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Werner E.G. Müller
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Biomedical Inorganic Polymers

Bioactivity and Applications of Natural and Synthetic Polymeric Inorganic Molecules

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Preface

Inorganic polymers are a relatively small group of molecules as compared to the large group of organic polymers. They comprise both short-chain polymers and long-chain polymers with one type of atom or two or more types of atoms in the polymer backbone. Examples are homochain polymers, e.g., polysilanes, polygermanes, polystannanes, and polysulfides, and heterochain polymers, e.g., polysilazanes, polyphosphazenes, polyborazylenes, and polythiazyls. Many of these polymers are not soluble or not stable in water, but some of them can be formed in aqueous solution even by enzymatic reactions, for example, inorganic polyphosphates and polysilicates. Previous studies on the biological effects of polymeric compounds mainly focused on organic polymers. Recent results revealed that also inorganic polymers may possess biological activity. Much effort on the study of inorganic polymers focuses on the application of such polymers in nanotechnology or, in the field of biomedicine, on their application in drug delivery, e.g., of silica. Inorganic polymers which are biologically active can be formed by living organisms, e.g., arsenicin A, a polyarsenic compound isolated from a marine sponge, or polymeric silicate ("biosilica") formed by diatoms and siliceous sponges, or polyphosphates that have been identified in numerous organisms, from bacteria and yeast to plants and humans. These polymers often have multiple functions, for example, inorganic polyphosphates can be used as antimicrobial compounds, as a source of energy-rich phosphate, as a modulator of gene expression, as a chelator for metal cations, or in mineralization of bone tissue and in blood coagulation and fibrinolysis, and silica as skeletal element with unique property combinations (mechanical stability and light transmission). The research on these compounds is currently in a rapid development. Several European consortia are concerned with the investigation and development of products made of such polymers, in particular polyphosphates and polymeric silica. In this volume of the series "Progress in Molecular and Subcellular Biology" recent developments in the state of knowledge on selected inorganic polymers are summarized. These polymers

include poly(arsenic) compounds, inorganic polyphosphates, polyoxometalates, polyvanadates, and polysilicates (biosilica). The biocompatibility, bioactivity, and stability of the latter polymers even allow a possible application in rapid prototyping procedures for the production of customized implants in surgery and dentistry.

Mainz, Germany

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Chapter 1
Chemical, Biochemical, and Biological Behaviors of Vanadate and Its Oligomers

Xiao-Gai Yang and Kui Wang

Contents

Abstract Vanadate is widely used as an inhibitor of protein tyrosine phosphatases (PTPase) and is routinely applied in cell lysis buffers or immunoprecipitations of phosphotyrosyl proteins. Additionally, vanadate has been extensively studied for its antidiabetic and anticancer effects. In most studies, orthovanadate or metavanadate was used as the starting compound, whereas these "vanadate" solutions may contain more or less oligomerized species. Whether and how different species of vanadium compounds formed in the biological media exert specific biological effect is still a

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mystery. In the present commentary, we focus on the chemical, biochemical, and biological behaviors of vanadate. On the basis of species formation of vanadate in chemical and biological systems, we compared the biological effects and working mechanism of monovanadate with that of its oligomers, especially the decamer. We propose that different oligomers may exert a specific biological effect, which depends on their structures and the context of the cell types, by different modes of action.

Since the 1980s, vanadium compounds have been considered as a new class of metal-based drugs. Their diverse biological effects have attracted considerable interest. Studies have ranged from elucidation of the underlying mechanisms to the synthesis and screening of new vanadium compounds, from speciation analysis in solution to their fundamental biochemical reactions, from in vitro study to animal model and preclinical study. Multiple reviews have covered these topics in recent years (Chen and Owens 2008; Crans et al. 2004; Evangelou 2002; Faneca et al. 2009; Goc 2006; Kiss et al. 2008; Scior et al. 2005; Thompson and Orvig 2006). However, whether and how different species of vanadium compounds formed in the biological media exert specific biological effect is still a mystery. In the present commentary, we focus on the biological effects of vanadate, which is the classical and the most widely studied vanadium compound. In view of its species formation in chemical, biochemical, and biological systems, we will extend the discussions to the effects of various species and provide clues to the question stated as above.

1.1 The Speciation of Vanadate in the Chemical, Biochemical, and Biological System

There are three kinds of reactions to dominate vanadate aqueous chemistry: self-condensation reactions, coordination reactions, and electron transfer reactions. These reactions are influenced by pH and concentration of vanadate.

1.1.1 Self-Condensation Reactions of Vanadate

The formation of isopolyoxometalate ions, $[M_xO_y]^n$, via oxygen-bridged M–(O)–M is the general behavior of early transition metals:

$$x\mathrm{MO_4}^{a-} + 2y\mathrm{H}^+ \rightleftharpoons \left[\mathrm{M}_x\mathrm{O}_{4x-y}\right]^{n-} + y\mathrm{H_2O}$$

The oligomerization from monomer to decamer comprises a cascade of protonation coupled with condensation (dehydration). The reverse reactions, hydrolysis of

the oligomers, will lead to deoligomerization (decomposition). During this process, a series of intermediate oligomers, i.e., V_2, V_3, V_4, V_5, and several others may coexist in the solution. The distribution of these oligomers depends on pH level and the initial concentration of vanadate:

$$2VO_4^{3-} + 2H^+ \rightleftharpoons 2[HVO_4]^{2-} \rightleftharpoons [V_2O_7]^{4-} + H_2O$$
$$2VO_4^{3-} + 4H^+ \rightleftharpoons 2[H_2VO_4]^{2-} \rightleftharpoons [HV_2O_7]^{3-} + H^+ + H_2O$$
$$3[H_2VO_4]^{2-} \rightleftharpoons [V_3O_9]^{3-} + 3H_2O$$
$$4[H_2VO_4]^{2-} \rightleftharpoons [V_4O_{12}]^{3-} + 4H_2O$$
$$10[H_2VO_4]^{2-} + 4H^+ \rightleftharpoons [V_{10}O_{28}]^{6-} + 12H_2O$$
$$[V_{10}O_{28}]^{6-} + H^+ \rightleftharpoons [HV_{10}O_{28}]^{5-}$$
$$[HV_{10}O_{28}]^{5-} + H^+ \rightleftharpoons [H_2V_{10}O_{28}]^{4-}$$

For example, in the range of pH 7–9, the main species in dilute vanadate solution are V_1, V_2, V_4, and V_5 (Faneca et al. 2009; Heath and Howarth 1981; Larson 1995; Tracey et al. 1995), and the presence of V_3 and V_4 was confirmed later by ^{51}V and ^{7}O NMR and potentiometry (Andersson et al. 1996), while at pH 2–6 and in concentrated solutions, the decamer (V_{10}) and its protonated species become predominant (Aureliano and Gândara 2005; Crans and Tracey 1998; Faneca et al. 2009). By comparing the ^{51}V NMR of sodium metavanadate, Iannuzzi et al. noted that at pH 8.71, in 100 mM solution of metavanadate, the main species are the V_1, V_2, V_4, and V_5, while in 1–5 mM solution,V_1 is predominant (Iannuzzi et al. 2006).

The foregoing discussions are based on equilibrium state. In fact, the solutions used are in metastable state and the species may be transformed during cell incubation. The formation of the lower oligomers V_2, V_4, and V_5 from monomer is rapid; hence the solution of metavanadate or orthovanadate contains small amounts of V_2, V_4, and V_5 inevitably (Crans et al. 1990). However, formation and decomposition of V_{10} are slow in neutral solution under ambient temperature (Aureliano and Gândara 2005; Druskovich and Kepert 1975). The metavanadate or orthovanadate solution turns to yellow color slowly due to the formation of V_{10}. Conversely, the solution prepared from solid decavanadate decomposes gradually on standing (Rubinson 1981).

Since oligomerization is initiated by protonation of vanadate anions, acidification favors oligomer formation. Kalyani et al. followed the oligomerization of 30 mM ammonium metavanadate solutions with varied pH by ^{51}V NMR spectra (Kalyani and Ramasarma 1992). By the variation of NMR peaks, they found at pH 7.0, V_4 is the major species accompanied by traces of V_1, V_2, and V_5, but none of V_{10}. After incubation at pH 5.0 for 4 weeks at room temperature, all vanadium was in the form of V_{10}. On this ground, the decavanadate solution was suggested to be prepared by acidifying and then re-neutralizing the metavanadate solution subsequently before adding to the buffered culture media. However, there are still V_2, V_4, and V_5 present in this process (Iannuzzi et al. 2006; Turner et al. 2011). A kinetic

study by means of UV–visible spectroscopy showed that the decomposition of V_{10} at 25 °C in the saline solution fits to a first-order kinetic process, with half-life of 16 h (Soares et al. 2007b). Since the deoligomerization is due to hydrolysis of the oligomers, dilution and high pH favor the decomposition.

As stated above, in biological studies, the solutions used are in metastable state and the species may undergo transformation during cell incubation. For this sake, studies at cellular level are influenced by how to prepare the solutions and how to run the experiments. In nonequilibrium state, the speciation at a particular time point depends on the rate of oligomerization and deoligomerization, which is determined by pH level and the initial concentration of vanadate.

In addition to the chemical consideration, the compartmentalization and dynamic state of the living cells may create dynamic intracellular microenvironments and thus alter the speciation of vanadate.

As is well known, the establishment and maintenance of an appropriate pH inside individual cellular compartment is critical for cellular functions. In eukaryotes, cytosolic pH was maintained roughly at pH ~ 7.4, but actually it varies in the range of pH 5–8 in different organelles as shown in Fig. 1.1. In the course of endocytic pathway, the pH value decreases successively in early endosomes, late endosomes, and lysosomes (Casey et al. 2010; Weisz 2003). The pH value of the intermembrane space is also generally regarded as significantly lower than that of the cytosol (Porcelli et al. 2005). Furthermore, several pathological conditions cause variation of intracellular pH, such as metabolic acidosis (Adrogue 2006; Kraut and Madias 2010). The altered pH was reported in transformed cells as well. It is observed that tumor cells typically have elevated organelle pH (Weisz 2003). Thus, it is conceivable that pH variations in a certain cellular compartment would cause speciation changes. Decavanadate formation would be possible in acidic vesicles, in muscle cells upon acidification, and even in intermembrane space of mitochondria (Aureliano and Crans 2009; Aureliano et al. 2002). In the local acidic environment, a series of oligomers formation of vanadate would also be more favored (Iannuzzi et al. 2006).

1.1.2 Coordination Reactions of Vanadate

Vanadate can react with a variety of mono- and polydentate ligands. Several reviews and monographs have covered this topic (Crans et al. 2004; Jakusch et al. 2011; Rehder 2008; Tracey et al. 2007). Given that vanadate has been dogmatically recognized as a structural and electronic analogue of phosphate, the two classes of vanadium compounds, vanadate esters and vanadate anhydrides, have been given more attention. These types of compounds are commonly used to explain the inhibitory and stimulatory effects of vanadate on ribonucleases, phosphatases, ATPase, some phosphorylases, and glucose dehydrogenase (Crans et al. 2004). Consequently, on the basis of well-characterized chemical model systems in test tubes, numerous extrapolations have been drawn to elucidate the mechanism concerning the in vivo effects of vanadate. However, currently it is

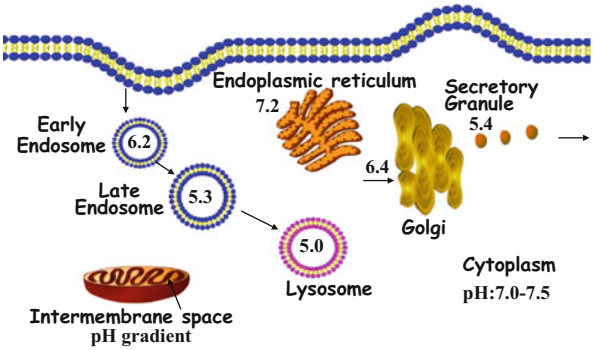

Fig. 1.1 A *cartoon diagram* showing some cellular organelles with typical pH values. Data adapted from Grabe and Oster (2001)

difficult to verify these reactions observed in test tubes occurred in vivo. Therefore, in this section, we focus on the coordination chemistry of vanadate in the scenario of biological systems.

It is found that vanadate, after oral uptake, in addition to the portions excreted with the feces, is mainly bound to serum proteins such as albumins and transferrin with a small amount of amino acids and other ligands (Jakusch et al. 2011; Zorzano et al. 2009). It also subjects to redox reactions (discussed in Sect. 1.1.3) and is partially reduced to vanadyl (VO^{2+}) (Macara et al. 1980).

Most portions of vanadate and vanadyl ions are bound to transferrin (Chasteen et al. 1986; Kiss et al. 2008; Sanna et al. 2009). Like Fe^{3+}, two VO^{2+} ions bind to the two iron-binding sites by the aid of HCO_3^- to stabilize the binding (Cannon and Chasteen 1975). V(V) species, as suggested by Kiss et al. (2012), bind to transferrin in form of VO_2^+ without requiring bicarbonate (Harris and Carrano 1984; Heinemann et al. 2002; Jakusch et al. 2009; Saponja and Vogel 1996).

VO^{2+} and VO_3^- are shown to bind to serum albumin as well (Ahmed-Ouameur et al. 2006; Ferrer et al. 2008). Human serum albumin binds VO^{2+} stronger than VO_3^-, with two binding sites, one strong and one weak, whereas VO_3^- binds by only one weak site (Purcell et al. 2001).

Computer modeling calculations were also used to understand the speciation of vanadate in serum. Based on the formation constants of twenty vanadate complexes with glycine, lactate, phosphate, citrate, histidine, albumin, transferrin, and also the ligands maltol and picolinate and the individual concentration, Pettersson's group calculated the distribution of these species in blood. The results illustrated that if the proteins were excluded, most of vanadate is present as $H_2VO_4^-$ and HVO_4^{2-}, ~12 % bound to glycine, and ~1–2 % to other constituents (mostly phosphate). If the proteins were included, more than 98% of the total vanadium is bound to transferrin (Gorzsás et al. 2006). This is confirmed by later experimental results (Jakusch et al. 2009, 2011), but some other species were recognized at low levels (Gorzsás et al. 2006).

In addition to the binding properties of monovanadate as stated above, more and more studies demonstrate that their oligomers should not be disregarded. In fact, the presence of a small portion of V_2, V_4, and V_5 may contribute to the protein binding.

Table 1.1 Redox potentials for inorganic vanadium species and selected physiological systems versus the normal hydrogen electrode (NHE), adapted from Rehder (2008)

Redox couples	E^0	$E^{pH=7}$
VO^{2+}/V^{3+}	+0.359	−0.462
$H_2VO_4^-/VO^{2+}$	+1.31	−0.34
VO_2^+/VO^{2+}	+1.016	+0.19
O_2/H_2O_2	+0.695	+0.295
½ O_2/H_2O	+1.23	+0.815

Another noteworthy fact is that the V_{10} is found to bind to albumin, leading to the formation of insoluble particles (Ashraf et al. 1995). The V_{10} binding to proteins is expected to be strong due to its unique structure (*vide infra*), and the binding may also prevent its decomposition (Soares et al. 2003, 2006).

Moreover, ligands that stabilize a metal complex in a lower oxidation state can promote the reduction of oxidized form. Therefore, the coordination reactions of vanadate can also affect the reducing tendency of vanadate in a biological system.

1.1.3 Electron Transfer Reactions of Vanadate

Vanadium shows a range of oxidation states (−1, 0, +1, +2, +3, +4, and +5). However, only three oxidation states, V(III), V(IV), and V(V), are relevant for biological systems (Rehder 2008).

Based on the standard reduction potentials (E^0) for inorganic vanadium species, there would be a lot of potent biogenic reducing agents capable of converting V (V) to V(IV) in acid solution (Baran 2008). However, the redox potentials of all the vanadium redox couples decrease dramatically with increasing pH. As seen in Table 1.1, under physiological system, in neutral solution (pH = 7) the oxidative ability of V(V) declined rapidly, so $H_2VO_4^-$ is less easily reduced.

However, in biological systems, as stated in Sect. 1.2, the reducing tendency of a mild reductant may be elevated by stabilizing V(IV) through complexation with biogenic ligands such as GSH and ATP, which are present in millimolar concentration in the cytosol.

As shown in Fig. 1.2, when vanadate encounters the cells, the membrane molecules stand in the frontier against the attacking vanadates. It is shown that vanadate is reduced to V(IV) by membrane-bound protein thiols during transport across the membrane (Yang et al. 2003; Zhang et al. 1997a). Recently, a two-electron transfer process in the hydrophobic environment in the membrane is proposed, i.e., the two-electron V(V)/V(III) redox chemistry may occur in the membrane (Crans et al. 2011).

In addition, vanadate may also stimulate nonenzymatic vanadate-dependent oxidation of NAD(P)H by using xanthine-oxidase reaction as a source of superoxide (Kalyani et al. 1992; Khandke et al. 1986; Liochev and Fridovich 1986), which will possibly lead to the formation of ROS or RONS. But it is still uncertain whether nonenzymatic vanadate-dependent NADH oxidation is actually coupled with NADPH oxidase-mediated superoxide production.

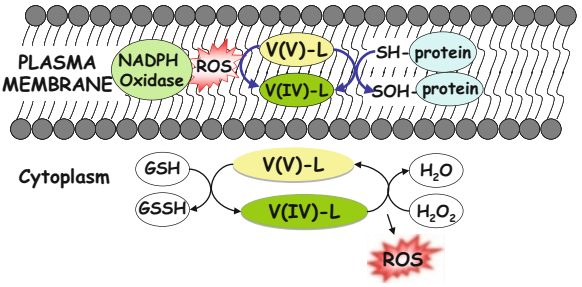

Fig. 1.2 Possible events happened when vanadate across membrane

In the cytosol, V(V) was found to be reduced to V(IV) by cytoplasmic glutathione(GSH) in a nonenzymatic way (Macara et al. 1980). The V(V) and V(IV) in the cytoplasm may interact with biomolecules in the cytoplasm and thus may result in the variation of redox potentials of V(V)/V(IV). Crans et al. also addressed that in V(V)-thiol redox reactions, the electron transfer reaction is promoted by the complexation of vanadium(IV)/(V) to the thiols (Crans et al. 2010).

In summary, the speciation of vanadate is determined by pH, vanadium concentration, and various biomolecules as ligands or reductants present in the intra- and extracellular fluids. Especially, the compartmentalization of organelles makes the vanadate speciation in biological system extremely complicated.

Vanadate is widely used as an inhibitor of protein tyrosine phosphatases (PTPase) (Gordon 1991) and is routinely applied in cell lysis buffers or immunoprecipitations of phosphotyrosyl protein. Additionally, vanadate has been extensively studied for its antidiabetic and anticancer effects. In most studies, orthovanadate or metavanadate was used as the starting compound, whereas these "vanadate" solutions may contain more or less oligomerized species, but the effects were usually attributed to monovanadate. This is reasonable in many cases, because pH was kept neutral and the concentration of vanadate was very low. However, as indicated above, in the local acidic environment, the formation of a series of oligomers would be favored. Additionally, by recent studies, the vanadate oligomers may be more reactive and may cause effects different from monomers. Thus in the following paragraphs, a brief account will be given to generalize the results obtained from the studies both with vanadate monomers and its oligomers.

1.2 Chemical and Biochemical Basis Underlying the Biological Effects of *Vanadate Monomers*

The mechanisms underlying the biological effects of vanadate are generally attributed to its two chemical properties: one is based on the structural analogy of vanadate to phosphate, and one is on the basis of the electron transfer reaction between V(IV) and V(V) in biological media.

1.2.1 Vanadate Ion as Phosphate Analogue

The biological effects of a nonessential metal ion can be considered as the manifestation of its similarity to corresponding essential ions (Wang 1997). Vanadate ion, in the form of VO_4^{3-}, is analogous to PO_4^{3-} by its structural and electronic similarity. In the phosphorylation reaction, a phosphate ion is transferred from the donor to the acceptor via a pentacoordinated trigonal bipyramidal transition state. Vanadate acts as a competitive inhibitor of the phosphatase by forming an analogue to mimic the substrate or mimic the intermediate complex between the donor and acceptor (Brandão et al. 2010; Davies and Hol 2004). Thus, it affects a great variety of phosphorylation-related physiological processes. Among them, the inhibition of protein tyrosine phosphatase (PTP), especially PTP1B, has been well studied and the results indicated that VO_4^{3-} inhibits PTP1B competitively (Huyer et al. 1997). X-ray crystal structures of vanadate complexes with PTP (Zhang et al. 1997b), acid phosphatases (Felts et al. 2006), and alkaline phosphatases (Holtz et al. 1999) suggested the mechanism with VO_4^{3-} binding in the transition state in place of PO_4^{3-}. The V–S linkage with a cysteine residue in the active site is similar to the thiol-phosphate linkage formed in the normal phosphatase catalysis (Zhang et al. 1997b). The inhibition of the PTP by vanadate enhances protein tyrosine phosphorylation and thus leads to intervention in the insulin-signaling pathway.

Another manifestation of vanadate as a phosphate analogue lies in the binding of vanadate monomer with ADP, which produces an ATP analogue, ADPV, and thus inhibits the activities of proteins (ATPase) (Zhang et al. 1996). Additionally, vanadate is considered as a substitute of phosphate ion in the crystal lattice of hydroxyapatite:

$$Ca_{10}(PO_4)_6(OH)_2 + nVO_4^{3-} \rightleftharpoons Ca_{10}(PO_4)_{6-n}(VO_4)_n(OH)_2 + nPO_4^{3-}$$

However, the incorporation may only occur when the hydroxyapatite is in an amorphous state and a small amount of vanadate ion does not produce any lattice distortion and has little effect on the strength of the P–O and O–H bonds (Etcheverry et al. 1984).

1.2.2 ROS Formation via Electron Transfer Reactions Between V(IV) and V(V)

The one-electron redox of V(V)/V(IV) generates superoxide radical $^{\bullet}O_2^-$ and then by dismutation $^{\bullet}O_2^-$ is converted to H_2O_2. Subsequently, a Fenton-like reaction between H_2O_2 and VO^{2+} converts H_2O_2 to $^{\bullet}OH$ radical. Among the ROS, H_2O_2 is the most stable and exhibits significantly physiological and the toxicological effects

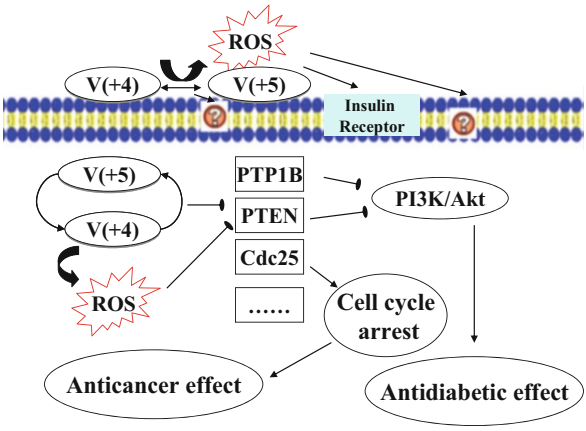

Fig. 1.3 Induction of ROS generation by vanadate and its derivatives may exert diverse biological effects. Vanadate can also inhibit the activities of PTP1B and PTEN directly as a phosphate analogue

(Shi and Dalal 1991, 1993; Sreedhara et al. 1997). The vanadate-induced H_2O_2 can act as a second messenger to activate different signaling pathways.

Considering that all the PTP superfamily of enzymes has a conserved cysteine residue in their catalytic domain, which must be in the reduced form for full activity (Savitsky and Finkel 2002), these enzymes might be direct targets of ROS. Therefore, it is conceivable that ROS-based inhibition of phosphatase should also be taken into account to examine the biological effects of vanadate rather than simply treat it as a phosphate analogue. For instance, as shown in Fig. 1.3, after a vanadium compound has penetrated the membrane, it may either inhibit the activities of PTP1B, PTEN, and CDC25 directly as a phosphate analogue or undergo one-electron electron transfer reactions by ROS formation to cause insulin-enhancing effects or cell cycle arrest. Besides the direct action of H_2O_2, the vanadate-induced H_2O_2 may turn back to coordinate with vanadate forming a series of monomeric and dimeric peroxovanadium species, V*m*X*n* ($m = 1, 2$; $n = 1, 2, 3$, with X stands for peroxo group) (Bortolini and Conte 2005; Pettersson et al. 2003). The peroxo species are more potent inhibitors of phosphatases than vanadate.

1.3 Chemical and Biochemical Basis Underlying the Biological Effects of Vanadate Oligomers

Theoretically, only the monomeric VO_4^{3-} is able to substitute PO_4^{3-} and inhibits phosphatases. In fact, the oligomeric species can also exert inhibitory effects, but probably by differential mode of action, some of which may stem from their different structures.

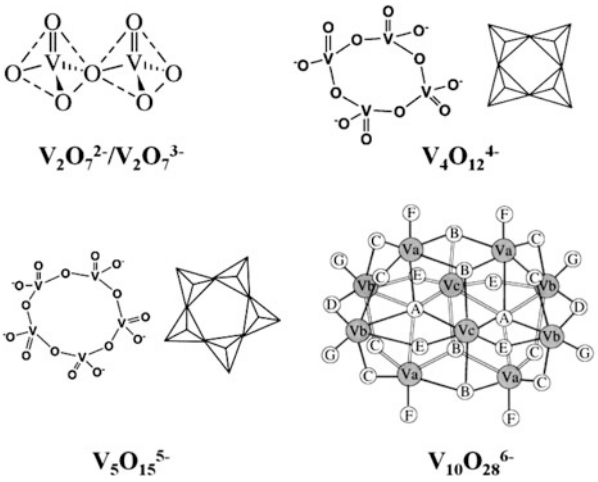

Fig. 1.4 Schematic drawings of tetrahedral vanadates V_2, V_4, V_5, and decavanadate

1.3.1 Structures and Properties of Oligovanadates

As shown in Fig. 1.4, lower oligovanadates are constructed from varied number of VO_4 units by sharing oxygen atoms, forming linear ($V_2O_7^{4-}$, V_2) and cyclic oligomers (V_4, V_5). Instead, V_{10} adopted a cage structure with octahedral VO_6 units. This structure renders it different from V_1, V_2, V_4, and V_5.

Firstly, this compact cage structure constructed from ten distorted octahedral VO_6 units with 28 shared oxygen atoms makes the polyanion $[V_{10}O_{28}]^{6-}$ relatively stable in solution. Although it tends to dissociate in neutral solution, but the reaction is rather slow.

Secondly, the basic oxygen surfaces and high negative charge density endow decavanadate with higher water solubility and nucleophilicity. These properties determined its high affinity to the positively charged sites.

Thirdly, the V(V) atoms in V_{10} are reducible by accepting one electron to yield V(IV). Since the electron transfer is affected by one or two vanadium atoms and only by the low-lying orbital, the V_{10} cage structure is basically unchanged in redox process. Thus, by V(V)/V(IV) shuttle, V_{10} can act as an electron transporter (Long et al. 2010).

1.3.2 Chemical and Biochemical Basis Underlying the Biological Effects of Decavanadate

Decavanadate is the only one among the oligomers isolated from the vanadate solution. A series of studies have been performed using solution of solid decavanadate or acidified vanadate solutions. In a recent review (Aureliano and

Crans 2009), Aureliano listed the effects of V_{10} on several enzymes and proteins. Most of the effects of V_{10} can be attributed to the strong affinity to multipositively charged sites of proteins and in a few cases accompanied with oxidation of thiol groups of proteins.

1.3.2.1 Binding Properties of Decavanadate

It is presumed that the nanosize clusters of V_{10} carrying a number of oxygen atoms in the surface have high affinity to bind with the positively charged domain of a protein (Soman et al. 1983). The binding causes conformation change or/and blocks the substrate binding of proteins.

V_{10} inhibits the nucleotide-dependent enzyme, adenylate kinase, which is not affected by monovanadate (Boyd et al. 1985; DeMaster and Mitchell 1973). The inhibition is explained by that V_{10} binds to adenylate kinase and fits across the phosphate-binding sites of both AMP and ATP sites and thus blocks nucleotide binding and inhibits phosphate transfer (Pai et al. 1977).

V_{10} binding may also result in the blocking of substrate binding to the enzyme. For example, it is able to inhibit rabbit skeletal muscle phosphorylases a and b by this way (Soman et al. 1983), while monovanadate not. Similarly, based on kinetic study and electrostatic potential maps of the surface of wild-type bovine pancreatic ribonuclease A (RNase A), Messmore et al. suggested that decavanadate inhibits RNase A by binding to the active site via electrostatic interaction (Messmore and Raines 2000).

Moreover, the protein-binding associated effect of decavanadate is unique in case of stabilizing the heat shock protein (Hsp90)–protein complex. Hsp90 is a chaperone protein, containing three domains: the ATP-binding, protein-binding, and dimerizing domains. ATP modulates the formation of Hsp90–protein complex, which stabilizes the protein. Both vanadate and V_{10} bind to Hsp90 and both stabilize Hsp90–protein complex but by different ways. The binding site of monovanadate was suggested to be the ADP/ATP-binding site of the Hsp90 N terminus, while V_{10} binds to the highly positively charged middle region and maintains Hsp90–protein interaction (Hou et al. 1992; Soti et al. 1998).

In some cases, decavanadate binds to the proteins in the form of nucleotide-bivalent ion (Mg^{2+})-V_{10} ternary complexes. MutS, a member of the ABC ATPases superfamily, plays an important role in repairing DNA biosynthetic errors. The inhibition by vanadate is attributed to a similar mechanism described above for other ATPases. But V_{10} binds to the ATP-binding region of MutS in forms of ADP–Mg–V_{10} and induces a steric impediment of the protein ATP/ADP exchange (Pezza et al. 2002).

Decavanadate binding to G-actin was found accompanied by thiol oxidation. The effect on G-actin polymerization is important in maintaining the integrity of cytoskeleton and also in muscle contraction. The interaction of decavanadate with G-actin was described as follows: decavanadate oxidizes cysteine thiol group with concurrent formation of vanadyl ions at first, and then the vanadyl ions bind to

actin, causes conformation change, and finally inhibition of G-actin polymerization (Aureliano 2011; Ramos et al. 2006, 2012). Differing from V_{10}, monovanadate does not interact with the cysteine thiol and acts merely as a phosphate analogue.

In summary, the actions of decavanadate might be ascribed mainly to its high affinity to specific positively charged sites of proteins, rather than as a phosphate analogue. Based on this property, decavanadate exhibits various effects on different proteins. Anyhow, the current experimental results are mostly obtained from biochemical studies, and the concentration is higher than expected in the organisms and cells. Thus further studies are necessary before ascertaining its biological significance. Other than this, the results as mentioned above are oriented to the phosphorylation-related proteins. It is expectable that the highly negatively charged decavanadate ions will bind to many proteins nonspecifically.

1.3.2.2 Redox Properties of Decavanadate

At cell level, mitochondrial pathway becomes more important in vanadate-associated redox processes. In vitro studies showed that decavanadate is stronger than vanadate in inducing membrane depolarization and inhibiting oxygen consumption to isolated hepatic and cardiac mitochondria (Soares et al. 2007a).

Aureliano's group had performed a series of studies on the impact of decavanadate on toadfish (Aureliano et al. 2002) and found it caused stronger oxidative stress and oxidative damages (Aureliano and Gândara 2005). It is interesting that differing from metavanadate, decavanadate did not induce cardiac mitochondrial ROS production and SOD activity, but reduce catalase activity. Similarly, by comparing intravenous exposure of decavanadate and vanadate (V_1–V_5) to marine teleost *Halobatrachus didactylus* (Lusitanian toadfish), they found that more vanadium was accumulated by mitochondria in case of decavanadate administration and decavanadate promoted stronger mitochondrial antioxidant enzymes activities than vanadate.

Putting the results together, we can see the importance of protein binding in V_{10}'s biological effects. However, most of the studies were limited to its biochemical actions; the biological effects and the outcomes were seldom reported. Based on current results, V_{10} is more toxic than vanadate, at least in the level of mitochondria. As to the contribution of V_{10} in the effects of vanadate, further studies are needed. Whether V_{10} is more active in redox reactions in biological systems than vanadate and how the in-cage electron transfer acts remains to be clarified.

1.3.3 Biological Effects of Vanadate Dimer and Tetramer

Since the lower oligomers are evidently present in solution as minor constituents and not isolated, their specific effects are hardly defined. Crans' group tried to clarify the different activities among V_1, V_2, V_4, and V_5 based on oligomer analysis

with ^{51}V NMR and the inhibition effect of vanadate solution. By this way, they claimed that in several cases, the observed effects of vanadate are in fact contributed by the oligomers, V_2 and V_4. They claimed that V_2 and V_4 are the acting species in vanadate solution to inhibit glucose-6-phosphate dehydrogenase (G6PD), but V_2 was the major inhibiting species with respect to NADP, and V_4, to G6P and to NAD (Crans and Schelble 1990). The inhibition of glycerol-3-phosphate dehydrogenase (G3PDH) was also suggested mainly by V_4, while dimer exhibits weaker effect (Crans and Simone 1991). In addition, in the inhibition of fructose-1,6-bisphosphate aldolase by vanadate, the active species was identified to be V_4. It is the tetramer that oxidizes the thiol group of aldose and thus inhibits aldolase irreversibly, whereas vanadate dimer is a reversible inhibitor (Crans et al. 1992). A similar case is that the contributor in vanadate-mediated specific photocleavage of myosin subfragment 1 was suggested to be V_4 (Cremo et al. 1990; Ringel et al. 1990).

Divanadate, $[V_2O_7]^{4-}$ may be envisaged as a pyrophosphate analogue. It presents in the solution of vanadate, but due to its low level and rapid conversion, it is difficult to define its specific effect. So far, the only supporting evidence was reported on the pyrovanadolysis as pyrophosphorolysis-like reaction (Akabayov et al. 2011). The role of pyrophosphate in biological effects is different from phosphate; thus the pertinent action of divanadate is intriguing.

1.4 Summary

The existing experimental results indicate that the effects of vanadate are the integrated manifestation of the species formed in biological systems. Among the species, the peroxocomplexes and the oligomeric vanadates, especially the decamer, are shown to bring about several effects different from monomeric vanadate. On account of species transformation, the various effects of monovanadate are discussed by its analogy with phosphate and its redox behaviors, including the formation and action of peroxocomplexes. However, due to the condensed cage structure and high negative charge density, decavanadate is unlikely to be a phosphate analogue but with a special multipoint binding ability to positively charged sites. Although the contributions and the behaviors of the dimeric and tetrameric vanadate species are still ill-defined, the studies have shown that they may exert differential modes of action on the enzymes or other biomolecules. Therefore, different oligomers may exert a specific biological effect or even the similar effect but via a different mechanism.

In this commentary, we only focus on the discussions on the interactions between vanadate and its oligomers with specific biomolecules without involving the scenario of certain biological systems. However, in order to elucidate the underlying mechanism of their biological effects, a detailed knowledge of genetic background of the cell types such as the expressions of tumor suppressors or oncogenes and redox state of various cells is required, which may be as biological

determinants to allow vanadate and its derivatives exert cell-specific effects. It is reported that vanadate induced cell cycle arrest at the G2/M phase by H_2O_2-activated ERK and p38 pathways (Zhang et al. 2003). But, there might be another mechanism leading to vanadate-induced cytotoxicity independent on H_2O_2 generation (Capella et al. 2002, 2007). Our group also demonstrated that vanadate can induce cell cycle arrest in HepG2 cells via an ROS-independent pathway (Fu et al. 2008), and by using antioxidants as synergistic agents, the damage to normal liver cells may be avoided (Wang et al. 2010). The study of antiproliferative effects of vanadate, tungstate, and molybdate on human prostate cancer cell line PC-3 demonstrated that all of the three oxoanions can cause G2/M cell cycle arrest but vanadate exerted much more potent effect in PC-3 cells than the other two oxoanions (Liu et al. 2012). The results reveal that ROS-mediated degradation of CDC25C is responsible for vanadate-induced G2/M cell cycle arrest. The study proposes a possible mechanism to clarify the differential effect of three oxoanions in biological systems beyond just considering that they are structural analogues of phosphate. The redox properties of vanadium may be important factors to exert pharmacological effects in human prostate cancer cells.

Therefore, the effects of vanadate and its derivatives might be cell specific, which means a result in one type of cell lines cannot be simply extended to another situation. However, if details of the specific conditions in experiment have been known and categorized including vanadium speciation, redox status and even the expressions of redox-sensitive transcription factors in the biological systems, we can optimize the performance of vanadate and its derivatives.

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Chapter 2
Structural Characterization of Inorganic Biomaterials

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Contents

Abstract Composite materials with unique architectures are ubiquitous in nature, e.g., marine shells, sponge spicules, bones, and dentine. These structured organic–inorganic systems are generated through self-assembly of organic matter (usually proteins or lipids) into scaffolds, onto which the inorganic component is deposited in organized hierarchical structures of sizes spanning several orders of magnitude. The development of bio-inspired materials is possible through the

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