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# Applications of $^{51}$V NMR spectroscopy to studies of the complexation of vanadium(V) by α-hydroxycarboxylic acids

Alan S. Tracey *

*Department of Chemistry, Simon Fraser University, Burnaby, BC, Canada V5A 1S6*

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**Contents**



**Abstract**

Vanadate complexes of α-hydroxycarboxylic acids form readily and reversibly in aqueous solution. 2-Methyl-2-hydroxypropanoic acid (α-hydroxyisobutyric acid) provides a convenient system to demonstrate the utilization of $^{51}$V-NMR spectroscopy in the study of the formation of various products and to provide examples of procedures used to determine product stoichiometries and equilibrium constants. α-Hydroxyisobutyric acid forms three major products with 1:1, 2:2 and 2:3 ligand to vanadium stoichiometries. The formation of products with this ligand is compared with reactions with similar ligands, 2-hydroxypropanoic acid (lactic acid) and 2-ethyl-2-hydroxybutanoic acid and to ligands of other oxidation states, most notably 1,2 glycols and oxalic acid. The dependence of product coordination geometry on ligand oxidation state is discussed. These studies may have relevance to the possible role of a vanadium(V) oxidation state in vanadium-dependent nitrogen fixation, an alternate to the molybdenum-dependent system.


*Keywords:* Vanadate; Vanadium(V); Lactate; Carboxylate; Hydroxycarboxylic acid; $^{51}$V-NMR; Aqueous equilibria; Equilibrium constants; Vanadium-dependent nitrogenase

## 1. Introduction

Historically, the relevance of vanadium to biological processes was only slowly recognized. However, the past decade has seen a vast increase in interest in the biological influences of vanadium [1,2]. Much of the impetus toward vanadium biochemical research derives from the fact that a number of vanadium complexes have insulin-mimetic or insulin-enhancing properties. However, the discoveries that showed that vanadium is found in the prosthetic group of both vanadium-dependent haloperoxidases [3,4] and nitrogenases [5,6] of various organisms has lead to extensive work on understanding the function of such enzymes and on developing chemical systems that mimic their function. The development of such functionality depends on obtaining a detailed knowledge of the chemistry associated with the ligands that give rise to such activity. Because of the nature of the systems, much of the chemistry involves reactions in aqueous media.

The vanadium-dependent nitrogenase contains homocitrate within the active site. Although the vanadium oxidation state in this enzyme is not thought to be V(V) [5,7], this oxidation state may well be involved during the process of nitrogen fixation. To aid in understanding the function of this enzyme, it is of some interest to know the chemistry associated with complexation reactions of vanadium(V) with α-hydroxycarboxylic acids. Such chemistry is also interesting because α-hydroxy-

* Tel.: +1-604-291-4464; fax: +1-604-291-3765.
*E-mail address:* tracey@sfu.ca (A.S. Tracey).

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carboxylic acids have an oxidation state between that of 1,2-diols and oxalic acid and it is known that complexation of vanadate by these two types of ligands leads to quite different coordination states.

The oxovanadium(V) anion, vanadate, reacts rapidly and reversibly with alcohols [8–11], phenols [12] and carboxylic acids [13–16] to form vanadate esters and acid anhydrides. Of course, vanadate also condenses with other weak acids, such as with itself to form divanadate [17] and similarly with phosphate to generate phosphovanadate [18]. There is no evidence from the studies of these complexes to suggest that ligands of these types induce a change in coordination geometry in the tetrahedral vanadate moiety.

Under forcing conditions, 1,3 bidentate ligands such as 1,3-propane diol react with vanadate [19]. However, this reaction has not been observed in aqueous solution [20]. This contrasts with the much more favourable reactions observed for 1,2 bidentate ligands such as ethylene glycol [21–23], carbohydrates [24,25], nucleosides [26–32], α-hydroxycarboxylic acids [13–16,33,34] and oxalic acid [13,35]. These ligands all induce a change in coordination geometry but, beyond this, they do it in a selective manner as suggested by X-ray crystal structure studies. Both 1,2 glycols [25,26] and α-hydroxycarboxylic acids [14,15] provide dimeric pentacoordinate complexes while oxalic acid gives rise to an octahedral monomeric complex [36]. However, the X-ray information derives from a highly selective procedure that often reveals little about the products occurring in solution. Despite this, X-ray structural data taken together with solution studies can often provide considerable insight into the structures of solution products.

Nuclear magnetic resonance (NMR) spectroscopy provides a powerful probe for study of solution compounds and the vanadium nucleus is particularly suitable for studies of vanadium(V) complexes. $^{51}$V is essentially a 100% abundant natural isotope with characteristics that are very favourable for NMR spectroscopy. Vanadium has spin 7/2 and consequently has a nuclear electric quadrupole moment. However, the quadrupole moment is moderate in size and its influences on NMR spectra are ameliorated by the large spin of the nucleus. Nevertheless, the influences of the quadrupole moment are quite evident in $^{51}$V-NMR spectra. Linewidths between 50 and a few hundred Hz are typical for this nucleus. The fast nuclear relaxation corresponding to such linewidths means that spectrum acquisition can be carried out very rapidly. Often 30 or more acquisitions per second can be accumulated without perturbing the resultant spectrum. The linewidths observed are often not a great hindrance to interpreting spectra because vanadium(V) has a large chemical shift range of about 2000 ppm. Furthermore, the large linewidths mean that line-broadening factors of 40 Hz

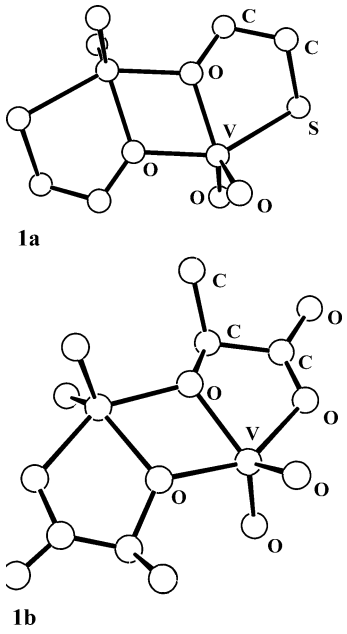



Fig. 1. X-ray structures of vanadium(V) complexes of β-mercaptoethanol (a) and of L-lactic acid (b).

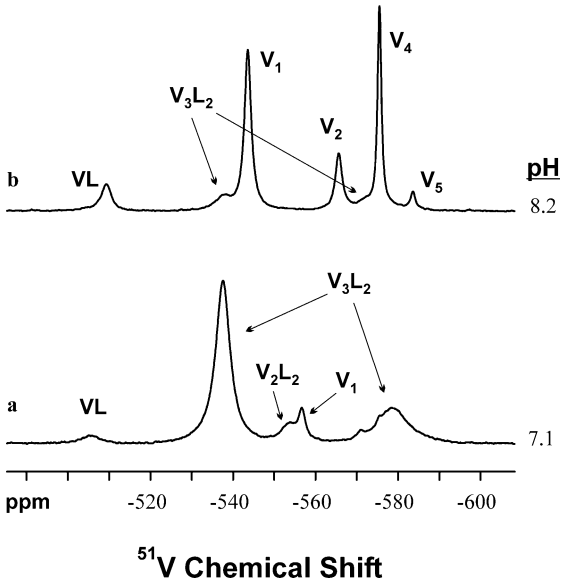



Fig. 2. $^{51}$V-NMR spectra showing the influence of 1 unit of pH on the distribution of products in an aqueous 2-ethyl-2-hydroxybutanoic acid–vanadate solution. Conditions of the experiments: 3.0 mM total vanadate, 30 mM total ligand, 1.0 M NaCl, 20 mM HEPES buffer and indicated pH.

or more can advantageously be applied to the spectra without degradation of the information content.

The structure of a β-mercaptoethanol complex of dioxovanadium(V) [37] (Fig. 1a) shows two five-coordinate vanadiums in a bridged dimeric structure that is also typical for glycol complexes. Such coordination is not significantly different from that observed with α-hydroxycarboxylic acids (Fig. 1b). In fact, this is the only form of coordination that has been found for these

types of ligands by X-ray studies. A chlorovanadium(V) complex of a diol has, however, shown a derivation of that coordination [38]. The mode of coordination is quite different with oxalate where a monomeric *cis*-coordinated bisoxalato complex in octahedral geometry has been defined by X-ray diffraction [36]. Furthermore, solution NMR studies have revealed only favourable formation of mono and bisoxalato complexes with no suggestion of dimer formation [13,35,39]. Glycols, like oxalate, give rise to only one major type of coordination, although, dependent on the ligand, isomeric complexes can be generated [21,23]. The situation is quite different with α-hydroxycarboxylic acids where $^{51}$V-NMR signals corresponding to several different types of products are observed [13,33].

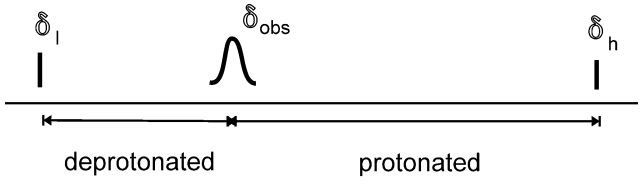
An early study of the complexation of vanadate by lactate revealed the occurrence of two major products and two minor ones [13]. One minor product was assigned to a monodentate-coordinated product. The second minor product was assigned to dimer-like product of mixed coordination. One of the major products was assigned to a monoligated monomeric trigonal bipyramidal complex. The assignment of this coordination was based on the $^{51}$V-NMR chemical shift and on the observation that this product could incorporate a second ligand with no apparent change in geometry. The second major product was assigned to a dimeric octahedral complex. Crystal structure studies of the vanadium(V) complex of 2-ethyl-2-hydroxybutanoic acid (*ehba*) [14] and of a similar complex with the 1,2-glycolato ligand adenosine [26], suggested the assignment of an octahedral coordination was incorrect. Subsequent structural data supported this view [15,16]. Clearly, rationalization of the X-ray data with the NMR studies was required.

A vanadium NMR spectrum of an aqueous solution of 3.0 mM vanadate in the presence of 30 mM *ehba* at pH 7.1 (Fig. 2a) shows four signals, −538, −554, −578 and −505 ppm. An additional minor signal (−557 ppm) is from the vanadate monomer. Of the four product signals, the signal at −554 ppm corresponds to a dimeric ($V_2L_2$) product of the type shown in Fig. 1b. With an increase in pH to pH 8.1 (Fig. 2b), the three major product signals decrease in intensity as the vanadium is displaced from the complexes to generate vanadate (−543 ppm at pH 8.1) and its oligomers (−566 ppm, divanadate; −576 ppm, tetravanadate; −584 ppm, pentavanadate). In contrast to the other product signals, the −505 ppm signal (VL) increases in intensity and also undergoes a change in signal position. This change in chemical shift suggests loss of a proton and such a loss will favor formation of this product at higher pH, as observed.

Although change in signal positions with pH can frequently be associated with changes in protonation state, there is no necessity that such a change occurs and sometimes there is no observed change or it is small. Typically though, deprotonation gives rise to nuclear shielding and a resultant high field shift in signal position of −20 to −30 ppm. However, this change in chemical shift can be quite large, up to about −70 ppm with peroxovanadate, for instance, or it can reverse sign and shift in a positive direction. The latter behavior is seen, for instance, with tetrahedral species such as vanadate monoanion (+22 ppm) and its alkoxo derivatives. This presumably, is a reflection of the different type of electronic environment about the vanadium nucleus. In the case here with the *ehba* ligand, the change in chemical shift of VL on deprotonation is −15 ppm and the p$K_a$ of $VL^-$ is 6.6±0.1. In agreement with the assigned coordination, the direction of change in chemical shift of this *ehba* complex is consistent with a pentacoordinated compound.

The relationship between signal position, pH and p$K_a$ is a simple one as depicted in Scheme 1. The systematic observation of chemical shifts as a function of the pH of the medium readily offers a graphical derivation of the p$K_a$ of the compound of interest. A particularly useful property of the equation of Scheme 1 is that the linear relationship requires a slope of one. If a full titration curve is not obtainable, as in Fig. 3a, a slope of one can be imposed by proper selection of an endpoint limiting chemical shift. It is, of course, critical under such an imposition, to ensure that a 'good' straight line is obtained (Fig. 3b). The intercept of the graph gives the p$K_a$ for the compound of interest. In the example of Fig. 3, the p$K_a$ obtained is 6.26±0.06 for the VL product formed with 2-hydroxy-2-methylpropanoic acid (α-hydroxyisobutyric acid or α-*hiba*).

With the α-*hiba* ligand, product NMR signals do not overlap with those of vanadate and its oligomers as much as the signals of the *ehba* complexes and thus this system is more amenable to NMR studies. Vanadium complexes of α-*hiba* give major product signals at −520 (VL), −549 ($V_2L_2$), −533, −538, and −569 ppm at pH 7.06. The assignment of the −549 ppm signal to the dimer, $V_2L_2$, can be verified by obtaining a $^{51}$V-NMR




$$pH = pKa + \log (\delta_l - \delta_{obs})/(\delta_{obs} - \delta_h)$$

Scheme 1. Diagrammatic representation of the influence of pH on a signal undergoing a protonation–deprotonation reaction. $\delta_l$, limiting chemical shift at low pH; $\delta_h$, limiting chemical shift at high pH; $\delta_{obs}$, the observed chemical shift.

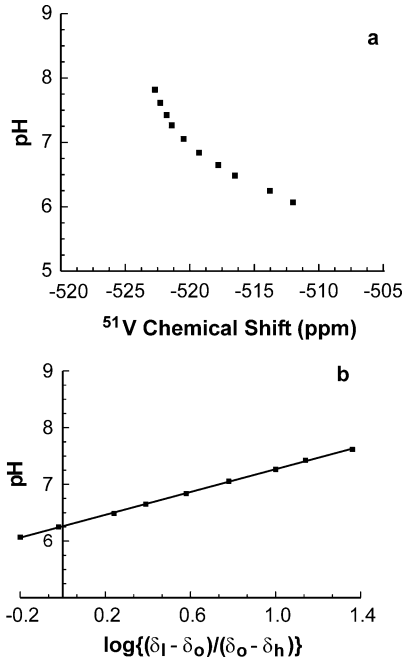



Fig. 3. Chemical shift dependence of the vanadium NMR signal from the 1:1 V–2-hydroxyl-2-methylpropanoic acid complex (a) and the graphical relationship of the observed shift to the p$K_a$ of VL as given by the Y-intercept of the graph (b).

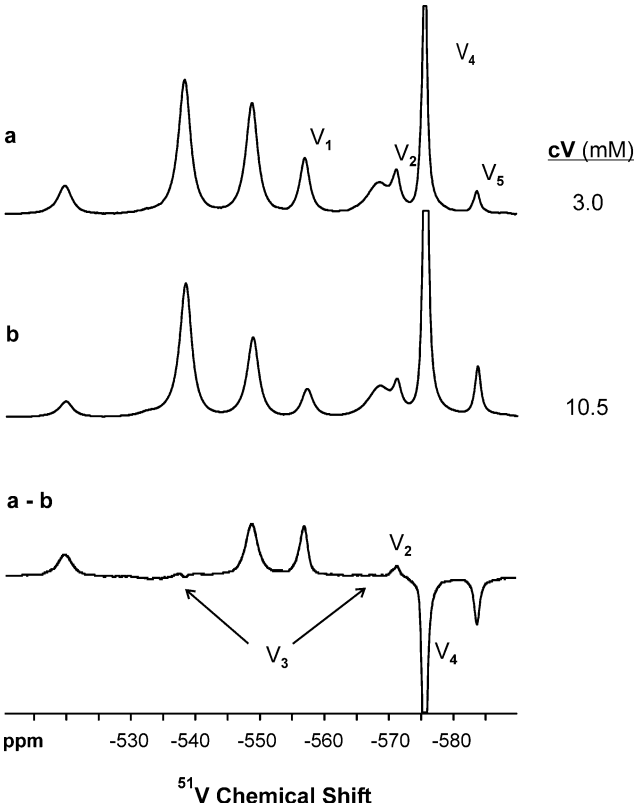



Fig. 4. $^{51}$V-NMR spectra chosen to demonstrate the relative changes (a–b) in product concentration accompanying changes in overall vanadate concentration (spectra a and b) at an effectively constant free ligand concentration. Conditions of the experiment: total 2-hydroxyl-2-methylpropanoic acid, 30 mM; 1.0 M NaCl; 20 mM HEPES buffer, pH 7.06.

spectrum immediately after dissolution of the crystalline complex in water or by ligand and vanadium concentration studies. A preliminary assignment of the −538 and −569 ppm signals (in fact of all signals) can be made by obtaining NMR spectra under conditions of relatively constant free ligand concentration and variable vanadate concentrations. For instance if a total ligand concentration of 30 mM is chosen and vanadate concentrations of 3 and 10 mM are compared, then the variation in the free ligand concentration is such that it can be neglected for the moment. If the free ligand concentration is constant or near constant, then variation of the free vanadate concentration will result in altered product formation according to the vanadium stoichiometry only, as given by the appropriate equilibrium equation. Complexes with a single vanadium will increase in concentration linearly with the free vanadate concentration, those with two vanadiums as the square of the free vanadate concentration, and those with higher nuclearity according to a third ($V_3$), fourth ($V_4$) or higher power ($V_n$), as required. If spectrum a corresponds to the spectrum of lower vanadate concentration and spectrum b to the higher then a simple test of nuclearity can be carried out. If the −538 ppm signal is chosen and its intensity is scaled to the same amplitude in the two spectra and subtracted (a–b), then all signals corresponding to compounds with a nuclearity lower than that of the −538 ppm signal will have a positive residual intensity while those signals corresponding to a higher nuclearity will have a negative residual intensity.

A similar test can be carried out for all signals in the NMR spectrum. If the identity of any one signal is known then all signals can be assigned. In all cases, the relative nuclearity can be specified.

Fig. 4 shows the result of the above test for the −538 ppm signal. The identities of the signals labeled $V_1$, $V_2$ and $V_4$ are known and the residual signal from $V_4$ is of opposite sign to the other two. Additionally, no residual −569 ppm signal was observed. Therefore, the −538 and −569 ppm signals must correspond to complexes with a $V_3$ stoichiometry. Detailed concentration studies [33] confirm the vanadium nuclearity and also show that the two signals correspond to complexes that contain two ligands, that is, they have the stoichiometry, $V_3L_2$. The integrated intensities of the −538 and −569 ppm NMR signals are in close to a 2:1 ratio (−538: −569) and are assigned to the same complex, one signal of intensity two corresponding to two equivalently substituted vanadiums and one signal corresponding to a single vanadium nucleus with a different mode of substitution. This stoichiometry is also assigned to the corresponding signals in the *ehba* complex and to the product originally thought to be a 2:2 mixed coordination complex in a study of the lactate complex [13]. On

Table 1
Chemical shifts of various vanadium complexes formed with α-hydroxycarboxylic acids in aqueous solution[a]

| Ligand | $^{51}$V chemical shift (ppm) | | | | |
|---|---|---|---|---|---|
| | $VL^-$ | $VL^{2-}$ | $V_2L_2^{2-}$ | | $V_3L_2^{3-}$ |
| (*S*)-(+)-2-hydroxypropanoic acid | −508[b] | −518 | −533 | −533 | −551 |
| 2-hydroxy-2-methylpropanoic acid | −505 | −523 | −549 | −538 | −569 |
| 2-ethyl-2-hydroxybutanoic acid | −495 | −510 | −554 | −538 | −578 |

[a] Lactate chemical shifts for ionic strength 1.0 M with KCl others for 1.0 M with NaCl.
[b] The value of −508 ppm was obtained by Lage Petterson for 0.15 M ionic strength with NaCl, see article this proceedings

this basis, Table 1 gives the chemical shifts of the various compounds formed with *lac* (L-(+)-lactic acid), α-*hiba* (2-methyl lactic acid) and *ehba*.

An additional NMR signal from a minor product can be observed at −533 ppm in the spectra of Fig. 4. Although not readily observable in the figure, at −533 ppm there is a downward depression in the difference spectrum of Fig. 4 and this suggests that this compound has a nuclearity higher than three. When the signal from the tetravanadate oligomer of Fig. 4 a and b is used as the reference for the difference spectrum, there is no evidence of a residual −533 ppm signal. It, therefore, appears that the compound has four vanadiums in it. The product corresponding to this signal has not been more fully characterized and no other signals were observed in the spectra.

The various equilibrium constants that describe the α-*hiba*–vanadate system are provided in Table 2, except that a formation constant for the minor product, mentioned above, is not given. Speciation diagrams can be constructed from the values of Table 2 and one such diagram (Fig. 5a) reveals the large changes in product distribution that are observed near pH 7 for

Table 2
Equilibrium constants for product formation in the aqueous α-*hiba*–vanadate system [a,b]

| Equilibrium equation | Equilibrium constant |
|---|---|
| $V_1^- \rightleftharpoons V_1^{2-} + H^+$ | $10^{(-7.98\pm0.05)}$ |
| $2V_1^- \rightleftharpoons V_2^{2-}$ | $(5.1\pm1.3)\times10^2$ |
| $V_2^{2-} \rightleftharpoons V_2^{3-} + H^+$ | $10^{(-8.15\pm0.10)}$ |
| $4V_1^- \rightleftharpoons V_4^{4-}$ | $(9.3\pm1.2)\times10^9$ |
| $5\ V_1^- \rightleftharpoons V_5^{5-}$ | $(1.9\pm0.4)\times10^{12}$ |
| $V_1^- + L^- \rightleftharpoons VL^{2-}$ | $24\pm1$ |
| $VL^- \rightleftharpoons VL^{2-} + H^+$ | $10^{(-6.16\pm0.06)}$ |
| $2V_1^- + 2L^- + 2H^+ \rightleftharpoons V_2L_2^{2-}$ | $(3.9\pm0.2)\times10^{20}$ |
| $3V_1^- + 2L^- + 2H^+ \rightleftharpoons V_3L_2^{3-}$ | $(1.2\pm0.1)\times10^{24}$ |
| $V_3L_2^{3-} \rightleftharpoons V_3L_2^{4-} + H^+$ | $10^{(-8.4\pm0.3)}$ |

[a] Complexation reactions studied for the pH range 6.07–7.82. Other products may form under more strongly acidic pH conditions. Vanadate concentration range 3–10.5 mM and α-*hiba* concentration range 0–35 mM under conditions of 1.0 M constant ionic strength with NaCl and 20 mM HEPES buffer.
[b] Abbreviations: $V_1^-$, $VO_4H_2^{1-}$; $L^-$, 2-hydroxy-2-methylpropanoate anion.

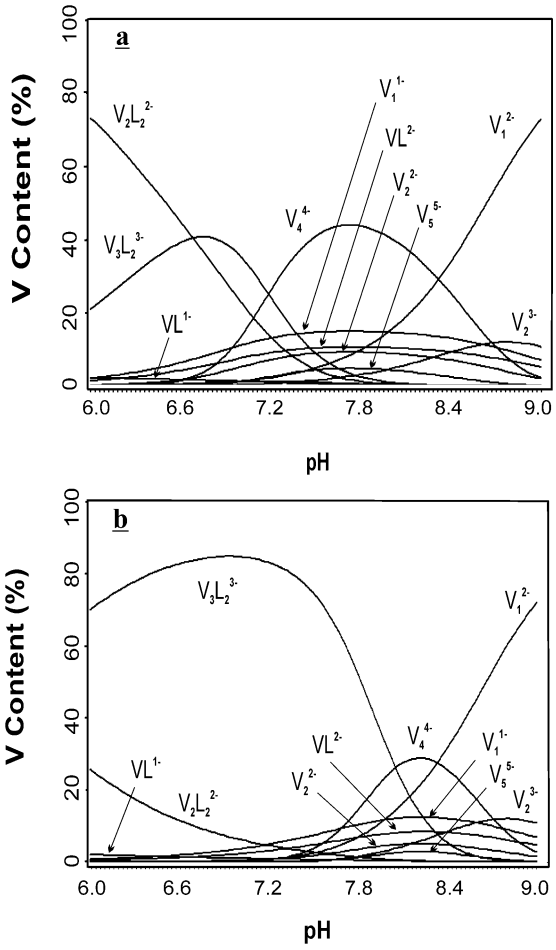



Fig. 5. Species distribution diagram showing the effect of pH on product formation in the aqueous 2-hydroxy-2-methypropanoic acid (α-*hiba*)–vanadate system (a) and the 2-ethyl-2-hydroxybutanoic acid (*ehba*)–vanadate system (b). Calculations are for total vanadate concentrations of 3.0 mM and total ligand concentrations of 30 mM. $V_1^{1-}$, $VO_4H_2^-$; L, α-*hiba* (a) or *ehba* (b) anion.

rather small changes in pH of the medium. Similar behavior is observed for the *ehba* ligand (Fig. 5b). Table 3 compares product formation constants for *lac*, α-*hiba* and *ehba* (the formation constant for the L-lactate $V_3L_2$ complex was calculated from the information contained in reference [13]).

With chiral ligands such as L-(+)-lactate, the two vanadiums and the individual ligands in $V_2L_2$ are

Table 3
Product formation constants for the complexation of vanadate ($VO_4H_2^-$) with α-hydroxycarboxylic acids [a]

| Ligand (L) | Equilibrium equations | | |
|---|---|---|---|
| | $V^- + L^- \rightleftharpoons VL^{2-}$ | $2V^- + 2L^- + 2H^+ \rightleftharpoons V_2L_2^{2-}$ | $3V^- + 2L^- + 2H^+ \rightleftharpoons V_3L_2^{3-}$ |
| *lac* [a,b] | 9.3 | $9.1 \times 10^{19}$ | $2.6 \times 10^{23}$ |
| *hiba* [b] | 24 | $3.9 \times 10^{20}$ | $1.2 \times 10^{24}$ |
| *ehba* [b] | 23 | $9.6 \times 10^{20}$ | $7.2 \times 10^{25}$ |

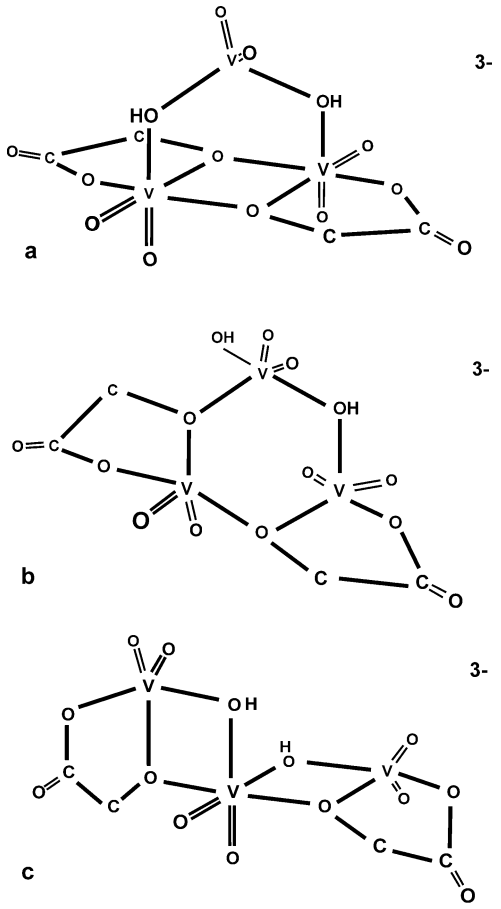
[a] Formation constants for 1 M ionic strength NaCl solution except for lactate which are for 1 M ionic strength with KCl and were calculated from the information in reference [13].
[b] *lac*, (*S*)-(+)-2-hydroxypropanoic acid (L-lactic acid): *hiba,* 2-hydroxy-2-methylpropanoic acid (α-hydroxyisobutric acid): *ehba,* 2-ethyl-2-hydroxybutanoic acid.

interconverted by rotation and, respectively, are identical. Therefore, $V_2L_2$ gives only one $^{51}$V-NMR signal. As of the requirements of coordination, only one such product can form. The situation is quite different for the diol case where, for instance, with the adenosine ligand, a number of products that correspond to various isomers are observed [26]. The evidence that is available suggests that the dimeric crystalline compounds of the type displayed in Fig. 1b do not change their coordination when dissolved in water [33]. If this is true, then the crystal structures available for $V_2L_2$ complexes can be used as a basis for assignment of a coordination geometry to $V_3L_2$. There seems to be three ways in which $V_3L_2$ might form. Taking the dimeric structure, Fig. 1b, it is possible that monoanionic vanadate adds across the face of the $\{VO\}_2$ plane in the fashion suggested by Scheme 2a. This gives rise to two vanadiums of octahedral coordination and one of tetrahedral coordination. With a chiral ligand such as lactate, the two octahedral vanadiums in this coordination scheme are equivalent. Consequently, observation of three NMR signals when a chiral α-hydroxycarboxylate ligand is complexed would lend strong support for such coordination. Such observations have not been reported.

It is also possible that $VO_4H_2^-$ inserts itself in a manner to afford a monocyclic $\{VO\}_3$ ring of pentacoordinate vanadiums, two of which bear the ligands as depicted in Scheme 2b. This mode of coordination seems unlikely because, even with achiral ligands such as *ehba* and α-*hiba* studied here, none of the vanadiums in such a ring system are equivalent. The NMR studies, both in water (α-*hiba*; −538, −569 ppm; *ehba*; −538, −578 ppm) and in acetonitrile (α-*hiba*; −519, −533 ppm), clearly suggest that two of the three vanadiums are equivalent.

An alternative way of generating the $V_3L_2$ complex is to insert the third vanadium between the two vanadiums of $V_2L_2$ in the manner suggested in Scheme 2c. This coordination mode provides one octahedral and two pentacoordinate vanadium centres. Chiral ligands in such a coordination scheme , as for **2a**, are identical. In principle, NMR studies cannot unambiguously differentiate between **2a** and **2c** of Scheme 2. However, because of a systematic influence of ligands on chemical shifts, the coordination depicted in Scheme 2c has tentatively been assigned to this product [33].

In itself, the coordination is quite unusual. Similar trivanadium species have not been reported. Additionally, the compound is quite readily formed (Table 3, Fig. 5). Formation of the α-*hiba* dimer, $V_2L_2^{2-}$, from two




Scheme 2. Possible coordination schemes for the bis ligated trivanadium complexes of α-hydroxyl carboxylic acids.

$VL^-$ precursors proceeds with a formation constant of $3.2 \times 10^5$ $M^{-1}$ compared with $3.1 \times 10^3$ $M^{-1}$ for formation of $V_3L_2^{3-}$ from $V_2L_2^{2-}$ and $V^-$. With the larger *ehba* ligand, formation of $V_2L_2^{2-}$ from the monomer decreases by a factor of 3 to $1.2 \times 10^5$ $M^{-1}$ while formation of $V_3L_2^{3-}$ from $V_2L_2^{2-}$ and $V^-$ increases by well over an order of magnitude to $7.5 \times 10^4$ $M^{-1}$. Conversely, with the smaller ligand, lactate, the formation of the dimer from 2 $VL^-$ ($5.2 \times 10^4$ $M^{-1}$) is smaller by a significant factor compared with the *hiba* and *ehba* ligands while formation of the trivanadium complex ($2.9 \times 10^3$ $M^{-1}$) is close to that for the *hiba* ligand. It is not at all evident what the source of this behaviour is. Clearly, the increases in formation constants with increases in ligand size cannot be attributed to steric interactions. The differences observed possibly are associated with the changes in p$K_a$ of the ligating groups as influenced by the moieties on the hydroxyl-bearing carbon, H, $CH_3$, and $CH_2CH_3$. Studies of the formation of aliphatic and aromatic vanadate esters have shown the importance of p$K_a$ on product formation [10,40]. Alternatively, there may be more subtle influences at work. For instance, the hydrophobic properties of the larger ligands might be important in promoting product formation.

The pH of the medium influences product formation. Product formation is determined not only by ligand and vanadate stoichiometries but also by the overall proton stoichiometry and by product p$K_a$ values. Under neutral conditions the product charge states are $V_2L_2^{2-}$ and $V_3L_2^{3-}$ and each complex requires incorporation of two protons when it is formed from $VO_4H_2^-$ and mono-anionic ligand. This contrasts with formation of VL which at neutral pH is $VL^{2-}$ and requires no protons for product formation. As a consequence of this proton stoichiometry, $VL^{2-}$ persists in solution with increase in pH. $V_3L_2^{3-}$ can lose a proton, p$K_a$ about 8.6, and, therefore, the proportion of this product relative to $V_2L_2^{2-}$ increases with increase in pH. Despite this, the overall proton stoichiometry of both $V_2L_2^{2-}$ and $V_3L_2^{3-}$ results finally in a rapid decrease in concentration and they are virtually nonexistent in solution at pH 9. Conversely, acidification of the medium assists product formation and since the H:V ratio is highest for $V_2L_2^{2-}$, an increase in acidity will promote formation of this product over the others and this trend will continue until $VL^{2-}$ is fully protonated. Further increases in acidity of the medium will not influence the $VL$–$V_2L_2$ ratio although changes in concentrations of other reactants will have an effect. These trends are clearly displayed in Fig. 5. Of course, additional products might be observed under different reaction conditions but such products have not been reported. Certainly the vanadate decamer, will be formed to an extent under acidic conditions and, ultimately, under very strongly acidic conditions the vanadate ion will act as a proton sink and its protonation will give the cationic species $V(O)_2(H_2O)_4^+$.

The three compounds of Scheme 2 have a common bidentate mode of complexation of the α-hydroxycarboxylate that is not significantly different from the coordination of 1,2-diol ligands. Even the presence of a coordinated peroxo group is insufficient to eliminate this as a viable mode for complexation [41,42]. A major difference between the chemistry of the diols and the α-hydroxy acids is that with the latter ligands there can be a high proportion of monomeric complex. For the 1,2-diols, even with such high affinity ligands as the nucleosides [43], the formation of monomer is at least a factor of ten lower than that found for α-*hiba* under comparable conditions.

The complexation of vanadate by homocitrate in a 1,2-fashion through the vicinal carboxylate and adjacent hydroxyl group [44] has been proposed for the FeV prosthetic group in vanadium-dependent nitrogenase [7]. It is interesting to speculate on the possible relevance of this coordination to the function of vanadium-dependent nitrogenase. The prosthetic group of this enzyme is not thought to contain vanadium in the V(V) oxidation state, but more likely it is V(IV). Additionally, the proposed coordination has vanadium in an octahedral environment. The chemistry associated with V(V) complexation of α-hydroxycarboxylic acids suggests, if V(V) is involved in the reduction cycle, that a five-coordinate structure is involved in the reaction. The likely candidate for modifying the vanadium coordination is the histidine imidazole that is coordinated in an octahedral complex. Removal of this ligand from the vanadium coordination sphere could moderate the redox potential of the prosthetic group by favoring a V(V) oxidation state. This opens the possibility that the histidine residue plays a role in the reductive process through its influence on the coordination about the vanadium nucleus.

The facile formation of the trivanadium species is a particularly intriguing aspect of the chemistry observed here. No similar compound has been reported for complexation by diols or other ligands. With the oxalato ligand, only monovanadium complexes are found which, on the basis of X-ray studies of the solids and the charge state in solution, almost certainly have octahedral coordination.

There is subtle balance between ligand properties and product coordination. There is no evidence that suggests aliphatic alcohols, even as the bis complexes, lead to an expansion of the coordination shell about vanadium, rather water is released. Similarly, even though they are bidentate ligands, the formation of either monomeric tetracoordinate or pentacoordinate products with diols is not at all favored, instead vanadate makes an accommodation by sharing ligating groups in a dimeric

structure. The five-membered ligand–vanadium ring generated by ligand complexation may well be strained in tetrahedral coordination. Pentacoordination relieves the strain and can do so by either retaining a hydroxo ligand or by dimerization. The available evidence shows that monomers, either tetracoordinate or pentacoordinate, are highly disfavored relative to the dimer. Estimates of the dimerization constant place it at about $5 \times 10^6\ M^{-1}$ [29,43,45]. It seems as though a monomeric pentacoordination scheme introduces too much electron density to the coordination sphere and vanadate compensates by sharing ligands in a dimeric structure.

The situation changes with the α-hydroxy acids where the increase in oxidation state means that such ligands are more highly electron withdrawing than are diol ligands. The incorporation of more electrons into the vanadium coordination sphere compensates for such a withdrawal of electrons. Two rather different ways of doing so are exhibited. In one way, a pentacoordinate monomeric product is formed where an additional hydroxo group serves as a source of electron density. This type of compound is highly favored over similar complexes of diols. An alternate method of attaining higher electron density is to insert a $VO_4H_2^-$ into the dimeric complex and thereby share ligating groups in an expanded coordination sphere about one or perhaps two of the vanadium nuclei (Scheme 2). Oxidation of the α-hydroxy carboxylic acid to oxalic acid further increases the electron-withdrawing capability of the ligand. In order to compensate for this, the coordination sphere is again expanded and only monomeric octahedral products have been described [13,39].

Arguments such as these suggest that vanadate complexation of the α-hydroxycarboxylic should be particularly sensitive to small changes in the electronic properties of the ligand. The significant changes in product formation on going through the series 2-hydroxypropanoic acid, 2-hydroxy-2-methylpropanoic acid and 2-ethyl-2-hydroxybutanoic acid bears this out.

Chemical constraints also place specific stereochemical requirements on the products. In the dimeric structure of the glycols and α-hydroxycarboxylic acid complexes, the 3-bonded bridging oxygen always derives from a hydroxl oxygen, not a carboxylate oxygen. In the case of chiral glycolic ligands, each ligand can be inserted into the structure in two ways to give up to three products. This is not possible with α-hydroxycarboxylic acids so only one type of dimer is obtained. Additionally, there is no hydroxyl oxygen in oxalate so that a dimer of the monooxalato complex would not be expected. The alternative is to expand the coordination sphere by incorporation either of water or a second oxalate group. Apparently, both such alternatives are adopted [13,35].

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