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pH-metric, UV–Vis and ^{51}V NMR study of vanadium(V) coordination to α-aminohydroxamic acids in aqueous solutions

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ABSTRACT

The full speciation of vanadium(V) complexation systems with glycinehydroxamic acid and three α-aminohydroxamic acids (α-alanine-, α-threonine- and α-lysine-) has been achieved using potentiometric and spectroscopic techniques. Formation constants were calculated in a systematic study at different concentrations and ligand-to-metal molar ratios. In each case, in a neutral medium, two complexes were identified with 1:1 and 1:2 metal-to-ligand ratios, both of which can either be protonated or deprotonated depending on the acidity or basicity of the medium. Structures are proposed based on ^{51}V NMR results. The 1:1 complex, VO_2L (VO_2^+ = dioxovanadium(V) ion and L^- = α-aminohydroxamate ligand), has a distorted trigonal bipyramidal structure in neutral medium and it exists as VO_2HL^+ in acidic and as $VO_2(OH)L^-$ in basic medium. The 1:2 complex, $VO_2H_2L_2^+$, which is formed in neutral medium, has an octahedral structure and also exists as $VO_2H_3L_2^{2+}$ and VO_2HL_2, in acidic and basic media, respectively. In all cases, only the hydroxamate group appears to be coordinated to the VO_2^+ group.

1. Introduction

The insulin-mimetic activity of vanadium salts in oxidation states (IV) and (V) has attracted considerable interest in recent years, as it raises the possibility of medicinal uses for these compounds as oral substitutes for insulin [1,2].

The study of the coordination chemistry of vanadium with different organic compounds is an important aspect of research in this area, as the toxicity exhibited by vanadium compounds, even at low dosages, is a factor that must be carefully considered. In these studies, the aim is to find nontoxic chelating agents that can facilitate the transport of vanadium through biological membranes. Numerous ligands containing nitrogen, oxygen and sulfur donor atoms have been tested for insulin-mimetic activities with positive results. Among these ligands, some hydroxamic acids, compounds bearing the group –CONHOH–, have yielded significant results. In particular, amino acid derivatives have provided encouraging *in vitro* and *in vivo* results from tests with glutamic-γ-hydroxamic acid and its vanadium (V) and (IV) complexes [3]. In addition, this class of organic weak acids comprises a set of very efficient ligands that interact with several metal ions, with the formation of strong complexes with iron(III), aluminum(III) and copper(II). These ligands are known to oxidize the low oxidation states of vanadium, molybdenum and chromium. They are also known as valuable compounds with several pharmacological [4–9] and biological activities [10–12].

Solution studies of systems containing vanadium(V) over a large pH range are essential in understanding what happens with these complexes in the body. However, the study of complexation reactions of vanadium(V) in aqueous solution is complicated by the tendency of this metal ion to hydrolyze, forming both mono- and polynuclear species. If vanadium(V) complexes are to play any biological role, they must be able to compete with the hydrolysis of vanadium(V) ions and to survive the specific conditions associated with gastrointestinal absorption. A severe pH change from pH 2 to 7, oxi-reduction reactions and the presence of components in food (such as bioligands and essential metals) can all interfere or compete with the absorption of these complexes. Identification of the stoichiometry of vanadium(V)-complex species and determination of their stability constants allows for simulation of the behavior of vanadium(V) in the presence of this and other ligands over large pH and concentration ranges.

Hydroxamic acids generally behave as bidentate ligands, coordinating metal ions by means of the carbonyl and deprotonated –NHOH group oxygen atoms, leading to the construction of stable five-membered rings. Possible coordination through the carbonyl oxygen and the nitrogen atom of the –NHOH group would lead to four-membered rings, which are less stable.

If additional coordinating groups are present, such as in aminohydroxamic acids, in which the amino group can be, for instance, in the α position in relation to the hydroxamic acid group, the

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number of coordination possibilities increases: the nitrogen atom of the amino group is able to participate in five-membered rings ((N,O) and (N,N) coordination modes), which may be very stable.

In dilute aqueous solutions, metavanadate (VO_3^-) is hydrolyzed, forming an almost colorless solution of $H_2VO_4^-$ that becomes dark brown upon addition of an aminohydroxamic acid, but does not suffer a significant change in pH. Both ligand and $H_2VO_4^-$ undergo deprotonation and protonation reactions. In order to determine the complete and accurate speciation in a given H^+-vanadium(V)-ligand system, the complete speciation of the two binary systems H^+-ligand and H^+-vanadium(V) must be known under the same experimental conditions.

We have demonstrated how combined potentiometric, spectrophotometric and ^{51}V NMR methods allow for the identification of several species and the determination of their formation constants in aqueous solutions containing vanadium(V) and hydroxamic acids (acetohydroxamic acid [13,14] and β-alaninehydroxamic acid [15]). We have also studied the formation of complexes of acetohydroxamic acid with vanadium(IV) and the stability of these vanadium(IV) species against air oxidation [16].

Now, we report the study of systems formed by vanadium(V) and a series of α-aminohydroxamic acids (shown in Scheme 1), exploring different coordination possibilities that are available in these hydroxamic acids. The study was performed in aqueous solution using the same experimental methods as in earlier works at 25 °C and with an ionic strength of 0.15 mol L^{-1} in NaCl. The study of these vanadium(V)-ligand systems is rather complex since different VO_2^+-ligand species may be formed that are protonated and deprotonated depending on concentration, pH and ligand-to-vanadium ratio.

2. Experimental

2.1. Reagents and solutions

All solutions were prepared using deionized water. Carbonate-free NaOH solutions were prepared from saturated solutions and standardized with potassium hydrogen phthalate. Solutions of aminohydroxamic acids (Sigma), used as received, were always prepared just before use, and their concentrations were checked by direct potentiometric titration with NaOH solutions. A 0.0125 mol L^{-1} vanadium(V) stock solution was prepared by dissolving $NaVO_3$ (Carlo Erba) in an excess of a standardized HCl solution.

2.2. Potentiometric measurements

Potentiometric measurements were carried out through the addition of carbonate-free NaOH solutions of known concentrations (ca. 0.15 mol L^{-1}) as titrants to mixtures of vanadium(V) and the ligand in different proportions. Large excesses of ligand over the vanadium concentration were maintained to avoid significant hydrolysis of the vanadium(V) ion. Possible vanadium(V) reduction was checked by back titrations, with negative results.

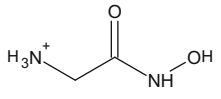
Measurements were done using a Metrohm Dosimat 10 mL burette and a Metrohm 670 Titroprocessor equipped with glass (6.0133.100, pH range 0–14) and reference (6.0733.100 Ag, AgCl/3 M KCl) electrodes, both Metrohm. A double-jacketed titration vessel was used to maintain a constant temperature of 25.0 ± 0.1 °C by circulating thermostated water. These solutions were protected from air by a purified nitrogen flow that was circulated beforehand through a 0.15 mol L^{-1} NaCl solution.

Solutions (15.00 mL each) to be titrated were prepared by adding a stock solution of vanadium(V) (2.00, 3.00 and 4.00 mL of 12.5 mmol L^{-1} vanadium(V) in 0.10 mol L^{-1} HCl) to ligand solutions (5.00, 7.50 and 10.00 mL of ca. 0.03 mol L^{-1}) and adjusting the ionic strength to 0.15 mol L^{-1} with NaCl solution. Solutions (1–6) are shown in Table 1.

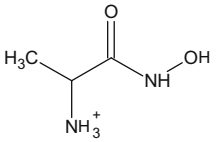
The electrode system was calibrated for $[H^+]$ before and after each series of measurements, by titration of HCl with standardized NaOH, or vice-versa, at an ionic strength of 0.15 mol L^{-1}. Data were analyzed with a computer program [17] to calculate the standard potential of the electrode (E_o, RT/F, A_j, B_j) under the experimental conditions employed. These values were then used to calculate the hydrogen ion concentration ($pH = -\log[H^+]$) from the measured potentials. The value of K_w used in the computations was $10^{-13.74}$.

2.3. NMR measurements

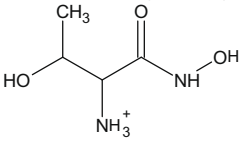
The ^{51}V NMR spectra were obtained at 105.2 MHz with a Bruker DRX400 spectrometer in the presence of 10% D_2O. Typical spectra required 1024 transients, obtained in ca. 10 min, and were referenced against an external sample of $VOCl_3$ (Aldrich), which was assigned as chemical shift of 0.0 ppm. Solutions were prepared in 0.15 mol L^{-1} NaCl medium with the addition of 10% D_2O. The concentrations of vanadium and ligand solutions are shown in Table 1. After recording, the NMR spectra were quantitatively evaluated using the Bruker software 1D WIN-NMR [18] to obtain both chemical



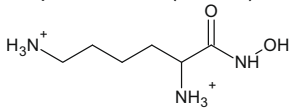
glycinehydroxamic acid (gha)
pK_{a1} = 7.42 (α-NH_3^+)
pK_{a2} = 9.14 (NHOH)



α-alaninehydroxamic acid (α-alaha)
pK_{a1} = 7.30 (α-NH_3^+)
pK_{a2} = 9.14 (NHOH)



α-threoninehydroxamic acid (α-threha)
pK_{a1} = 6.69 (α-NH_3^+)
pK_{a2} = 8.90 (NHOH)



α-lysinehydroxamic acid (α-lysha)
pK_{a1} = 6.87 (α-NH_3^+)
pK_{a2} = 9.14 (NHOH)
pK_{a3} = 10.60 (ε-NH_3^+)

Scheme 1. Fully protonated forms of the hydroxamic acids studied.