2O)]$ is formed (A complex in Fig. 7, saltrp = N-salicylidene-L-tryptophanate) which in a solution of water-pyridine form crystals of $[Hpy^+]_4[C_{14}H_{13}N_2^+]_2[V_{10}O_{28}^{6-}]$ characterized by X-ray diffraction identified as B (Fig. 7) as one of the counter ions of the decavanadate moiety [24,74]. In the mechanism, a pyridine attacks the β-carbon atom of the tryptophan molecule in A, eliminating the side

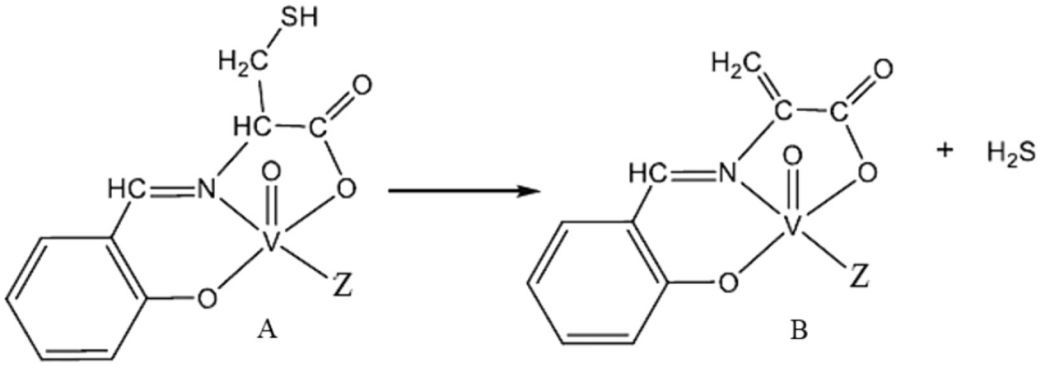


Fig. 6. Desulphydration of cysteine. Modified from Ref. [24].

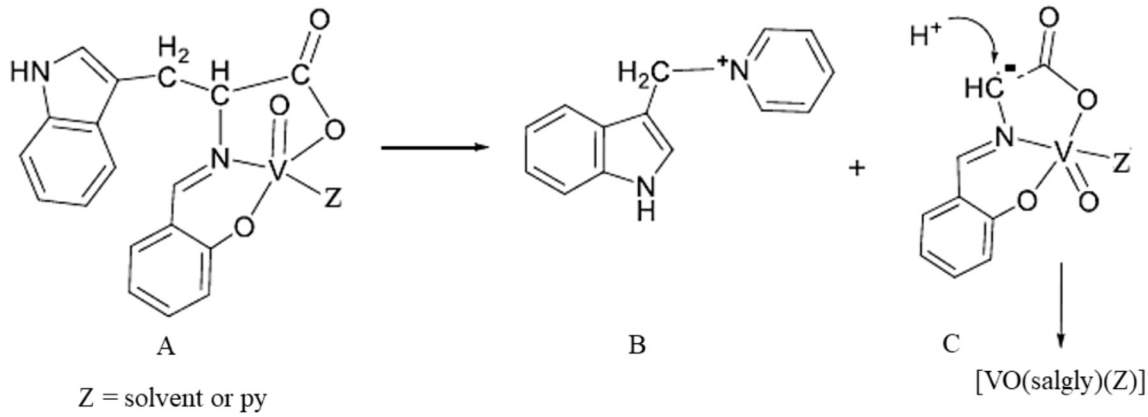
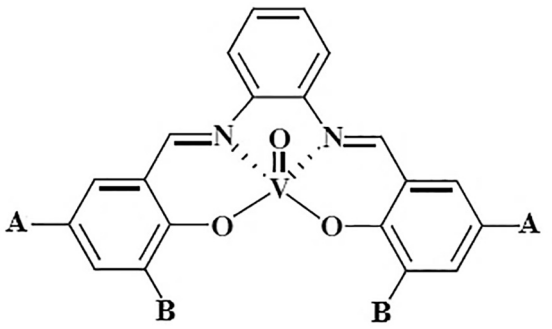


Fig. 7. Cation (B) is removed from the complex (A = $[V^{IV}O(saltrp)(H_2O)]$), by the attack of the a pyridine molecule to the β-carbon atom of the tryptophan, in this process the side group would bind again to the β-carbon atom of 10, this would lead to the racemization of the amino acid (see Fig. 5). Modified from Ref. [24].



A = ^{t}Bu	B = ^{t}Bu	VO(tetra-^{t}Bu)salophen
A = ^{t}Bu	B = H	VO(di-^{t}Bu)salophen
A = OMe	B = H	VO(di-OMe)salophen
A = H	B = H	VOsalophen
A = Cl	B = H	VO(di-Cl)salophen
A = Cl	B = Cl	VO(tetra-Cl)salophen

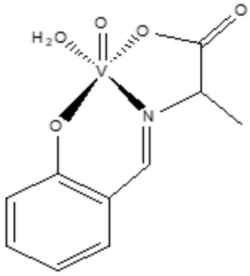
Fig. 8. The expected complexes structure of V(IV)O(salophen) derivate. Modified from Ref. [12].

group of trp and producing the complex C (Fig. 7) which may react with a proton to yield the complex N-salicylideneglycinate.

For the system V(IV)O-sal-phe, when the complex [V^{IV}O(sal-L-Phe)(H_2O)] (sal-L-Phe = N-salicylidene-L-phenylalaninate) is dissolved in a mixture of solvents water/pyridine, it forms crystals of the dimer [{$V^{V}O_2(py)_2$}(μ-C_2O_4)] with oxalate acting as a symmetrical bis(chelating) bridge [24,76]. The oxalate results from reductive coupling of CO_2, which is the decarboxylation product of the amino acid. The vanadyl N,N′-bis(salicylidene)-o-phenylene diamine (salophen) complexes, were characterized by cyclic voltammetry, UV/Visible spectroscopy and theoretical calculations in MeCN (acetonitrile), THF (tetrahydrofuran) and DMF (N,N-dimethylformamide) [12]. The expected complexes structure based on experimental evidence is shown in Fig. 8.

Fig. 9 shows a vanadium mono nuclear complex with O-N-salicylideneimine acidate, which structure ([V^{IV}O(Sal-Ala)(H_2O)]) was elucidated by X-ray diffraction in 1985 [77], whereas Table 5 presents a summary of the vanadium complexes where at least one of the parts of the ligands model pyridoxal, the structures reported have been characterized by EPR, UV/Vis, CD, NMR and/or XRD. The complex [VO(pyr-D,L-Ile)(2,2′-bipy)] [26] is the only vanadium Schiff-base complex containing an amino acid and pyridoxal, characterized by XRD.

The aqueous chemistry of V(V) is of great interest for the rational drugs design, since vanadate and its derivatives species are structurally analogous to phosphate, which is very important



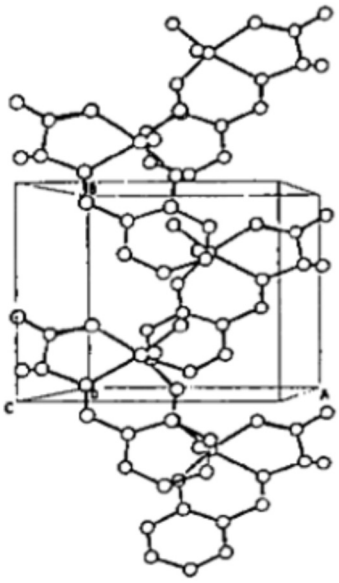


Fig. 9. XRD structure obtained for vanadium O-N-salicylieneamino acidato complex Modified from Ref. [77].

Table 5
Several vanadium-pyridoxal complexes which structure was studied by magnetic, spectroscopic techniques.

Complex	Ref.
Vanadium(IV) complex [VO(pyr-D,L-Ile)(2,2′-bipy)]	[26]
Mixed-valence complex of V(IV)/V(V). Na[V_2O_3(salSer)$_2$]5H_2O (salser = N-salicylideneserinate)	[57]
Vanadium(IV) complex [VO(salTrp)(H_2O)] (salTrp = *N*-salicylidene-L tryptophanate)	[74]
V(IV) complex VO(salGlyGly)(H_2O), (salGlyGly = N-salicylideneglycylglycinate; n = 1.5–3.0)	[78]
V(V) complex [VO{N-(2-oxido-L-naphthylmethylene)-ala-OBu-(HOBu) (product of reaction of vanadyl sulfate, L-alanine and 2-hydroxynaphthaldehyde with subsequent aeration in sec-butyl alcohol)	[79]
Dinuclear vanadium(V) complex [V_2O_3(salVal),(H,O)] (salval = N-salicylidene-L-valinate	[80]
The reaction of V(IV)O with salicylaldehyde, asparagine and pyridine forms [VO(salasn)(py)(H_2O)]	[81]
V(IV) complex [VO(salcys)(H_2O)] where salCys = *N*-salicylidene-cysteinato	[75]
[VO(salCys)(bipy)]·1·2H_2O where salcys = *N*-salicylidene-cysteinato and bipy = 2,2-bipiridine	[75]

in biological systems and is involved in an extensive number of biological recognition and bio-catalytic systems [15,82–85]. Close to neutral pH, vanadate(V) exists as a monovalent ($H_2VO_4^-$) and divalent (HVO_4^{2-}) anion; while the vanadium acid (H_3VO_4) is unstable and decomposes at pH ≈ 1 to form VO_2^+, becoming the major species. Close to pH = 7, $H_2VO_4^-$ and HVO_4^{2-} oligomerize to form dimeric, tetrameric, and pentameric structures [15].

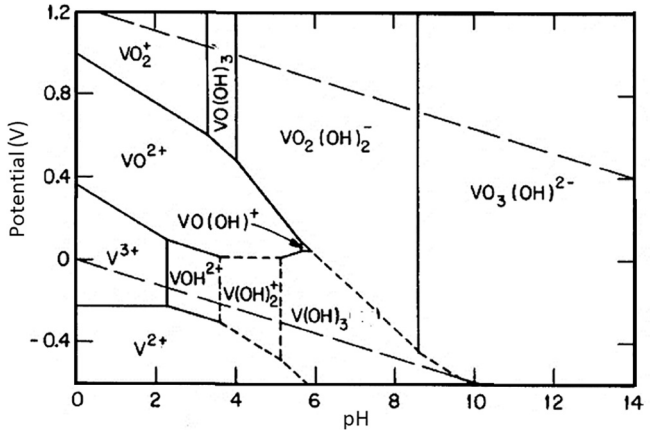


Fig. 10. Pourbaix's diagram of vanadium. Modified from Ref. [15].

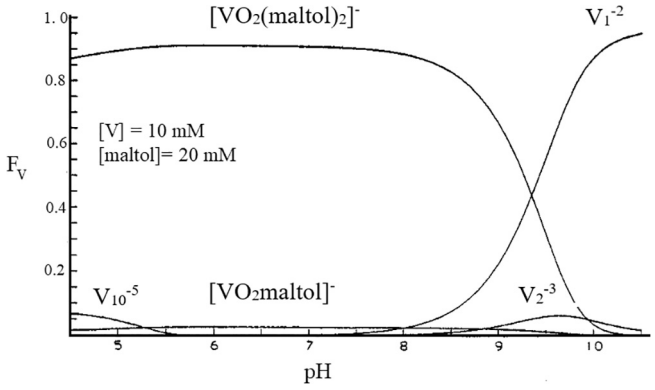


Fig. 11. Speciation diagram of vanadate-maltol system at 25 °C, ionic medium = NaCl 0.150 mol·dm^{-3}, [V(V)] = 10 mM, [maltol] = 20 mM. Modified from Ref. [91].

Pourbaix's representation (Fig. 10), is a diagram of the relative abundance of different species depending on the potential as a function of pH for different systems in aqueous phase, it shows that V(IV) is the most stable species in solution at low pH, while V(V) predominates at high pH [16,86,87].

At $2 \leq pH \leq 6$, the majority vanadate(V) species is the decameric compound $[V_{10}O_{28}]^{6-}$ and its various protonated forms; this species is thermodynamically unstable at pH ≥ 7, but between $3 \leq pH \leq 6$, the decavanadates are formed [15,86,87]. Studies based on ^{51}V NMR have shown that, in colorless solution of oxovanadates (at concentration of mM) and from neutral and alkaline pH, monomers of vanadium (V1), dimers (V2), trimers (V3), tetramers (V4) and pentamers (V5) are formed and coexist [86–88].

The biological effects of vanadium, especially V(IV) and V(V) ions, are partly due to its ability to form stable complexes with a large number of biogenic ligands [89,90]. Some of these ligands are maltol, lactate and citrate, the last two are present in blood serum with average concentrations of 1.5 (lactate) and 0.1 mM (citrate). The speciation in the system vanadate(V)-maltol is complex, at pH < 7, because despite vanadate(V) forms complexes at acidic pH, a reduction to V(IV)O may occur. Pettersson et al. studied this system from neutral to slightly alkaline solutions, and in blood serum at physiological pH (pH = 7.4) using potentiometry, ^{51}V NMR and EPR [89,91]. These experimental conditions, reduction may also occurs, although at a rather low rate, allowing a detailed study of the system and determining the speciation of the vanadate-maltol system. The speciation diagram is presented in Fig. 11, where the most abundant species at physiological pH is the $[VO_2(maltol)_2]^-$ complex.

When lactate (lac) is used as a ligand, the complexation is only favored at acidic conditions. Fig. 12A shows the distribution species diagram for vanadate-lactate system, the most abundant lactate vanadium(V) species in acidic media are the complexes $[V_2(Lac)_2]^{2-}$ and $[V_3Lac_2]^{3-}$ [89,92], where "V" is a short designation for the oxido or dioxidovanadium center. At the physiological pH = 7.4, $[VLac]^-$ is the only existing species. When hydrogen peroxide is added to the medium, the speciation diagram is showed in Fig. 12B, where the complex $[V_2(O_2)Lac_2]^{2-}$ is the most abundant lactato species at physiological pH [89,92].

For vanadate-citrate system, the species distribution diagram (Fig. 13) indicates that the only species formed at physiological

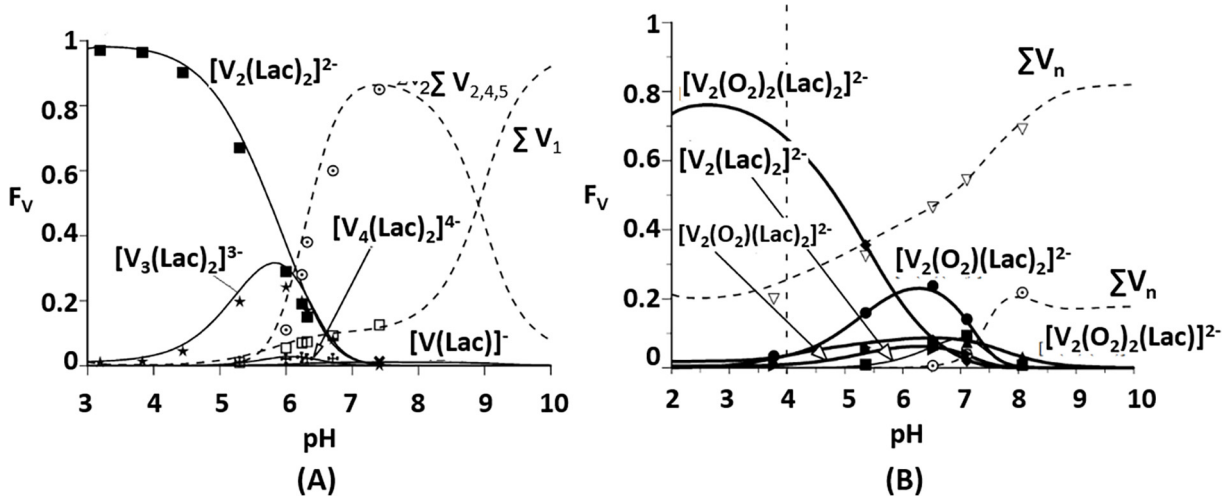


Fig. 12. Speciation distribution diagram at 25 °C using NaCl 0.150 mol·dm^{-3} as ionic medium for: (A) vanadate-lactate system, [V(V)] = 10 Mm, [lac] = 15 mM (B) vanadate-lactate-H_2O_2 system, [V(V)] = 15 mM, $[H_2O_2]^+$ = 20 mM, $[lac]^-$ = 135 mM. Modified from Ref. [92].

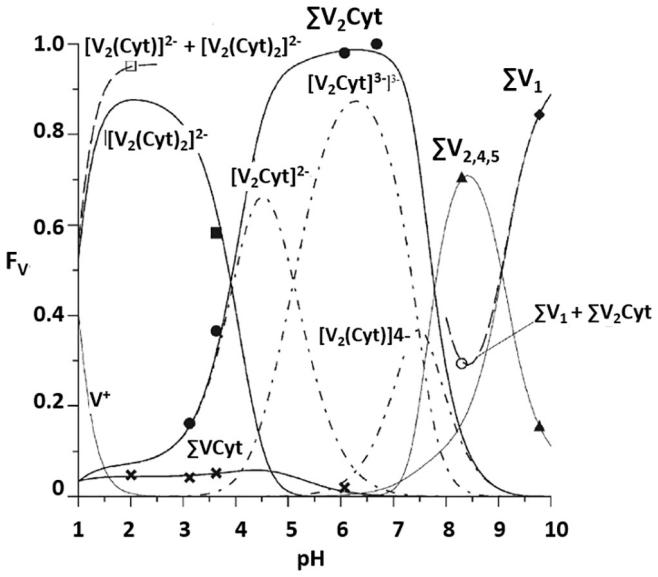


Fig. 13. Speciation distribution diagram for vanadate -citrate system at 25 °C using as ionic medium = NaCl 0.150 mol·dm^{-3}, [V(V)] = 15 mM, [Cyt] = 45 mM. Modified from Ref. [93].

pH is the complex V_2Cyt^{4-}; whereas for vanadate-lactate-citrate system, at acidic pH, the formation of binuclear species $V_2CytLac_n^-$ was detected, where *n* has values of 2 and 3 [89,93].

As vanadate and phosphate are structurally analogous a similar behavior is expected for both species. In this context, exploring potential biological activity of adenosyl-vanadates (analogs of adenosylphosphates), speciation studies were done to evaluate the interaction between vanadate and adenosine in aqueous solution, including imidazole (Im), one of the building units of adenosine (Ad). Experimental results revealed that in binary system vanadate-Adb(Fig. 14A) at 4 ≤ pH ≤ 9, the main species in solution is a binuclear complex $[\{VO_2Ad\}_2]^{2-}$; while in the ternary system vanadate-Ad-Im (Fig. 14B) the mononuclear complex $[VO_2Im(Ad)]$- is detected [89,94].

The speciation of vanadate-picolinic acid (Pic) system studied by potentiometric titrations and ^{51}V NMR, is shown in Fig. 15A. The analysis indicated the formation of the complex $VPic_2^-$ over a wide pH range (1.5–8.5). Spectroscopic studies with ^{51}V NMR revealed that the most abundant species formed between 3 ≤ pH ≤ 7 are three geometric isomers of $VPic_2^-$ (Fig. 15B) [89,95].

Both V(IV)O and V(V) (and possibly V(III)) chemistry are relevant in the blood stream, and it is thought that the presence of a reducing agent (e.g. ascorbic acid, cysteine) could be effective to reduce V(V) to V(IV)O. Nevertheless, the presence of O_2 molecules in the blood may lead to oxidation to V(V), thus an equilibrium is established between V(IV) and V(V) species [96]. The study at physiological pH and ionic strength, with histidine (H-His-OH) and vanadate shows that they form at least two weak complexes through the amino group of the ligand [97]. Amino acids and peptides such as lysine, glutamic acid, glycine, and glycylglycine showed weak vanadate interactions with similar affinity for VO^{+2} cation [98–104]. Using ^{51}VN MR spectroscopy, it was established the equilibria between diperoxovanadates and a number of di- and tripeptides (glycyltyrosine, glycylserine, glycylthreonine, glycylglutamic acid, glycyllysine, glycyltryptophan, tryptylglycine, tryptyltryptophan, tryptyltyrosine, glycylglycylserine and tyrosylglycylglycine, tryptylglycylglycine) in aqueous solution [100]. The complexes characterized were ML species, where L represents the di- or tripeptides and M is a diperoxo vanadate.

The systems vanadate-glycylglycine [102], vanadate-alanylglycine [105], vanadate-prolylalanine [105] and vanadate-alanylhistidine [106] were studied by potentiometric titration and ^{51}V NMR spectroscopy. The models that best adjusted to experimental data indicate the formation of ternary species $(H^+)_p(H_2VO_4^-)_q(L)_r$ in all systems. The equilibria studied are written with the components H^+, $H_2VO_4^-$ and L. Thus the complexes are formed according to:

$$pH^+ + qH_2VO_3^- + rL \rightleftarrows (H^+)_p(H_2VO_4^-)_q(L)_r$$

The complexes are often given in the notation (p,q,r). $H_2VO_4^-$-glycylglycine and $H_2VO_4^-$-alanylhistidine have (p,q,r) values of (0,1,1) and (1,1,1) respectively, suggesting the formation of two complexes in every system. Instead, the $H_2VO_4^-$-alanylglycine and $H_2VO_4^-$-prolylalanine complexes, have (p,q,r) values of (0,1,1) indicating the formation of only one complex in both systems. Table 6, indicates the formulation of complexes of V(V)-di- or tripeptides and V(IV)-di- or tripeptides analyzed by XRD where phen represents phenanthroline.

The study of V(V) with apoTransferrin (a blood plasma glycoprotein), showed that that this protein is able to bind two V(V) similarly to other metal ions, and the stability constants of the

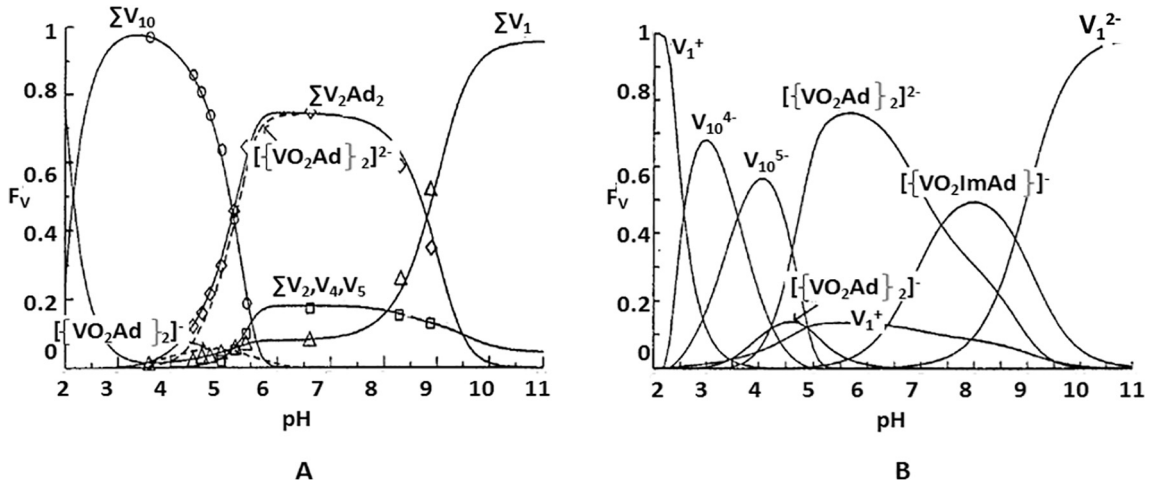


Fig. 14. Species distribution diagram for vanadate-adenosine system at 25 °C using as ionic medium = NaCl 0.600 mol·dm^{-3}, [V(V)] = 5 mM, [Ad] = 20 mM, (A). Species distribution diagram for vanadate-adenosine-imidazole system at 25 °C using as ionic medium = NaCl 0.600 mol·dm^{-3}, [V(V)] = 1.25 mM, [Ad] = 20 mM, [Im] = 320 mM (B). Modified from Ref. [94].

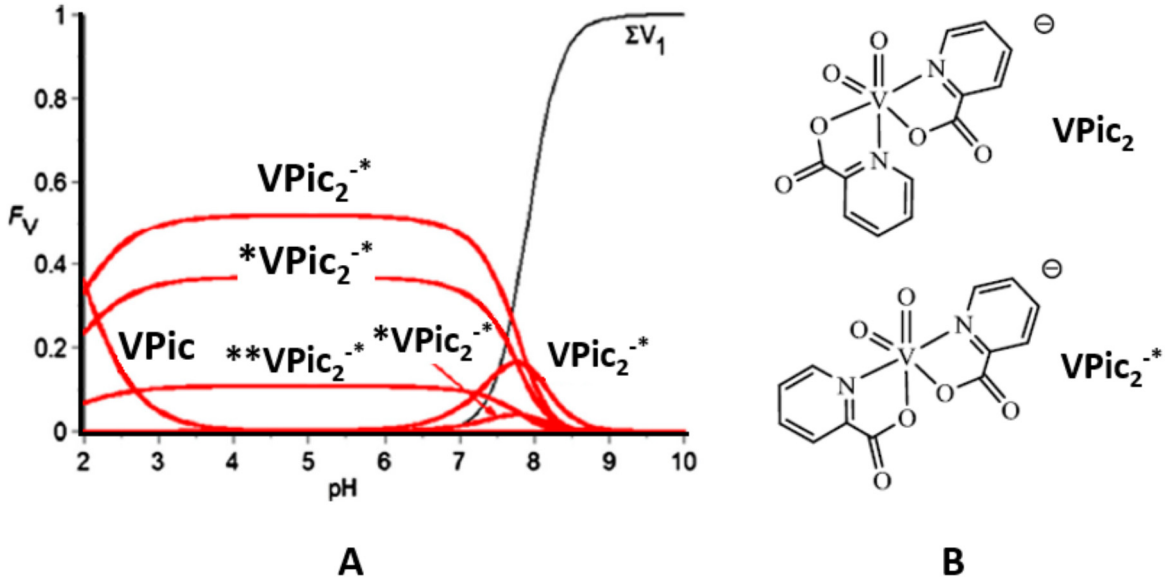


Fig. 15. Species distribution diagram for vanadate-picolinic acid system at 25 °C using as ionic medium = NaCl 0.150 mol·dm^{-3}, [V(V)] = 1 μM, [Ad] = 20 Mm (A). Possible structures of the two main geometric isomers $VPic_2^-$ and $VPic_2^{-*}$ (B). Modified from Ref. [89].

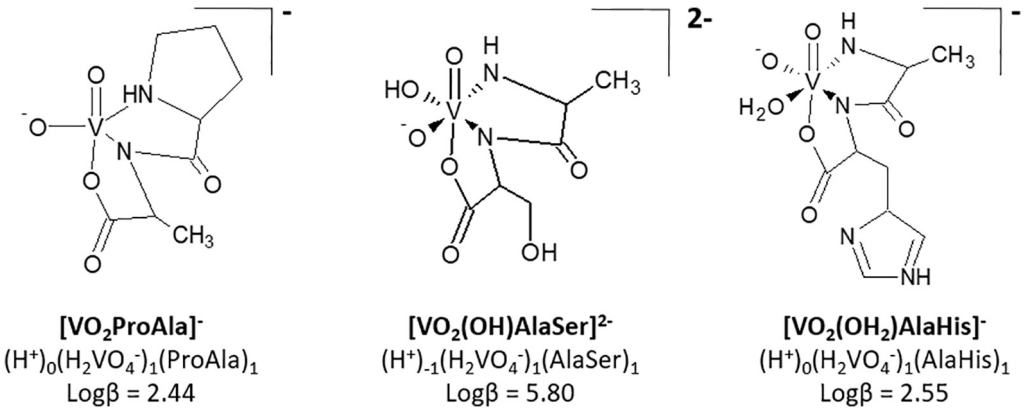
Table 6
Compounds V(V)-di- or tripeptides synthesized (structure characterized by XRD).

Compound	di- or tripeptide	Ref.
	V(IV) Complexes	
[VO(GlyTyr)(phen)]	Glycyltyrosine	[107]
[VO(GlyAla)(phen)]	Glycylalanine	[108]
[VO(GlyVal)(phen)]	Glycylvaline	[108]
[VO(GlyPhe)(phen)]	Glycylphenylalanine	[108]
	V(V) Complexes	
$[NEt_4][VO(O_2)(GlyGly)]1{\cdot}.58H_2O$	Glycylglycine	[109]
$[VO(NH_2O)_2(GlyGly)]H_2O$	Glycylglycine	[110]
$[\{VO(VanSer)H_2O\}_2]\mu$-O],	Vanser is the Schiff base formed from o-vanillin and L-serine	[111]

apoTf-V(V) interactions are 3-4 orders of magnitude higher than those with inorganic anions (phosphate, sulfate, hydrogen carbonate) [96]. There is also evidence that the coordination of the metal to the apoTf is through two tyrosine side chains [24,52,69,72,82,96,112,113]. Upon investigations carried out by the group of Pettersson with dipeptides such as Pro-Ala, Ala-Gly, Ala-His and Ala-Ser, tentative structures for a few of the complexes with dipeptides were proposed [89] and are depicted in Fig. 16.

Due to the multiple biological interest of oxovanadium systems with amino acids and Schiff bases derived from amino acids and peptides have also been extensively investigated. Pessoa et al. studied the systems $V^{IV}O$-glycylglycine [114], $V^{IV}O$-glycylglycylglycine [114], $V^{IV}O$-glycyl-aspartic acid [115], $V^{IV}O$-glutathione [116] and $V^{IV}O$-oxidized glutathione [117] using potentiometric titration and spectroscopic analysis (UV/Visible absorption, EPR and circular dichroism). Table 7 shows the speciation model proposed that best fit to experimental data; pH^+, qM, rL and sOH^- are the groups that conform the complexes $(M)_q(L)_r(H^+)_p(OH)_s$ where M and L denotes VO^{2+} and Schiff bases derived from amino acids respectively and p,q,r,s denotes the stoichiometric coefficient of the groups that conform the complexes.

On the other hand, Table 8 shows other studies done by potentiometry and spectroscopy, involving the complexation of V(IV)O ion with the tripeptides containing L-histidine or L-cysteine (V(IV)O-HisGlyGly, V(IV)O-GlyGlyHis and V(IV)O-GlyGlyCys [118], the coordination of V(IV)O with a tripeptide, which contains salicylic acid and the amino acids L-glycine or L-alanine (V(IV)O-SalGlyAla) [119] as well as the dipeptide formed between salicylic



$[VO_2ProAla]^-$
$(H^+)_0(H_2VO_4^-)_1(ProAla)_1$
Logβ = 2.44

$[VO_2(OH)AlaSer]^{2-}$
$(H^+)_{-1}(H_2VO_4^-)_1(AlaSer)_1$
Logβ = 5.80

$[VO_2(OH_2)AlaHis]^-$
$(H^+)_0(H_2VO_4^-)_1(AlaHis)_1$
Logβ = 2.55

Fig. 16. Examples of V(V) complexes proposed to be formed with some dipeptides. Modified from Ref. [89].

Table 7
Binary species for the V(IV)O-Schiff bases derived from amino acids and peptides, where M and L denotes VO^{2+} and Schiff bases derived from amino acids respectively.

V(IV)O-glycylglycine [114]	V(IV)O-glycylglycylglycine [114]	V(IV)O-glycyl-aspartic acid [115]	V(IV)O-glutathione [116]	V(IV)O-oxidized glutathione [117]
MLH	MLH	MLH_2	MLH_3	MLH_4
ML_2H_2	ML_2H_2	MLH	MLH_2	MLH_3
MLOH	MLOH	MLOH	MLH	MLH_2
		ML_2H_3	ML_2H_2	MLH
		ML_2H_2	MLOH	ML
		ML	$ML(OH)_2$	MLOH
		ML_2H		$ML(OH)_2$

Table 8
Binary or ternary species for the V(IV)O-(dipeptide/tripeptide).

V(IV)O-HisGlyGly [118]	V(IV)O-GlyGlyHis [118]	V(IV)O-GlyGlyCys [118]	V(IV)O-SalGlyAla [119]	V(IV)O-SalGly [120]
MLH	MLH	MLH_2	MLH	MLH
ML_2H_2	ML_2H_2	MLH	ML	ML
MLOH	MLOH	MLOH	MLOH	MLOH
		ML_2H_3	$ML(OH)_2$	$ML(OH)_2$
		ML_2H_2		ML_2OH
		ML		
		ML_2H		

acid and glycine (V(IV)O-SalGly) [120]. This table is based on the speciation model proposed that best fit to experimental data; pH^{+}, qM, rL and sOH^{-} are the groups that conform the complexes $(M)_q(L)_r(H^{+})_p(OH)_s$, where M and L denotes VO^{2+} and dipeptide or tripeptide respectively and p,q,r,s denotes the stoichiometric coefficient of the groups that conform the complexes.

The systems V(IV)O-HisGlyGly, V(IV)O-GlyGlyHis and V(IV)O-GlyGlyCys, demonstrated that these oligopeptides in a ligand-metal molar ratio of 10 or 15, can keep V(IV)O ion in solution at pH values around neutrality. $VOL(OH)_2$ species are formed with a (NH_2, N^{-}, N^{-}, COO^{-}) donor set for HisGlyGly, (NH_2, N^{-}, N^{-}, N_{im}) for GlyGlyHis and (NH_2, N^{-},N^{-}, S^{-}) for GlyGlyCys [118].

4. Bioinorganic implication and application of vanadium complexes

In previous sections, we have described the importance of vanadium at industrial level, the chemical speciation of binary and ternary complexes with amino acids and very briefly their importance at the biological level. The studies of chemical speciation in aqueous solution are fundamental to know the nature, abundance and stability of the different species in solution, because they represent an essential requirement to evaluate the biological activity of promising therapeutic targets [121–126]. In this section we will discuss the applications of vanadium compounds, especially vanadium complexes with (non)essential amino acids, in pharmacology and medical therapeutics, as well as their importance in bioinorganic chemistry. Metal compounds have been used for medicinal applications since ancient times [127]; however, the use of drugs of organic origin has governed the development of modern medical chemistry. The discovery of cisplatin, for example, and its potent anti-tumor activity [16,128], has led many of researchers worldwide to focus on the study of inorganic medical chemistry. In fact, coordination chemistry compounds and organometallic compounds, using different metal centers, have been evaluated in cancer, endemic tropical diseases as Chagas, leishmaniasis and viral infections such as Dengue, SARS and HIV [16,129,130].

Although, there are reports of the application of vanadium in the eighteenth century, the biological importance of vanadium was recognized early in 1904 when showed its fungostatic effect on yeast [131]. However, the interest in bioinorganic vanadium chemistry became most notable in the late 1970s, when Cantley and coworkers reported on the inhibition of (Na,K)-ATPase by vanadate, disclosing biological consequences of the chemical similarities between vanadate(V) ion and phosphate [132]. The fundamental differences between vanadate(V) and phosphate is in the type of reactions in which they participate (e.g. V and/or P ester formation) and in their acid-base equilibria, at physiological pH, the vanadate(V) is mainly in its $H_2VO_4^{-}$ form, while phosphate is present as $H_2PO_4^{-}$ and HPO_4^{2-} in approximately equal concentration [5,82]. Phosphate presents a transition state penta-coordinated, whereas vanadate(V) easily reaches a coordination number of five, acquiring a distorted trigonal bipyramid geometry [5,24,82] this cause that vanadate and other oxovanadium clusters compounds can inhibit phosphatases and phosphorylases (alkaline phosphatases, acid phosphatases, tyrosine-protein phosphatases, ribonucleases, phosphordiesterases, phosphoglucomutase and glucose-6-phosphatase) with different efficiency, and where the activity of a phosphate-dependent enzyme may be inhibited when vanadate is incorporated into the active site replacing the phosphate [3,5,15,82–84,133]. Thus, the interaction between vanadate (V) and proteins occurs through the binding of moieties similar to those formed by phosphate. One example of this interaction is the phosphorylation of tyrosine residues, where vanadate(V) also forms esters with Tyr residues mimicking their phosphorylation process [15,82].

Vanadium is considerably more electrophilic than phosphorous, V–O bonds in vanadate are about 15% longer than the corresponding P–O bond in phosphate, and the P–O bonds are more covalent with respect to V–O bonds [82]. These differences are meaningful because when simple geometrical calculations are done, the volume of vanadate shows an increase of 25–40% relative to phosphate (assuming a similar molecular geometry) [82]. It was highlighted that, for small molecules, the squared pyramidal geometry is the most common, but in presence of proteins, the trigonal bipyramidal is better supported [83]. A comparison of the molecular geometry of vanadate and phosphate relevant for several proteins is shown in Fig. 17.

Vanadate has been identified as a moiety that may bind at the active site of certain enzymes, such as proteins phosphatases. In

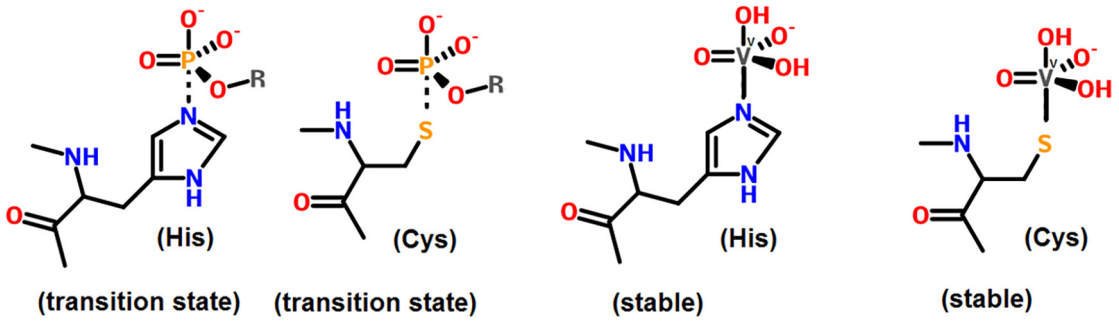


Fig. 17. Comparison of geometries of vanadate and phosphate relevant at the physiological level. Modified from Ref. [5].

the PTP1B (protein tyrosine phosphatase 1B), vanadium forms coordinated penta and hexa complexes involving a bidentate bond with the carboxyl group of the aspartate [5,24]. The enzyme PTP1B plays a crucial role in the signaling of the insulin receptor, because it is a negative regulator of the pathway [134]. In fact, the antidiabetic activity of the vanadium compounds [82] is linked to the formation of a transition state stable analogue, which binds strongly to the active site of PTP1B, leading to its inhibition [135,136]. Unlike the phosphoester, the vanadate esters bound to the active site of the enzyme, are not easily released, causing inhibition of PTP activity [24]. Lyonnet et al. (1899) observed for the first time that oral administration of Na_3VO_4 decreased glycosuria in diabetic patients [137]. At present, PTP1B inhibition has been proposed as the main insulin-mimetic target, and a significant number of vanadium complexes have been investigated as antidiabetic potentials. Nevertheless, by reducing V(V) to V(IV) it is possible to reverse the inhibition, and it can be reached by the presence of glutathione and/or other biological reducing agents [24]. Other important vanadium-enzyme complexes are the vanadium bromoperoxidases (VBPO) – one of these was the first enzyme discovered that use vanadium as a cofactor – and the vanadium nitrogenases (V-Nases), found in nitrogen-fixing bacteria of the genus *Azotobacter* (*chroococcumvinelandii*) [24,82,138,139].

It is well known that vanadium can expand its sphere of coordination and easily switch between different states of oxidation in a given physiological environment. From the most common oxidation states of vanadium, only oxidation states (III), (IV) and (V) were found to be involved in biological systems [50], since V(II) is able to reduce water to hydrogen [5,25]. The most common oxidation states of vanadium in biological systems, especially in mammals, are V(V) (d^0) and V(IV) (d^1), since V(III) (d^2) is very susceptible to oxidation processes. However, stable V(III)-transferrin human complexes have been found [82,140,141] in addition to the presence of V(III) in the final storage stage of ascidians, where the concentration of V reaches values up to 350 mM, being the V used as venom for potential predators [4,142,143].

Vanadium compounds were originally considered, for many years, as potential oral drugs for the treatment of patients with diabetes mellitus, however; with the development of insulin in 1922, the interest of metal-based drugs decreased. At the end of the 70s, the insulin-like effect of vanadium compounds in several experimental models was consolidated, among them, the stimulation of glucose transport, glycolysis and glycosynthesis, among other carbohydrates metabolism events [144,145]. In 1985, inorganic salts such as $NaVO_3$ and $VOSO_4$ were considered again for the treatment of diabetes, but these inorganic salts presented several problems, such as, gastrointestinal distress and low absorption. For this reason, further studies with inorganic salts of vanadium were discarded and newer researches were made towards the complexation of V(IV)O with bidentate organic ligands such as maltolato [146–148], dmpp (1,2-dimethyl-3-hydroxy-4-pyridinonate) [149–151] and picolinate [148,152] with special attention for the later one, since picolinic acid is the intermediate metabolite of tryptophan and it is therefore less toxic to mammals organism promoting as well the absorption of various metals in the small intestine [153]. The chelating effect of the carrier ligand greatly influences the efficiency of the compound because determines the re-adsorption and improves the biodistribution, stability and tolerability of the metal ion in the organism [5,24,96]. One of the most important compounds is the bis(ethylmaltolate)oxovanadium(IV) (BEOV) from Akesis Pharmaceuticals Inc., which was suspended in phase II due to some problems despite its good clinical efficacy in patients with type 2 diabetes [90,148]. The $V^{IV}O(dmpp)_2$ (bis(1,2-dimethyl-3-hydroxy-4-pyridinonate)oxovanadium (IV)) complex has exhibited antidiabetic activity increasing glucose uptake in adipocytes promoting the phosphorylation of the Akt1, a key protein in insulin signaling [149]. A chronic *in vivo* treatment in with $V^{IV}O(dmpp)_2$ decreases hyperglycemia and improves glucose tolerance [151]. Fig. 18 shows the molecular structure of $V^{IV}O(Ethylmaltolato)_2(H_2O)$, $V^{IV}O(maltolato)_2(H_2O)$, $V^{IV}O(dmpp)_2$ and $V^{IV}O(Pic)_2$.

Amino acid complexes have been an alternative in bioinorganic chemistry for the development of vanadium compounds with promising applications. Goldwaser et al. [154] used L-glutamic acid γ-monohydroxamate (L-Glu(γ)HXM) as a vanadium ligand, observed that, in this study, the system markedly enhances the lipogenesis and glucose uptake in rat adipocytes, this latter effect was related to an increase of GLUT4 translocation. In addition,

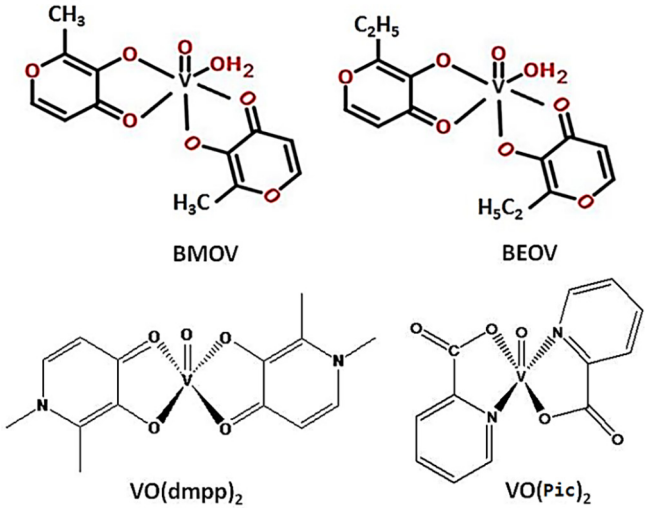


Fig. 18. Chemical structures of BMOV ($V^{IV}O(maltolato)_2(H_2O)$), BEOV ($V^{IV}O(etil-maltolato)_2(H_2O)$), $V^{IV}O(dmpp)_2$ (bis(1,2-dimethyl-3-hydroxy-4-pyridinonate)oxovanadium (IV)), $V^{IV}O(Pic)_2$ (bis(picolinato)oxovanadium(IV). Modified from Refs. [24,149,152].

the activity of this complex on lipid and carbohydrate metabolism was blocked by wortmannin, a known inhibitor of phosphoinositide 3-kinase (PI3K), thus consolidating its mimic effect [154]. As expected, treatment of rats with streptozotocin-induced diabetes showed a greater hypoglycemic effect compared to $NaVO_3$ [154].

Karmaker et al. showed that the vanadium complex with poly-γ-glutamic acid (VO-γ-PGA), a polymer of this non-essential amino acid, produces a hypoglycemic effect, decreases glycosylated hemoglobin levels and improves glucose tolerance in streptozotocin-induced type 1 diabetic mice [155,156] and in KKA^y mouse model of diabetes type 2 [157]. The FT-IR and EPR studies shows that VO^{2+} coordinates with the carboxylate groups of the chain, forming two forms of the complex: carboxylate (O)-VO-$(OH_2)_3$ or/and carboxylate (O)-VO-$(OH_2)_2$ [155,157,158].

Further studies conducted by Hu et al. (2010) showed that VO-γ-PGA improves some markers of renal and hepatic damage in diabetic rats compared to $VOSO_4$. Likewise, this complex decreased both triglycerides and blood fatty acids on alloxan induced diabetes rats [158]. It is worth mentioning that, one of the main undesirable consequences of inorganic vanadium intake is its effect in the lipid metabolism which is still unclear. For example, in healthy rats treated via oral with $VOSO_4$, it has been observed an increase of total cholesterol, LDL and blood triglycerides [159]. In fact, patients with impaired glucose tolerance treated with $VOSO_4$ showed an increment of the basal triglyceride levels from 1.35 ± 0.61 to 1.70 ± 0.46 mmol/L ($p = 0.018$) [160], so treatment with inorganic vanadium in patients should be studied more exhaustively with respect to the lipid metabolism, given that, an elevated blood levels of triglycerides and cholesterol may be associated with increased cardiovascular risk [161]. Vanadium complexes can be considered as drug delivery system presenting a better therapeutical effect than classical inorganic vanadium salts observed in '*in vivo*' studies for the evaluation of their anti-hyperglycemic activity and also in insulin-mimetic activity performed '*in vitro*' [155]. The insulin-mimetic effect exerted by some vanadium compounds may be attributed to the stimulation of the autophosphorylation of insulin receptors, however, this depends on the animal tissue and the species under study, for example, in rat lung cells and rabbit cells, the autophosphorylation of the insulin receptor could not be determined [162–165]. On the other hand, these insulin-mimetic effect of vanadium compounds can be due the stimulation of kinases enzymes by translating signals used by insulin into the MAPKs and PI3K proteins, which are responsible for the regulation of the metabolism and mitogenic effects of insulin. Additionally, the inhibition of PTP1B due to the administration of vanadium complexes, activates the signaling of PI3K → Akt through the increment of the tyrosine phosphorylation of Irβ and IRS of the tyrosine phosphorylation [2,166]. Further results suggested that, in fact, the inhibition of PTPases, especially tyrosine phosphatases, is the main mechanism of their insulin-mimetic effect, being here where certain vanadium compounds behave as reversible inhibitors while other compounds perform irreversible inhibitions by modifying the protein due to redox processes [167].

Lu et al. [168] showed that treatment with the vanadium and glutamate complex, $Na_2[V(V)O(Glu)_2(CH_3OH)]\cdot H_2O$ ($1\cdot H_2O$), was not only able to inhibit human PTP1B *in vitro*, but also other types of PTPs, such as Src homology phosphatase 1 (SHP-1), hematopoietic tyrosine phosphatase (HePTP) and T-cell protein tyrosine phosphatase (TCPTP). The inhibitory activity was attributed to the largest complex formed at physiological pH [168]. SHP-1 has been established as a negative regulator of insulin-induced glucose metabolism. Inhibition of this phosphatase increases the glucose uptake through enhanced insulin receptor signaling [169,170]. Only some oxovanadium(IV) complexes have shown an inhibitory effect on SHP-1, suggesting that these compounds, such as $Na_2[VO(Glu)_2(CH_3OH)]$ and 2-((5-Nitro-2-oxybenzylidene)amino) benzoato-diaqua-oxovanadium(IV), play an important role in enzyme selectivity [168,171]. The bisperoxovanadium compounds has been described as inhibitor of PTEN (phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase) [172,173], another important counter-regulator of insulin signaling [173,174]. However, inhibition by vanadium complexes with amino acids has not been demonstrated.

Vanadium compounds have not only been studied as antidiabetic and insulinomimetic agents, but also for the treatment of parasitic diseases of tropical origin, for cancer and as protectors of tissue damage induced by chemical agents and oxidative stress [2,5,175–179]. Some vanadium compounds, such as vanadylsulphate, sodium vanadate and peroxidovanadates have shown antitumor activity in experimental models *in vitro* and *in vivo* [177–182]. Vanadocene dichloride [183], vanadium(III)-L-cysteine complexes [47], complexes Metvan $[V^{IV}O(SO_4)(4,7\text{-Mephen})_2]$ [2,24,184], vanadium complexes with flavonoids and other polyphenols [185], semicarbazone derivatives [186], vanadium-Schiff base complexes [179,187], have demonstrated antitumor properties, which have been studied in different types of cell lines, inhibiting cell proliferation throughout the range of concentrations studied. The chemical structure of different vanadium compounds with antitumor activity is shown in Fig. 19.

Both inorganic vanadium and some of the vanadium complexes lead to cell apoptosis through classical intracellular events such as cell cycle arrest, dissipation of the mitochondrial membrane potential, induction of mitochondrial permeability transition pore, cytochrome *c* release, activation of proapoptotic protein, activation of caspases, DNA fragmentation and formation of apoptotic bodies, which leads to cell death [189,190]. All this is mediated by activation of various signaling molecules such as MAPK, NF-kB and reactive oxygen species (ROS) [189,191–194]. Possibly, P53 is the key protein for these effects of vanadium compounds, since a large number of tumor cells have defects in the gene encoding this protein [195]. In case of p53-deficient mouse embryo fibroblasts, vanadate inhibit the cell cycle and induce apoptosis; whereas in functional p53 cells, vanadate promote the S phase favoring proliferation [196]. The ammonium monovanadate is able to induce apoptosis in both rats with breast cancer 7,12-dimethylbenz(a) anthracene induced and MCF-7 cells culture, accompanied by a strong expression of p53 [197]. Recently, vanadium complexes such as, $[VO(oda)(phen)](H_2O)_{1.5}$, $[phenH][VO(nta)(H_2O)](H_2O)_{0.5}$ or $[4\text{-}NH_2\text{-}2\text{-}Me(QH)][VO(nta)(H_2O)](H_2O)$ were reported to induce apoptosis of human pancreatic ductal adenocarcinoma through a mechanism that involves ROS increase [198].

Although there is evidence to suggest that the antineoplastic action of vanadium compounds is partly due to inhibition of PTP1B, the cellular mechanism is more complex and involves significantly increased oxidative stress [189,199,200]. It is noteworthy that, the inhibition of PTP1B, is carried out both by the direct union of the compounds and the post-translational modifications induced by the reactive oxygen species, the inhibitory process involves the ROS-induced oxidation of cysteine^{215} within the active site of PTP1B, so that it abrogates its nucleophilic function [201,202]. The role of PTP1B in cancer has been extensively investigated, recently, it was determined that the increased expression of this enzyme contributes robustly to the development of some types of tumor, especially in breast cancer [203–204]. Vanadium complexes such as oxodiperoxo(1,10-phenanthroline) vanadate (pVphen) [202], oxidovanadium(IV) complexes with oxodiacetate (oda) and 2,2′-bipyridyl, (VO(Oda)bipy) and o-phenanthroline (VO-(oda)phen) [193], V(V)-peroxido-betaine [205], Metvan [184] as well as V(III)-L-cysteine [47,188], have shown a close link between antitumor activity and increased production of ROS in various cancer lines. Metvan has been the most successful vanadium complex tested as antitumoral, concentrations in the range

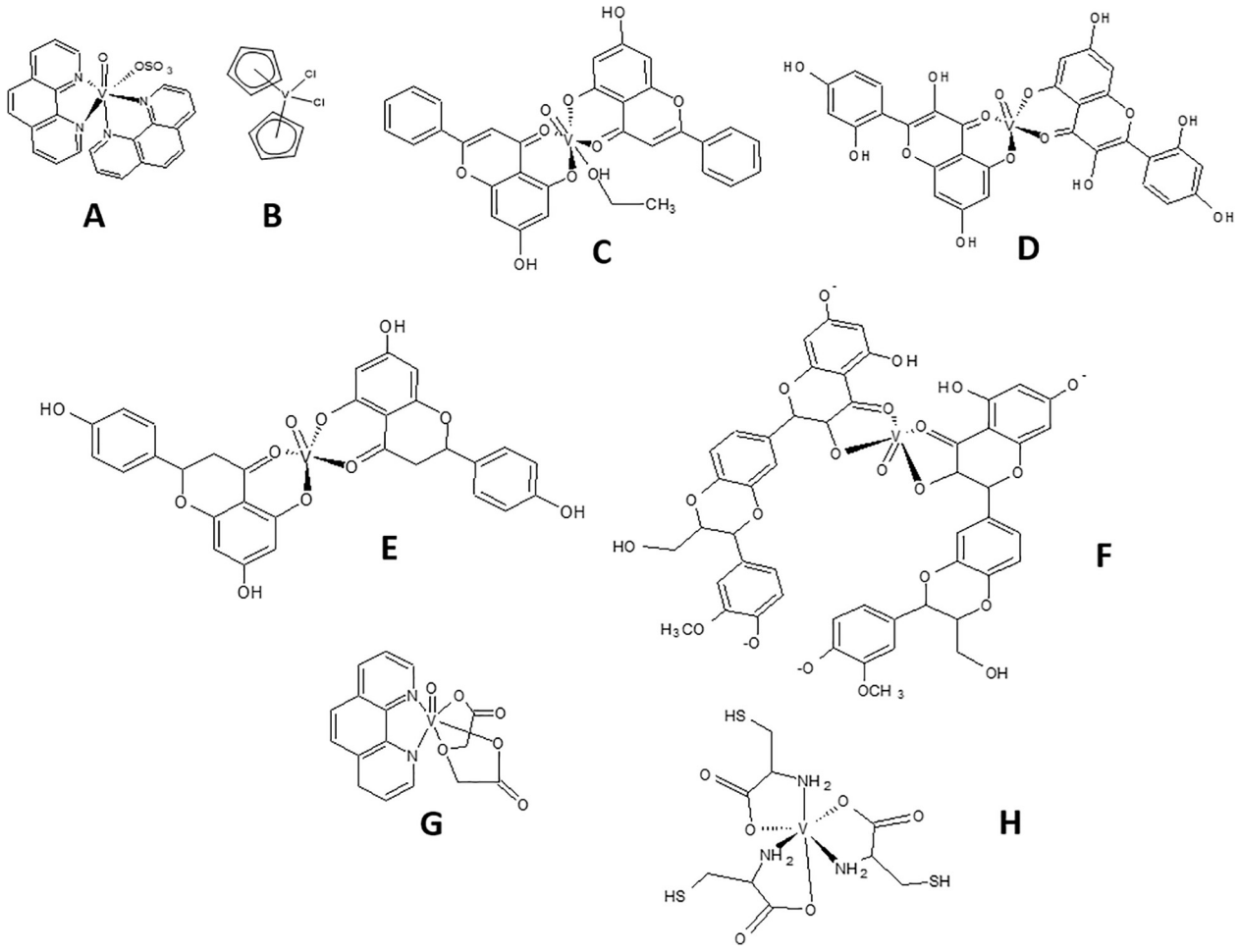


Fig. 19. Chemical structure of various vanadium compounds with anti-tumor activity. A) Metvan. B) Vanadocene dichloride. Vanadium complexes with: C) Chrysin. D) Morin. E) Naringenin. F) Silibinin G) VO(oda)phen. H) V(III)-L-Cysteine. Based on Refs. [2,24,48,179,184–188].

of μM have induced cell apoptosis in different tumor lines, such as leukemia cells, multiple Myeloma cells, breast, prostate, ovarian, and testicular cancer cells, demonstrating a high efficiency compared to cisplatin [2,17,184,189,206].

The dual role of vanadium complexes is manifested in the synthesis of vanadium complexes with phenolic compounds or flavonoids. It is widely known that these types of natural products have antioxidant, cytotoxic and chemosensitizing properties [207,208]. Among the most outstanding complexes are: those of naringenin [185], morin [209] chrysin and silibinin [210]. In the late of 1990s, it was shown that some vanadium compounds also had chemopreventive effects, since chelating compounds may have a significant effect on improving the antioxidant and antitumor properties of flavonoids [2]. Aiming to this fact, the synthesize of V(IV)O with flavonoids such as Morin and Silibinin, proved in line cells MG-63 for the study of osteosarcoma, gave very promising results [209,211,212]. Vanadium compounds of 1,10-phenanthroline or 8-hydroxyquinoline derivatives with antitumor properties, induced cell death by apoptosis, with IC_{50} values lower than cisplatin [24]. It is important to mention that, 8-hydroxyquinoline (8HQ), is a privileged structure which is present in many natural products and has been used as a pharmacophor in the design of compounds with biological activity for different types of neurodegenerative diseases and herpes [213]. 8HQ enhances the bioavailability of vanadium complexes by increasing the ability to penetrate the lipid-rich cell membrane [2].

Evangelou et al. demonstrated that the vanadium(III)-L-cysteine was able to decrease the rate of tumor growth and thereby the survival of benzo[a]pyrene-induced cancer rats. In fact, this amino acid vanadium complex has exhibited much greater potency than vanadylsulphate in benzo[a]pyrene-induced leiomyosarcomas in Wistar rats [180,181]. Interestingly, solution of vanadium(III) with L-cysteine (pH approx. 7, L/M = 20) showed a cytotoxic effect in hepatoma cells, with reduced cell viability to 70% at concentrations of 100 μM of vanadium species concentration in the culture medium [47], however, the state of protonation of the cysteine coordinated to the metallic center was not reported, so it is not clear which species is responsible for the effect in this paper. It should be noted that liver cancer is considered one of the most aggressive and metastatic, and has very limited therapeutic alternatives [182]. So it has been of great importance to study new antineoplasics against this type of cancer. Vanadium (III)-L-cysteine is the main complex with amino acids with antineoplastic activity and is organovanadium with better profile in combination therapy with anticancer agents [46,47,180,181,188]. However, the biotransformation of this type of complexes and the intimate molecular mechanisms by which these biological effects are exerted are unknown. Recently, Basu et al. (2017) have established some aspects of the cellular and molecular mechanism of the vanadium(III)-L-cysteine complex on a murine model of breast cancer, where this complex showed decreased tumor volume and was able to activate proapoptotic signaling, which involves the

dissipation of the mitochondrial membrane potential, induction of Bax, release of mitochondrial cytochrome *c*, activation of caspases 3 and 9, induction of p53 expression and DNA fragmentation, as well as inhibition of antiapoptotic protein Bcl-2 [188].

The treatment with V(III)-L-cysteine complex as prepared in [48] increases the antineoplastic effect of cyclophosphamide on mice with implanted breast cancer cells and also increases the effects of cisplatin on human breast cancer and lung cancer cell lines, MCF-7 and NCI-H520, respectively [188,214]. Antitumor and chemosensitizing effects of this complex are accompanied by an important antiangiogenic and antimetastatic activity, V(III)-L-cysteine decreases levels of vascular endothelial growth factor A (VEGF-A) and matrix metalloproteinase 9 (MMP-9), inducers of angiogenesis and metastasis respectively [188]. The inhibition or reduction of metalloproteinases *in vitro* suggests that this mechanism may be linked to the antimetastatic activity observed *in vivo* in the work of Papaioannou (2004) [48]. The complexes of vanadium with cysteine (including V(IV)O-L-cysteine methyl ester), are able to protect non-neoplastic cells from cyclophosphamide-induced toxicity, producing a reversal of increases ROS, nitric oxide and transaminases, as well as by enhancing the activity of antioxidant enzymes: catalase, superoxide dismutase and glutathione peroxidase in the liver of experimental animals [175,188]. In addition, the chemoprotection of V(IV)O-L-cysteine methyl ester against cisplatin or cyclophosphamide-induced toxicity, has been established in bone marrow cells and in lymphocytes, with a decrease in the DNA fragmentation, apoptosis and chromosomal aberrations [215,216]. Currently, it is known that these cysteine complexes exhibit protective effects on renal damage cisplatin-induced in mice, where the oxidative stress reduction and antioxidant status restoring play a critical role [176]. Fig. 20 shows a summary of the possible mechanism of action for the antitumor activity of V(III)-L-cysteine complex.

The nature of the ligands may play an important role in the selectivity, potency and type of biological activity exerted by vanadium complexes. In the case of amino acids as ligands, they may have an additional effect of interest, such as L-cysteine which is a known chemoprotector [219,220], or other amino acids that have been reported to produce or contribute to the antitumor effect [220]. An excellent example is represented by glycine, which has been studied for its anti-inflammatory and cytoprotective properties, Bruns et al. (2014) show that glycine inhibits angiogenesis in human hepatocellular carcinoma cells culture, through decrease VEGF-A expression [221,222]. However, some vanadium complexes with glycine or glycinate have shown antineoplastic activity, such as vanadium N-(2-hydroxy acetophenone) glycinate, which has shown an important cytotoxic effect on human T-cell acute lymphoblastic leukemia, human colorectal carcinoma, human breast cancer, and human astrocytoma cell lines, without showing toxic effect on normal fibroblast cell line mice. Likewise, in mice with cancer induced by Ehrlich cell ascites carcinoma and Sarcoma 180 cell transplantation, this complex was able to decrease tumor survival. Although the toxicity of vanadium is well known, this vanadium complex with glycine presented low toxicity in experimental animals [223]. The differential toxicity of vanadium species, complexes and biotransformation products must be studied more thoroughly to define the mechanistic toxicology of vanadium compounds. Recently, it was shown on human colorectal carcinoma cells, that vanadium N-(2-hydroxy acetophenone) glycinate induces apoptosis by mechanisms that include mitochondrial damage, DNA damage and increased ROS [187].

The selectivity of vanadium compounds on neoplastic cells vs. normal cells has been described. However, in normal hepatic cells cultured with sodium metavanadate, bis(acetylacetonato)oxovanadium(IV) or bis(maltolato)oxovanadium(IV), ROS are increased compared to HepG2 hepatoma cells [217,224], possibly this type of vanadium compounds may not be able to mitigate the toxic effects of anti-cancer agents on healthy cells. This suggests that cysteine-containing compounds might be promising vanadium complexes with chemosensitizing and chemoprotective function and are promising for their use in combination therapy.

Another important mechanism, of some vanadium compounds to also exhibit antiproliferative and cytotoxic effects, might be through interactions with DNA [24,179,225,226] either by interacting

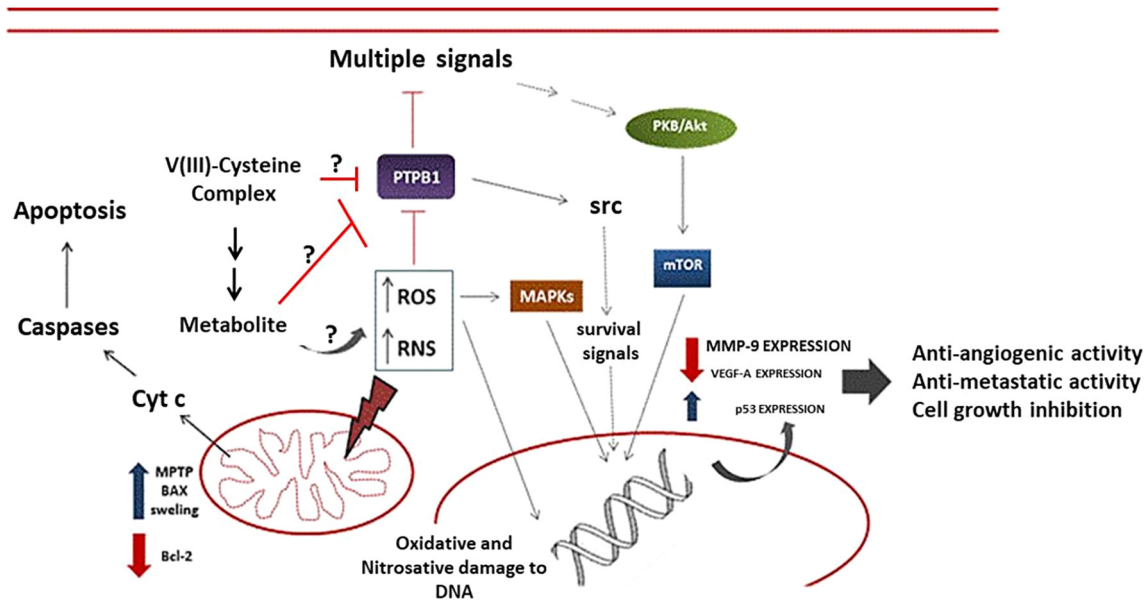


Fig. 20. Representation of cellular targets involved in the antitumor mechanism of the Vanadium(III)-L-cysteine complex or its possible metabolites. Vanadium complex induces apoptosis of cancer cell through change of mitochondrial function, proapoptotic factor release from mitochondria and alteration of genetic expression. PTPB1: protein-tyrosine phosphatase 1B, mTOR: mammalian target of rapamycin, Akt: serine-threonine protein kinase B, ROS: reactive oxygen species, RNS: reactive nitrogen species, MAPKs: mitogen-activated protein kinases, MPTP: mitochondrial permeability transition pore, Bax: Bcl-2-associated X protein, Bcl-2: B-cell lymphoma 2, Cyt c: cytochrome *c*, Src: homology region 2 domain-containing phosphatase-1, MMP-9: matrix metalloproteinase-9, VEGF-A: vascular endothelial growth factor A. Based on Refs. [188,189,217,218].

with DNA's nucleotide phosphate groups as propose in the case of vanadocene complexes [183,227] or through the direct intercalation with DNA such as vanadium complex of 4-pyridinecarboxylic acid, 2-[(2-hydroxy)-1-naphthalenylene] hydrazide and 1,10-phenanthroline (VO-(Pahn)phen), resulting in increased ROS and oxidative DNA damage [191,198,228]. Some vanadecene complexes with non-essential amino acids have been reported in the literature [183,229], such as proline and glycine; however, it is unknown whether this class of complexes produces antitumor effects or whether it is capable of interacting with the genetic material.

It is also important to mention that, the drug-receptor interaction in biological systems, may be due to the reversible or irreversible interaction of the vanadium compound with the amino acids of proteins. In the case of vanadium haloperoxidases, the complex is formed between vanadium and histidine. For example, vanadate(V) ions are coordinated through a histidine residue of *A. nodosum* bromoperoxidases. For this reason, many vanadium complexes are reported in the literature in order to simulate the mode of coordination with the histidine residue [230,231].

Some vanadium compounds have also been tested against parasitic diseases. The therapeutical target of these compounds are against *Trypanosoma cruzi, Leishmania* spp. and *Entamoeba histolytica*, that cause trypanosomiasis, leishmaniasis and amoebiasis, respectively [16]. There are only a few available drugs in the market against these parasites, presenting as well some toxic side effects. Parasites responsible of these diseases develop rapid resistance to active drugs and for this reason it is important to develop newer therapeutic arsenal against these diseases [16,232,233]. The inclusion of a metal center to these anti-parasitic drugs improves its pharmacological properties, the formation of metal complexes serves to modulate the activity of the possible drug [16]. These strategies were used by Sanofi-Aventis to develop Ferroquine, the first organometallic drug with potential anti-malarial activity [16].

Polypyridyl ligands have been relevant in the search for new therapeutic agents against parasitic diseases [234–240]. The antitrypanosomal and antitumor activity of ligands type N,N,O [2-(benzothiazol-2-yl-hydrazonomethylphenol (HL1) and 2-(benzothiazol-2-)-yl-hydrazonomethyl)-6-methoxyphenol (HL2)] have been evaluated by complex formation $[V^{V}O_2(L1)]$, $[V^{V}O_2(L2)]$, $[V^{IV}O(L1\text{-}H)(phen))]$, demonstrating that all these compounds have antiproliferative activity in μM range, with high cytotoxic activity [234]. The main vanadium therapeutic agents with anti-parasitic properties are mainly composed of $[V^{IV}O(SO_4)(H_2O)_2(NN)]$ and $[V^{IV}O(L\text{-}2H)(NN)]$ type compounds and mainly possess V(IV)O with polypyridyl derivatives of 1,10-phenanthroline (NN) [2,24,235], where the key mechanism of action of vanadium compounds with anti-parasitic activity may result either from intercalation of the phen moiety of the complex in DNA, or inhibition of some specific parasite enzymes by the metal center, or some other mechanism involving synergistic effects of the metal and phen ligand [16,235].

In vitro studies of anti-*T. cruzi* activity, have demonstrated that they depend mainly on the nature of the ligand, with the following order of increasing activity being found $[V^{IV}O(L\text{-}2H)(bipy)]$ ‹ $[V^{IV}O(L\text{-}2H)(dppz)]$ ‹ $[V^{IV}O(L\text{-}2H)(phen)]$ ‹ $[V^{IV}O(L\text{-}2H)(epoxyphen)]$ ‹ $[V^{IV}O(L\text{-}2H)(aminophen)]$ [2]. The chemical structure of polypyridyl ligands capable of intercalating with DNA is shown in Fig. 21.

Chagas disease (American Trypanosomiasis) has been evaluated with compounds $[V^{IV}O(L^2\text{-}2H)(L^1)]$ wherein L^1 represents a bidentate polypyridyl ligand; whereas L^2 corresponds to a salicylaldehyde semicarbazone derivative [236]. The spectroscopic characterization showed that the ligand semicarbazone occupies equatorial positions around a distorted octahedral geometry, where the biological activity of the compound could be due to interactions with DNA biomolecule [236]. Fernández et al. synthesized a novel series of complexes $[V^{V}O_2(L\text{-}2H)]$ and $[V^{IV}O(L\text{-}2H)(NN)]$ including bipy or dppz (dipyrido[3,2-a: 2′,3′-c]phenazine) as co-ligand, where NN represents polypyridyl DNA intercalator [238]. The $[V^{IV}O(L\text{-}2H)(dppz)]$ complex proved to be 15 times more toxic than the others to *T. cruzi*, demonstrating as well, good *in vitro* activity against *T. brucei brucei* [238]. Scalese et al. evaluated new prospects for Chagas' disease based on vanadium drugs, synthesizing a series of compounds $[V^{IV}O(L\text{-}2H)(NN)]$ using as ligands 3,4,7,8-tetramethyl-1,10-phenanthroline (tmp) and different salicylaldehyde semicarbazone derivatives (L1–L7) [239]. The most active compounds showed significant *in vitro* activity against *T. cruzi* than the reference drug Nifurtimox, whereas the Molecular Docking studies showed that the biological activity presented cannot be explained only by a DNA intercaling mechanism of the metallo drug [239].

On the other hand, a series of compounds formulated as [VO(L-2H)(phen)] were evaluated on *L. panamensis*, *L. chagas* promastigotes and intracellular amastigotes [240]. Only [VO(L1-2H)(phen)] (L1 = 2-hydroxybenzaldehyde semicarbazone) and [VO(L3-2H)(phen)] (L3 = 2-hydroxy-3-methoxybenzaldehyde semicarbazone) demonstrated to possess anti-leishmanial activity, exhibiting greater activity against the promastigote form of the parasite, obtaining values of IC_{50} = 2.74 and 2.75 μM quite low for *L. panamensis* promastigotes, and IC_{50} =19.52 and 20.75 μM for intracellular amastigotes of *L. panamensis* and presenting as well, low toxicity in mammalian THP-1 cells [240].

Decavanadate compounds ($(NH_4)_6V_{10}O_{28}{\cdot}6H_2O$) have also shown inhibitory activity *in vitro* on *L. tarentolae* promastigotes that influence the growth of *Leishmania* spp. probably due to the inhibition of phosphatases [241]. It has been suggested that the efficiency of certain vanadium compounds with anti-parasitic activity can be due to their easy consumption by the cells and their efficiency towards certain targets. Phen molecules, for example, might be te relevant drug, its activity is being improved by the metal center. DNA intercalator capabilities or some other characteristics, might be the relevant factor. Additionally, vanadium compounds may undergo to ligand exchange reactions producing newer species that may not contain the original ligand [2].

Another promising therapeutic application of vanadium compounds refers to their antiviral action. Vanadium-thiourea and vanadium polyoxotungstene-substituted compounds have shown potent anti-HIV activity towards infected T cells [242,243]. In particular, $[(V^{IV}O)_2(V^{V}O)(SbW_9O_{33})_2]$ have exhibited antiviral activity

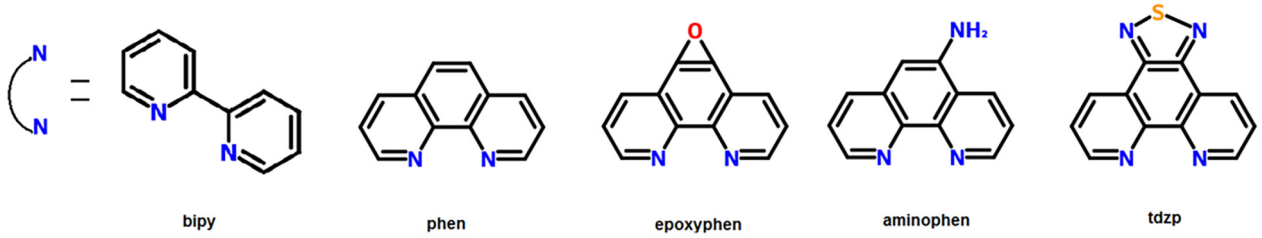


Fig. 21. Chemical structure of polypyridine ligands capable of intercalating with DNA Modified from Ref. [2].

not only against HIV-1 but also have shown *in vitro* activity against of influenza, dengue, fever and severe acute respiratory syndrome (SARS) [2]. This compound decomposes in vanadate(V) and tungsten(VI), which seem to be the true active species [2]. V(IV)O-porphyrin complexes have also shown inhibitory effects on HIV-1 when were evaluated on Hut/CCR5 replication cells, where all these complexes have showed anti-viral activities compared to the vehicle control [244,245]. The effect of porphyrin on the complex, is to stabilize the metal center, which is unstable at physiological pH, additionally, it makes the complex oxidovanadium (IV)-porphyrins more soluble in aqueous media and avoids demetallization reactions [245]. One of the main goals of anti-HIV drugs is the reversal of transcriptase; the oxidovanadium(IV)-porphyrin compounds have reversed transcriptase after 30 min of incubation, when binding CD4 protein with an energy of -138.61 kcal mol^{-1} [244] in this way preventing virus from entering the host cell [2,245]. The activity of V(IV)O-porphyrin complex has been measured using Elisa method [244]. The chemical structures of the oxidovanadium(IV)-porphyrins complex is shown in Fig. 22.

Current efforts are made to improve the biotransformation of the possible metallodrug from the gastrointestinal tract to the target cells, since many of the candidate compounds are unstable at the gastrointestinal pH and only less than 2% of vanadium is absorbed in an oral dose. In addition, researches are focused to reduce the gastric irritation, to improve the blood transport and to study the possible inflammatory reactions at the cellular level, since vanadium compounds increase the production of ROS and reactive nitrogen species (RNS) by multiple mechanisms [24,96,246].

In the blood plasma, blood-proteins such as apotransferrin (apoTf) and albumin (HSA), can interact with, for example, vanadate anions(V), cationic species $(V^{IV}O)^{2+}$, neutral or charged $V^{IV}OL$ species serving as transporters [96]. It is important to note that, for therapeutical purposes, it is not essential to know the oxidation state of vanadium transported in the blood plasma, what is really

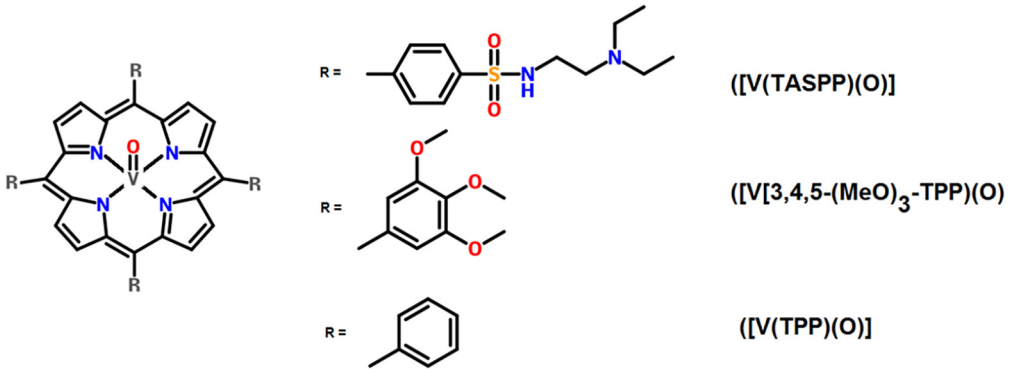


Fig. 22. Chemical structure of V(IV)O-porphyrin compounds. Modified from Ref. [144].

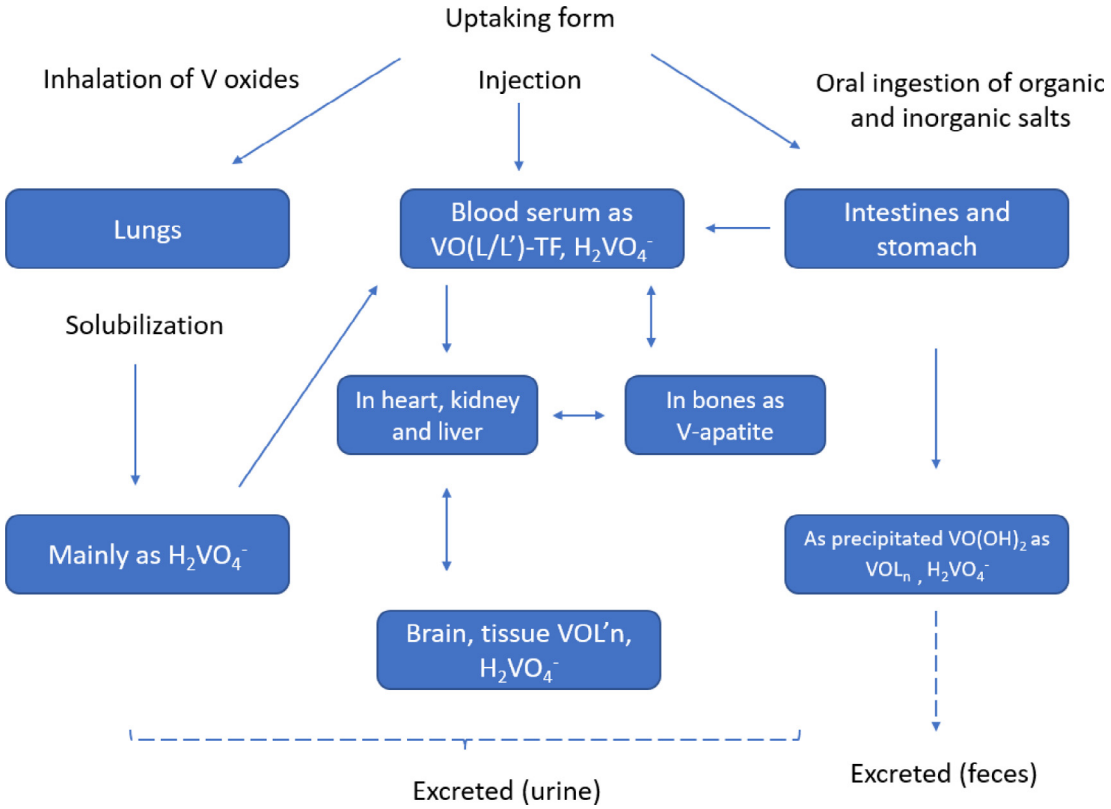


Fig. 23. Schematic representation of global vanadium speciation in the body. In blood and in each organ speciation of vanadium occurs. Modified from Ref. [2].

important is to know the biodistribution of vanadium, although the knowledge of the form of the metal ion is fundamental for the targeted cells [2,96].

When vanadium enters in either form in the bloodstream, it is bound to plasma proteins allowing its uptake and distribution to internal tissues such as heart, liver and kidney, and to external tissues such as the brain, muscles and adipose tissue. During the first 24 h, the vanadium content in blood is reduced by about 30% [5]. Whereas within the erythrocytes the VO_2^+ is reduced to VO^{2+}, which can be partially released as a genuine drug capable of binding to hemoglobin (Hb), or can be coordinated as an intact complex to histidine residues as was suggested with the VO(maltol)Hb complex [69]. An analogous situation occurs with VO(picolinate)$_2$ [247]. Fig. 23, can be seen the different metabolizing pathways of vanadium in the organism.

Vanadium-based drugs may be consumed orally by encapsulation, avoiding therefore, potential alterations of the compound due to the strongly acidic conditions in the stomach [2,248]. This important result was reported by Sakurai et al. [249] who evaluated different forms of oral application of oxidovanadium complexes in order to replace insulin injections in insulin-dependent patients. Two different methods of oral administration of vanadyl complexes were evaluated, including complexation and capsulation. The pharmacokinetic studies showed that enteric-coated capsules increase the bioavailability of active oxidovanadium species [249]. Other ways of vanadium incorporation is through the application of intravenous injections, by inhalation, etc. Vanadium compounds, once they enter into contact with the blood plasma and its components, suffer a series of ligand exchange reactions. Such compounds are mainly components of low molecular mass such as citrate and lactate or with high molecular weight ligands such as transferrin, albumin and immunoglobulin G., where changes on the oxidation state of the metal may also occur [2,51,52,67,69,82,96], for example, reducing agents such as ascorbate, glutathione and NADH can reduce V(V) to V(IV) or even V (III) [2,5], while oxidizing agents such as NAD^+, O_2, O_2^{2-} and O^{2-} can convert V(IV) to V(V) [24].

5. Perspectives and conclusions

As was observed throughout this review, the chemistry of vanadium and especially its interactions with amino acids has been well studied, demonstrating the importance of this metal at industrial, biochemical and pharmacological level. From the bioinorganic point of vanadium, has been shown to be essential for the correct biological functioning of a limited number of organisms and enzymes, such as vanadium nitrogenases and vanadate-dependent haloperoxidases. The vanadium compounds also showed potential applications in the medical field, especially regarding to the treatment of diabetes and cancer, where the vanadium complexes with L-glutamate and with L-cysteine respectively, have established an interesting window for discovery of new drugs. Additionally, several vanadium complexes with essential and non-essential amino acids have shown a better safety profile in preclinical studies, suggesting that these compounds may be less toxic than inorganic vanadium compounds. However, the efficacy and safety of vanadium complexes as potential metallodrugs should be investigated more thoroughly. The authors of the present manuscript consider that the research area focused on vanadium chemistry will continue its development with the obtainment of new compounds with direct impact on the inorganic medicinal chemistry. The findings reported in the literature suggest that the use of amino acids and derivatives as vanadium ligands is highly promising, not only because they are biomolecules of high biochemical, physiological and nutritional value, but also because of the beneficial and therapeutic potential exerted by an important number of them.

6. Dedicatory

The authors of the present article dedicate the same to the memory of Professor Dr. Felipe Brito (1930–2017), considered the father of solution chemistry in Venezuela, for all his contributions in the development of Chemistry throughout his >50 years of scientific career in our country.

Acknowledgements

To the Deanship of Investigation and Development of the Universidad Simón Bolívar and to the Pharmaceutical Research Institute of the Faculty of Pharmacy of the Universidad Central de Venezuela for the economic financing to carry out the present scientific investigation.

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