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Review

Speciation in aqueous vanadate–ligand and peroxovanadate–ligand systems

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ABSTRACT

In the present focused review, the speciation studies of aqueous vanadate–ligand (L) and peroxovanadate–L systems are addressed. The paper focuses solely on the systems studied at our department in the context of potential insulin-enhancing effects, including the following ligands: imidazole, alanylhistidine, alanylserine, lactate, picolinate, citrate, phosphate, maltol, and uridine. We summarise the results of detailed and thorough potentiometric (glass electrode) and ^{51}V NMR (Bruker AMX-500 MHz) spectroscopic studies, performed at 25 °C in 0.150 M Na(Cl), a medium representing human blood. The importance of experimental conditions is discussed and illustrated. A detailed overview of our methodology, based on combining potentiometric and ^{51}V integral and chemical shift data by means of the computer program LAKE, is also given. We list the important steps of equilibrium analysis and the kinds of information available from different sets of NMR spectra. The ligand picolinate is chosen to exemplify our working method, but conclusions are drawn from all systems, reviewing trends and common features. An overview of all systems is given in two tables, including e.g. types and number of species formed. Previously unpublished modelling results at physiological conditions are also shown for all peroxovanadate–ligand systems.

1. Introduction

Diabetes mellitus is arguably the costliest metabolic disorders of our times with substantial and far-reaching societal consequences [1]. Its worldwide incidence is increasing so explosively [2] that it is often referred to as "epidemics", even though it is not directly contagious, instead largely owing to sedentary lifestyle and obesity. Currently, the most common treatment for both type I and type II diabetes is insulin, but there is an active search for alternatives, especially for cases of type II, which represents the majority of diabetic patients. An ideal substitute for insulin should meet various criteria, such as favourable absorption properties, stability in body fluids, high specificity and low toxicity, etc. [3]. In addition, it should also preferably be orally applicable, unlike insulin.

(Peroxo)Vanadium compounds represent one class of possible candidates that could complement insulin-based treatments. Although such potential of this transition metal has already been documented more than a 100 years ago [4], it has only generated much interest over the past decades [5–9]. Since then, insulin-like effects of vanadium compounds have been described both in vitro [10–14] and in vivo [3,15–25]. Importantly, these effects have not been the results of a stimulated insulin secretion by vanadium [16,19] as plasma insulin levels did not increase during the treatments. Thus, they are manifested by other mechanisms, which must at least partly be different from that of insulin [3,26] and may even vary from compound to compound [27,28]. Although the exact mechanisms are not yet fully understood, the vanadate–phosphate similarity is thought to lay behind them, leading to the involvement of vanadium in various enzymatic processes [29], most notably in the inhibition of protein tyrosine phosphatase (PTPase).

Hydrogen peroxide has also been found to express insulin-like effects to some extent, but more interestingly, these effects are synergistically enhanced when applying vanadium and hydrogen peroxide together [30]. This could be owing to an irreversible oxidation (and thus inhibition) of the PTPase enzymes by the formed peroxovanadates [31].

Unfortunately, the low absorption and specificity of vanadium, as well as the low stability of peroxo compounds, lead to problems with toxicity and side effects. On the other hand, the properties of

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the compounds can be altered and fine-tuned by using different ligands. These ligands should facilitate e.g. uptake and transport, and thus eliminate or greatly reduce problems, or even increase effectiveness.

Although a vanadium compound has recently completed phase I in human clinical trials [20], arguably the greatest promise for more rapid progress in therapeutic applications lies in veterinary medicine. Sadly, diabetes is increasing among pets too, owing to malnutrition and insufficient physical activities [32,33]. Regular subcutal injections in animal treatment, however, are rather troublesome, and oral medication is much desired.

Speciation studies are fundamental for the basic research of these fields, as modelling of various conditions can be done by the obtained pH-independent formation constants. The models can then be used in e.g. drug design and production, or to gain insight to the fate of vanadium in the presence of various ligands, such as blood constituents [34]. Although they are very useful and the results and knowledge they provide are much appreciated by researchers in the field, speciation studies are tedious and hard to conduct with great precision. For instance, in order to study a four-component H^+—$H_2VO_4^-$—H_2O_2-ligand system, all subsystems (H^+—$H_2VO_4^-$ [35], H^+-ligand, H^+—$H_2VO_4^-$—H_2O_2 [36] and H^+—$H_2VO_4^-$-ligand) must be known under the same experimental conditions. Our group has almost 30 years of experience in this field and was the first to report the complete speciation of pentavalent vanadium in an extensive pH region ($1 < pH < 10$) and in one and the same ionic medium [37]. The medium chosen at that time was 0.600 M Na(Cl), representing the conditions in sea water. Later, the speciation and its medium-dependence was studied in other ionic media too [35], most notably in the physiological medium of 0.150 M Na(Cl), representing human blood.

The current focused review is dedicated entirely to studies of pentavalent vanadium systems in 0.150 M Na(Cl) medium at 25 °C, carried out in our group. The ligands featuring in these studies include imidazole (Im) [36], alanylhistidine (Ah) [38], alanylserine (As) [39], lactate (La) [40], picolinate (Pi) [41], citrate (Cit) [42], phosphate (P) [43], maltol (Ma) [44,45], and uridine (Ur) [45].

For illustrative purposes, we have chosen picolinate (Pi) as the ligand to exemplify the methodology, but conclusions are drawn from all systems. Finally, we focus on reviewing trends in the complexing ability of the different ligands to vanadate and peroxovanadate and show previously unpublished modelling results.

2. Experimental

Descriptions of chemicals, analysis, equilibration of solutions, as well as concentration and pH ranges, are given in the references for each ligand system and are not repeated here.

The equilibria are written with the components H^+, $H_2VO_4^-$, H_2O_2 and L^{n-}, and complexes are formed according to

$$pH^+ + qH_2VO_4^- + rH_2O_2 + sL^{n-} \rightleftharpoons (H^+)_p(H_2VO_4^-)_q(H_2O_2)_r(L)_s^{p-q-sn} \quad (1)$$

Thus, both stoichiometries and charges are obtained for each species.

Complexes are given the notation $V_qX_rL_s^{m-}$. X is used instead of the peroxo-ligand to shorten the formulae. For example, in the picolinate system, VX_2Pi^{2-} denotes a two minus charged diperoxovanadate monopicolinate species. Isomeric species, having the same composition and charge, are differentiated by asterisks (e.g. VX_2Pi^{2-} and $^*VX_2Pi^{2-}$). V_n represents inorganic vanadates in the figures. The total concentrations of vanadate, hydrogen peroxide and the ligand are denoted $[V]_{tot}$, $[H_2O_2]_{tot}$ and $[L]_{tot}$, respectively.

In some of the $H^+ - H_2VO_4^-$-L systems, the pH range had to be restricted due to various reasons, such as reduction of V(V) in certain ternary systems, slow equilibrium accompanied by substantial loss of peroxide in some quaternary systems, oxidation of the ligand, etc. Please consult the references given for each studied ligand to find the pH-ranges used to calculate $\log\beta$ values in each system.

The studies were performed using combined potentiometric and ^{51}V NMR spectroscopic techniques. The pH measurements (glass electrode) were performed either as potentiometric titrations or on individually prepared NMR solutions. The ^{51}V NMR integral and chemical shift data were recorded on a Bruker 500 MHz spectrometer and the chemical shifts are given in ppm relative to $VOCl_3$.

Multinuclear NMR (^1H, ^{13}C, ^{31}P, ^{14}N, ^{17}O), ESR and mass spectrometry have been used to gain additional information regarding structures, decomposition products, the reduction of vanadium(V) to vanadium(IV), etc. However, no data from these measurements have been included in calculations.

Experimental data have been evaluated with the least squares program LAKE [46], designed to handle multimethod data simultaneously. In the studies summarised here, this means potentiometric and quantitative ^{51}V NMR integral and chemical shift data. To obtain reliable deconvoluted NMR data, WIN-NMR was used. Calculation and plotting of distribution diagrams were performed using WIN-SGW [47], a program package based on the SOLGAS-WATER algorithm [48].

3. Results and discussion

As it has been stated earlier, knowing the full speciation and NMR characteristics of all relevant subsystems under the same experimental conditions is vital before attempting to study any of the ternary (H^+—$H_2VO_4^-$-ligand) and especially quaternary H^+—$H_2VO_4^-$—H_2O_2-ligand) systems. The temperature is one obvious parameter that needs to be kept constant, but another – equally important, yet very often overlooked and underestimated – factor is the ionic medium. By this, we mean the medium as is, not only the ionic strength. We have demonstrated earlier that both the nature and the concentration of the cation play important roles in determining the predominant species in H^+—$H_2VO_4^-$ system [35]. To demonstrate the substantial ionic medium dependence, distribution diagrams are constructed at a given $[V]_{tot}$ (1.00 mM) in three different Na(Cl) media (Fig. 1). Striking differences are found at neutral pH (the so-called metavanadate range): most vanadium is bound in the tetramer at 0.600 M Na(Cl) (artificial sea water medium), but in the "physiological" medium (0.150 M Na(Cl)), the monomer becomes the predominant species. This underlines the importance of choosing experimental conditions for the studies very carefully, bearing in mind the intended use of the obtained formation constants. In line with this, the speciation studies reviewed here have been carried out in 0.150 M Na(Cl) medium, in order to model conditions similar to that of human blood. Since anionic vanadate species are dominant in most of the pH range, (except at low pH, where the so-called pervanadyl cation (VO_2^+) dominates), the cation concentration in the medium was kept constant and the anion concentration was allowed to vary somewhat, hence the notation Na(Cl).

As can also be seen from Fig. 1, the hydrolysis of pentavalent vanadium, V(V), is very complex. Besides monomeric species, a variety of polyoxovanadate species with nuclearities 2–6 and 10 are known to form in equilibrated solutions. The charges vary from +1 to −6. In fact, the speciation in the binary $H^+/H_2VO_4^-$ system alone is already too complex to be studied with only one experimental method, e.g. potentiometry. Luckily, ^{51}V is an ideal NMR nucleus, and the combination of ^{51}V NMR and potentiometry provides a powerful tool for speciation. Another significant advance was the development of the least squares computer program LAKE