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Vanadium(V) Complexes of α-Hydroxycarboxylic Acids in Aqueous Solution

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^{51}V NMR and IR spectroscopic studies of the complexes formed between vanadate and the α-hydroxylic acid ligands, (*S*)-2-hydroxypropanoic acid (L-(+)-lactic acid), 2-hydroxy-2-methylpropanoic acid, and 2-ethyl-2-hydroxybutanoic acid were carried out for aqueous 1 M ionic strength (NaCl) solutions. Three major products in V to L stoichiometries of 1:1, 2:2, and 3:2 were identified from vanadate and ligand concentration studies, while a pH variation study allowed charge states to be determined. At pH 7.06, the formation constants for the predominant reactions were (26 ± 1) M^{-1}, ($V + L \rightleftarrows VL$); ($6.8 \pm 0.4) \times 10^3$ M^{-1}, ($2VL \rightleftarrows V_2L_2$); and ($3.5 \pm 0.3) \times 10^3$ M^{-1}, ($V_2L_2 + V \rightleftarrows V_3L_2$). Dissolution studies of various crystalline products were carried out for aqueous, nonaqueous, and mixed solvent systems. These studies combined with information available from X-ray structural studies provided a basis for the assignment of solution state structures. Pentacoordinate vanadium in a trigonal-bipyramidal geometry was proposed for the both the 1:1 and 2:2 complexes when in aqueous solution. Observed changes in ^{51}V chemical shift patterns were consistent with a cis fusion in octahedral coordination for the central vanadium of the 3:2 complex, while the remaining vanadiums retained a pentacoordinate geometry.

Introduction

Much of the current interest in the aqueous chemistry of vanadium has its origins in the remarkable biochemical impact of this metal. The vanadium(V) oxoanion, vanadate, is an inorganic analogue of phosphate. Dependent on the role of phosphate in the native system, vanadate can either activate or inhibit phosphate metabolizing enzymes. As an activator of functionality, vanadate seems to simply replace phosphate as a prosthetic group that allows substrate binding and promotes subsequent chemistry at a site remote from the vanadate (phosphate) center.[1,2] Vanadate seems most effective as an inhibitor when it is located in a position where chemistry would normally be done on a phosphate group in the corresponding position. This was exemplified a number of years ago when a uridine complex of vanadate was shown to be a potent ribonuclease inhibitor.[3] Subsequent studies have delineated the role of vanadium in such systems[4−7] and revealed the importance of the trigonal bipyramidal coordination in the inhibition process. Detailed studies of product formation with various glycols, including monosaccharides[8−10] and nucleosides,[11−14] have revealed a rather uncomplicated aqueous chemistry inherent to such systems. With increase in oxidation state of the ligating diol to oxalate, a very simple chemistry is found, there are only two dominant products, mono- and bisoxalato complexes.[15,16] However, the increase in oxidation state of the ligand from diol to oxalate is mirrored by an increase in vanadium coordination number from five to six.

Ligands such as lactate and similar α-hydroxy acids represent an intermediate state of oxidation, and, thus, it is not too surprising that the aqueous chemistry of vanadate in the presence of such ligands is more complex than has been observed for either of the extreme situations. It is certain from X-ray crystallography studies that α-hydroxy ligands can provide crystalline derivatives with a coordination[17−19] similar to that of diol complexes.[11] However, a number of products are observed in solution, and it seems likely they are of differing coordination geometries or, in the case of multinucleated products, even of mixed coordination. Over the years, considerable progress has been made in our understanding of aqueous

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vanadate chemistry, but questions concerning the identity of solution products formed in the presence of α-hydroxy acids still do arise. Although the chemistry is of considerable interest in its own right, these systems serve as models for enzymic reactions,[20] for instance as model compounds in the study of vanadium-dependent nitrogenases.[21] It is imperative for such studies that detailed information about the systems is available.

Crystalline compounds for which X-ray structures are available reveal a dimeric structure and a common coordination geometry about the vanadium in both diol and α-hydroxylic acid complexes.[10,11,17,18] The geometry at each vanadium center corresponds to a distorted trigonal bipyramidal coordination in a cyclic $[VO]_2$ core, where bridging occurs via a hydroxyl-derived oxygen atom of each of the ligands. Such a cyclic structure seems to be one of the defining characteristics of vanadate chemistry and its formation apparently is the driving force for the dimerization reaction.

A crystalline complex of 2-ethyl-2-hydroxybutanoic acid gives a ^{51}V NMR signal at −556 ppm when dissolved in water.[17] However, after equilibration several signals corresponding to additional products are observed. Similarly, NMR studies of vanadate with (*S*)-2-hydroxypropanoic acid (L-(+)-lactic acid) revealed the formation of a number of products. A question that immediately comes to mind is whether the structure of any of the observed solution products corresponds to that of the crystalline material, and if so, can a systematic assignment of chemical shifts be made for a series of related ligands. In this report, some aspects of the lactate and related α-hydroxy acid systems have again been explored, but the emphasis in this work has been placed on 2-hydroxy-2-methyl-propanoic acid (α-hydroxyisobutyric acid). This ligand provides well resolved vanadium signals so that some of the complications arising with the related ligands are reduced or eliminated. Solution equilibrium studies, X-ray crystallography, and ^{51}V NMR and FTIR spectroscopy has been used in our attempt to characterize these systems.

Experimental Section

Materials. All chemicals used in this work are reagent grade. Divanadium(V) pentoxide (Aldrich Chemical Co.), tetraethylammonium hydroxide (20% aqueous solutions), L-(+)-lactic acid, α-hydroxyisobutyric acid, 2-ethyl-2-hydroxybutyric acid, *N*-(2-hydroxyethyl)piperazine-*N*′-ethanesulfonic acid (HEPES buffer) (Sigma Chemical Co.), bis(triphenylphosphoranylidene)ammonium chloride, and tetraphenylarsonium chloride (Sigma-Aldrich) were used without further purification.

Solutions. The techniques utilized here for the studies of solution equilibria have been described elsewhere[15] and are summarized briefly below. A stock solution of 0.06 M vanadate was prepared. An α-hydroxyisobutyric acid stock solution of 1.0 M concentration was prepared by dissolving the required amount of the compound in distilled water. HEPES buffer (0.4 M) and 4.0 M NaCl stock solution were both prepared in distilled water. All solutions were prepared at an ionic strength of 1.0 M by adding appropriate amounts of NaCl. For calculation of the ionic strength of the solutions, it was assumed that all of the carboxylic acid groups were fully deprotonated throughout the pH range used in the experiments reported here. Caution has been taken when the solutions are prepared at lower pH values so as to minimize formation of decavanadate. Appropriate amounts of ligand, buffer, and NaCl were first diluted by distilled water to 1.0−2.0 mL less than the final volume (10 mL). The pH of the solution was adjusted to about 0.2 pH units below the desired pH value by adding NaOH solution and then the appropriate amount of vanadate as $H_2VO_4^-$ in a stock solution. The final volume was reached by adding more water, and the pH was adjusted to its final value. At no time was acid added to the vanadate solutions.

Complexes of α-Hydroxycarboxylic Acids with Vanadate. i) $[VO_2(OC(HCH_3)COO)]_2(NEt_4)_2$. Solid V_2O_5 (0.182 g; 1 mmol) was added to a solution of 20% (W/W) aqueous solution of tetraethylammonium hydroxide (1.5 mL) and water (4 mL). The resultant slurry was warmed to 60 °C with constant stirring to obtain a clear solution of tetraethylammonium vanadate. This solution was filtered, and solid lactic acid (0.36 g; 4 mmol) was added with constant stirring. The pH of the resultant solution, which was initially ∼3.0, was raised to ∼6.3 by adding Et_4NOH. A continuous stream of air was then passed through the solution until a viscous liquid was obtained. About 10 mL of acetonitrile was added to this liquid. Further additions of diethyl ether, until the solution became somewhat cloudy (7 mL), yielded a needle shaped pale yellow crystalline product after sitting. Cooling of the solution afforded a higher yield of the product. The crystals were filtered and dried in vaccuo. Yield: 0.366 g (61%). Anal. calcd for $[VO_2(OC(HCH_3)COO)]_2(NEt_4)_2$: C, 43.83; H, 8.03; N, 4.65. Found: C, 44.08; H, 8.36; N, 4.65.

ii) $[VO_2(OC(HCH_3)COO)]_2(Ph_3P{=}N{=}PPh_3)_2$. To a viscous liquid, obtained as described above, an acetonitrile solution (15 mL) of bis(triphenylphosphoranylidene)ammonium chloride (1.148 g; 2 mmol) was added, and the resultant mixture was left in air overnight. The pale yellow crystalline compound obtained was filtered, washed with acetonitrile, and dried in vaccuo. Yield: 1.109 g (78%). Anal. calcd for $[VO_2(OC(HCH_3)COO)]_2\ (Ph_3P{=}N{=}PPh_3)_2$: C, 65.99; H, 4.83; N, 1.97. Found: C, 65.77; H, 4.83; N, 1.99.

iii) $[VO_2(OC(CH_3)_2COO)]_2(NEt_4)_2$. An equimolar amount of α-hydroxyisobutyric acid was added to tetraethylammonium vanadate solution (prepared as described above). A stream of air was passed over the resultant material (pH = ∼6.8) to yield a solid product. The solid compound thus obtained was recrystallized from an acetonitrile/diethyl ether (1.5:1) mixture. Two types of pale yellow crystals were obtained, larger square-shaped and smaller needle-shaped ones. It was observed that slow crystallization of the compound from acetonitrile and diethyl ether afforded only the square crystals, whereas rapid crystallization provided both types of crystals. Also at higher pH (≥7), formation of needle shaped crystals was favored; at pH < 7, square crystals were formed more easily. Attempts to isolate only the needle shaped crystals in a form suitable for X-ray studies failed. Anal. calcd for $[VO_2(OC(CH_3)_2COO)]_2(NEt_4)_2$: C, 45.69; H, 8.32; N, 4.44. Found: C, 45.87; H, 8.52; N, 4.33.

iv) $[\{VO_2(OC(CH_3)_2COO)\}_2VO_2(OH)_2](NEt_4)_3$. For preparation, see procedure iii above. Needle shaped crystals resulted. Anal. calcd for $V_3C_{32}H_{74}O_{14}N_3$: C, 43.77; H, 8.50; N, 4.79. Found: C, 43.82; H, 8.55; N, 4.65. ^{51}V NMR (CH_3CN): −519, −533 ppm with intensity ratio 1.0:0.51 for the −519:−533 signal ratio.

v) $[VO_2(OC(CH_3)_2COO)]_2(Ph_4As)_2$. The solid mass obtained from the mixture of α-hydroxyisobutyric acid and tetraethylammonium vanadate (2 mmol) was dissolved in 15 mL of water, and tetraphenylarsonium chloride (0.82 g, 2 mmol) was added with stirring. The clear solution was kept in air. The fine, shiny pale yellow crystals thus obtained were filtered and washed, first with a 1:1 water−acetonitrile mixture, followed by 1:1 acetonitrile−ether mixture, and finally with ether. Yield: 0.95 g (81%). Anal. calcd for $[VO_2(OC(CH_3)_2COO)]_2(Ph_4As)_2{\cdot}2H_2O$: C, 57.32; H, 4.81. Found: C, 57.24; H, 4.76.

vi) $[VO_2(OC(CH_2CH_3)_2COO)]_2(NEt_4)_2$. An equimolar amount of 2-ethyl-2-hydroxybutyric acid was added to a tetraethylammonium vanadate solution (2 mmol), the pH of the resultant solution (pH = ∼2.8) was raised to ∼6.1, and finally the solution was left in air overnight. A pale yellow crystalline compound was obtained. It was filtered, washed with an acetone−water mixture (2:1), and then dried in vaccuo. Yield: 0.56 g (82%). Anal. calcd for $[VO_2(OC(CH_2CH_3)_2COO)]_2(NEt_4)_2$: C, 48.95; H, 8.81; N, 4.08. Found: C, 48.94; H, 8.97; N, 3.99.

vii) $[VO_2(OC(CH_2CH_3)_2COO)]_2(Ph_4As)_2$. The crystalline compound ($[VO_2(OC(CH_2CH_3)_2COO)]_2(NEt_4)_2$) obtained from the above

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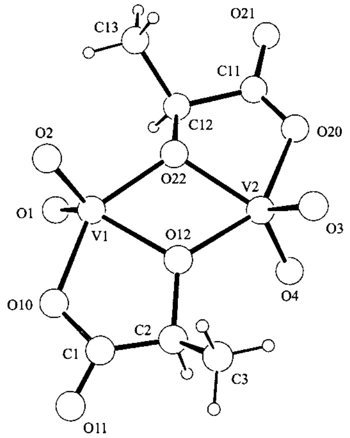

Figure 1. X-ray structure diagram of the bis ligand divanadium complex formed between vanadate and L-(+)-lactic acid.

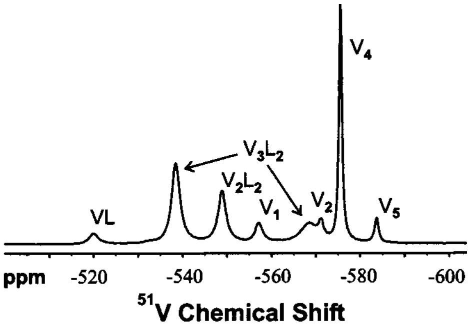

Figure 2. ^{51}V NMR spectrum of an aqueous solution of vanadate with α-hydroxyisobutyric acid at pH 7.06. Conditions of the experiment: 9 mM total vanadate, 30 mM α-hydroxyisobutyric acid, 20 mM HEPES buffer, and 1.0 M ionic strength (NaCl).

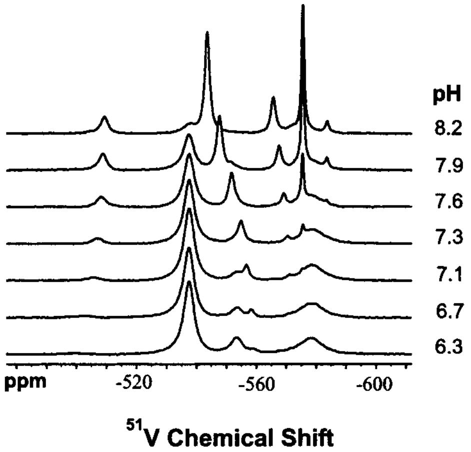

Figure 3. ^{51}V NMR spectra showing the pH dependence of product distribution in the equilibrium reactions of vanadate with 2-ethyl-2-hydroxybutyric acid. Conditions of the experiments: total vanadate, 3 mM; 2-ethyl-2-hydroxybutyric acid, 30 mM and 1.0 M ionic strength (NaCl); 20 mM HEPES buffer; pH as indicated. Bottom trace signal positions: V_3L_2, −538, −578 ppm; V_2L_2, −554 ppm; VL, −500 ppm; V_1, −559 ppm.

process was dissolved in 15 mL of water, and tetraphenylarsonium chloride (0.82 g, 2 mmol) was added with stirring. The clear solution was kept in air. The fine, light yellow crystals obtained were filtered and washed thoroughly with a 1:1 water−acetonitrile mixture, followed by 1:1 acetonitrile−ether mixture, and finally with ether. Yield: 0.8 g (67%). Anal. calcd for $[VO_2(OC(CH_2CH_3)_2COO)]_2(Ph_4As)_2$: C, 60.38; H, 5.07. Found: C, 60.47; H, 5.09.

Spectroscopy. ^{51}V NMR spectra were obtained from a Bruker AMX600 NMR spectrometer operating at 157.7 MHz at ambient temperature (21 °C). Vanadium chemical shifts are reported relative to the chemical shift of $VOCl_3$ at 0 ppm. The following NMR parameters were used: pulse width 60°; spectral width 62 kHz; acquisition time 0.06 s; number of scans, 20,000; line broadening, 40.0 Hz; frequency domain size, 16 K.

FTIR spectra were obtained from a BOMEM MB-102 instrument. All solution spectra were observed using a 0.15 mm zinc−selenide cell. Aqueous solutions were prepared with water at pH 7.00. In each of the mixed solutions spectra, the absorbance of individual solvent mixtures were recorded and used as the reference.

Analytical Methods. Equilibrium equations were obtained as summarized in the text. Analytical equations, generally in linear form, were derived as outlined, and the data were subjected to least-squares analysis. All errors are reported at the 95% confidence level.

Results and Discussion

X-ray Diffraction. Attempts to grow crystals of the lactatovanadate complexes suitable for X-ray crystallography proved only partially successful. The soft crystalline material, $[VO_2(OC(HCH_3)COO)]_2(Ph_3P{=}N{=}PPh_3)_2$, which was finally utilized did not afford a high quality diffraction pattern. The data were suitable for obtaining a low resolution structure (see Supporting Information) and established unambiguously the atom connectivity within the complex. The structure obtained (Figure 1) did not differ in any important aspects from that recently reported for the cesium salt of the lactate complex[18] or those of other α-hydroxy acids.[17−19] The structure of this crystalline material was necessary for the assignment of NMR and IR signals in the dissolution studies.

Solution Studies of Vanadate with α-Hydroxycarboxylic Acids. Previous studies of the equilibria between vanadate and its lactate complexes in aqueous solution showed the presence of products giving rise to ^{51}V NMR signals at −517 and −533 ppm. A third signal (−550 ppm) corresponding to a minor product was also observed under appropriate reaction conditions. Structural assignments were made in the early studies of this system,[15] but expansion in the information base over the past years makes it imperative that those assignments be revised. Unfortunately, X-ray crystals structures are available for only the coordination scheme depicted in Figure 1, while NMR studies clearly show multiple types of complexes. An initial ^{51}V NMR survey of the solution chemistry, not unexpectedly, revealed a close correspondence in the complexation of vanadate by various α-hydroxy acids. For both 2-ethyl-2-hydroxybutanoic acid (EHBA) and 2-hydroxy-2-methypropanoic acid (α-hydroxyisobutyric acid, α-HIBA) at pH 7.0, three distinct ^{51}V signals and one additional broad signal were observed in the NMR spectrum. Figure 2 shows a ^{51}V NMR spectrum of 9 mM vanadate solution, at pH 7.06, containing 30 mM α-HIBA. Three major product resonances occur at −520, −538, and −549 ppm. There is an additional very broad signal at −569 ppm while, with EHBA, a correspondingly broad signal occurs at −579 ppm. The remaining signals are from vanadate, V_1, its dimer, V_2, and tetramer, V_4, as indicated in Figure 2. The spectra obtained from vanadate solutions with EHBA were similar to those of α-HIBA solutions. However, an initial pH variation study of the interaction of vanadate with EHBA (Figure 3) revealed that there might be substantial problems with fully characterizing this system throughout the desired pH range. Other preliminary investigations suggested that the α-HIBA system would be a better system for a detailed study. To this end, the various NMR signals were studied as a function of α-HIBA, vanadate, and hydrogen ion concentration.

When the total vanadate concentration was varied at a fixed 30 mM α-HIBA concentration at pH 7.06, it was observed that

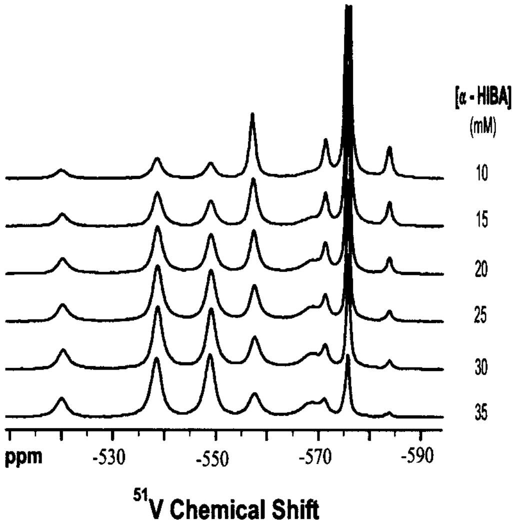

Figure 4. ^{51}V NMR spectra showing the change in relative intensities of the various vanadate signals as the α-hydroxyisobutyric acid concentration is increased. For assignment of signals, see Figure 2. Conditions of the experiments: 3 mM total vanadate; α-hydroxyisobutyric, as indicated; 20 mM HEPES; 1 M constant ionic strength (NaCl); and pH 7.06.

the relative signal intensities of the −556 (V_1) and −520 ppm signals remained constant while those of the −538 and −549 ppm signals increased strongly relative to that of V_1 (Supporting Information). Additionally, the −538 ppm signal increased in intensity relative to that at −549 ppm. These observations indicated that the species giving rise to the −520 ppm signal contains one vanadium nucleus while those corresponding to the −538 and −549 ppm signals contain more than one vanadium atom. Moreover, the number of vanadium centers corresponding to the −538 ppm signal is greater than that corresponding to the −549 ppm signal.

When the ligand concentration was increased in a stepwise fashion with a constant 3 mM total vanadate (pH 7.06), it was observed that the −549 ppm signal increased in intensity relative to the −538 ppm signal. This indicated that the corresponding products did not have the same V:L stoichiometry. Since the increase in the −520 ppm signal was small relative to the −538 and −549 ppm signals (Figure 4), it followed that the −520 ppm product has fewer ligands than either the −538 or −549 ppm products. Taken together, these observations suggest that the following equations might describe the equilibria in this system, where $[V_1]$ is the concentration of uncomplexed vanadate at −556 ppm.

$$2V_1 \overset{K_{120}}{\rightleftharpoons} V_2 \quad [V_1]^2 K_{120} = [V_2] \tag{1}$$

$$4V_1 \overset{K_{140}}{\rightleftharpoons} V_4 \quad [V_1]^4 K_{140} = [V_4] \tag{2}$$

$$V_1 + L \overset{K_{111}}{\rightleftharpoons} VL_{-520} \quad [V_1][L]K_{111} = [VL]_{-520} \tag{3}$$

$$2V_1 + 2L \overset{K_{122}}{\rightleftharpoons} V_2L_{2-549} \quad [V_1]^2[L]^2 K_{122} = [V_2L_2]_{-549} \tag{4}$$

$$3V_1 + 2L \overset{K_{132}}{\rightleftharpoons} V_3L_{2-538} \quad [V_1]^3[L]^2 K_{132} = [V_3L_2]_{-538} \tag{5}$$

The remaining product signal (−569 ppm) was quite broad and more difficult to characterize. However, in the vanadium concentration study, this signal increased in amplitude more rapidly than the signal from V_2, but not as fast as that from V_4. This behavior is demonstrated by Figure 5 , where the 3.0 and 10.5 mM total vanadate spectra are shown together with a difference spectrum. For the difference spectrum, the −538 ppm signals of the two spectra were scaled to the same amplitude and the spectra subtracted. Signals with a lower vanadium stoichiometry than the −538 ppm product give positive residual signals (V_1, V_2, VL, and V_2L_2); those with higher vanadium stoichiometry provide negative residual signals (V_4 and V_5).

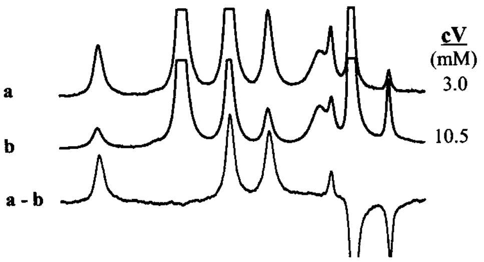

Figure 5. ^{51}V spectra of 3.0 and 10.5 mM total vanadate with 30 mM α-hydroxyisobutyric acid, and the difference spectrum is shown. In the difference spectrum, residual signals with a higher vanadium stoichiometry than correspond to the −538 ppm compound are negative, those with a lower vanadium stoichiometry are positive. For signal assignments, see Figure 2. Conditions of the experiments: variable total vanadate concentration, as indicated; α-hydroxyisobutyric acid, 30 mM; 20 mM HEPES; 1.0 M ionic strength (NaCl); and pH 7.06.

In the difference spectrum (Figure 5a−b), no residual −569 ppm signal intensity was observed. This indicates that the −538 and −569 ppm signals correspond to identical vanadium stoichiometries. The signals, apparently, then derive from a trinuclear species. Since any V_3L_2 product would not be expected to have three chemically equivalent vanadiums, it seems likely that the −569 ppm signal corresponds to one of the three signals expected, with the remaining two being observed at −538 ppm. This agrees with the relative signal intensities where, as near as can be judged, the −538 ppm signal intensity is twice that of the −569 ppm signal. Thus, for the calculations of free ligand concentration, it was assumed that the broad peak at −569 ppm originated from a V_3L_2 product that contains two types of vanadium centers in a 2:1 ratio. On this basis, free L can be calculated from the conservation equation (eq 6), where $[V_3L_2]_{total} = 1/3(cV_3L_{2-539} + cV_3L_{2-569})$ and c indicates a vanadium atom concentration.

$$[L]_{free} = [L]_{total} - [VL]_{-520} - 2[V_2L_2]_{-549} - 2[V_3L_2]_{total} \tag{6}$$

Previous studies with lactate[15] have shown that two products of VL stoichiometry are formed, one apparently being in rapid exchange with free vanadate. A suitable reference for ascertaining stoichiometries is then required and is provided by V_4. Combination of eq 2 with eq 3 gives eq 7, where the signal at −556 ppm is assumed to derive from V_1 and a VL.

$$\frac{cV_{556}}{[V_4]^{1/4}} = \frac{1}{K_{140}^{\;1/4}}(1 + [L]K_{111}^{\;0}) \tag{7}$$

From the data, $K_{140} = (1.3 \pm 0.6) \times 10^{10}$ M^{-3} and $K_{111}^{0} = 2.3 \pm 2.6$ M^{-1}. As a check, V_5 instead of V_4 was utilized as the reference compound, and the value of K_{111}^{0} obtained was 2.6 ± 1.6 M^{-1}. This value of K_{111}^{0} is a little larger than the value for lactate but, within the 95% confidence intervals, is not significantly different. This product is expected to correspond to a reaction between vanadate and the hydroxyl group of the α-hydroxy acid. Condensation with hydroxyl groups to form vanadate esters is a well-known reaction for vanadate. There

Table 1. Formation Constants for Various Products of the Reaction of Aqueous Vanadate with α-Hydroxyisobutyric Acid[a]

equilibrium equation	formation constant	pH
$V_1 + L \rightleftharpoons VL^{b1}$	$(26 \pm 1)\ M^{-1}$	7.06
$2V_1 + 2L \rightleftharpoons V_2L_2^{b2}$	$(4.6 \pm 0.2) \times 10^6\ M^{-3}$	7.06
$3V_1 + 2L \rightleftharpoons V_3L_2^{b3}$	$(1.6 \pm 0.1) \times 10^{10}\ M^{-4}$	7.06
$V_2L_2 + V_1 \rightleftharpoons V_3L_2$	$(3.5 \pm 0.3) \times 10^3\ M^{-1}$	7.06
$2VL \rightleftharpoons V_2L_2$	$(6.8 \pm 0.4) \times 10^3\ M^{-1}$	7.06
$V_1^- + L^- \rightleftharpoons VL^{2-}$	$(24 \pm 1)\ M^{-1}$	variable
$VL^- \rightleftharpoons VL^{2-} + H^{+b4}$	$10^{(-6.2 \pm 0.1)}$	variable
$2V_1^- + 2L^- + 2H^+ \rightleftharpoons V_2L_2^{2-}$	$(3.9 \pm 0.2) \times 10^{20}\ M^{-5}$	variable
$3V_1^- + 2L^- + 2H^+ \rightleftharpoons V_3L_2^{3-}$	$(1.2 \pm 0.1) \times 10^{24}\ M^{-6}$	variable
$V_3L_2^{3-} \rightleftharpoons V_3L_2^{4-} + H^+$	$10^{(-8.4 \pm 0.3)}$	variable

[a] All errors in parameters are quoted at the 3σ level. [b] For 2-ethyl-2-hydroxybutyric acid, the equilibrium constants at pH 7.1 are: *b1*, 20 ± 3 M^{-1}; *b2*, $(3.3 \pm 0.7) \times 10^6\ M^{-3}$; *b3*, $(2.7 \pm 0.6) \times 10^{11}\ M^{-4}$; and *b4*, $pK_a = 6.6 \pm 0.1$

may be some contribution from reaction at the carboxylate group to form an acid anhydride, a reaction observed with other carboxylic acids.[22]

The formation constant ($K_{111}{}^1$) for the VL product giving a signal at −520 ppm can be obtained from eq 3 by plotting $[VL]_{-520}/[L]$ against $[V_1]$ to yield a straight line of slope $K_{111}{}^1$. The concentration of V_1 is provided from that of V_4 by eq 2. When the data was plotted, a good linear relationship was obtained, and the value determined to be $K_{111}{}^1 = (26 \pm 1)\ M^{-1}$. At sufficiently high ligand concentrations, this type of product can incorporate an additional ligand as has been shown for lactate and glycerate.[15] This and other formation constants are summarized in Table 1.

Formation of the −549 ppm product follows directly from eq 4 (if a V_2L_2 stoichiometry is assumed) by using eq 2 to give the V_1 concentration and the conservation equation, eq 6, to give the noncomplexed L concentration. The linear correlation obtained was fully consistent with a V_2L_2 stoichiometry and provided a formation constant $K_{122} = (4.6 \pm 0.2) \times 10^6\ M^{-3}$ at pH 7.06. An equally good correlation was obtained for the −538 ppm product when a V_3L_2 stoichiometry was assumed. From eq 5, a plot of the concentration of the −538 ppm product versus $[V_1]^3[L]^2$ should be linear. This was observed (Supporting Information), and $K_{132} = (1.64 \pm 0.09) \times 10^{10}\ M^{-4}$.

Although the −569 ppm signal has been tentatively assigned to one signal of the two expected for a symmetrical V_3L_2, it is possible to support this assignment by treating the −569 ppm signal and that from V_2 (−572 ppm) as a single superimposed signal. Combining eq 2 with eq 5 and plotting the experimental data appropriately gives $K_{132} = (1.3 \pm 0.2) \times 10^{10}\ M^{-4}$. The good agreement between this and the above value of K_{132} strongly supports the assignment of the −538 and −569 ppm signals to the same V_3L_2 product.

As observed for the EHBA system (Figure 3), there is a substantial influence of pH on the spectra of the α-HIBA complexes. Figure 6 shows the effect of changing the pH of a 3 mM total vanadate solution containing 30 mM α-HIBA. At pH 6.07, no product corresponding to the −520 ppm (VL) signal was observed, and all vanadate was converted to other products, with V_2L_2 being the major product and V_3L_2 being the minor one. At pH 6.65, a moderate amount of free vanadate was released, and a small signal for VL was observed. The proportion of V_2L_2 relative to V_3L_2 decreased markedly. By pH 7.43, V_2L_2 was almost missing from solution, V_3L_2 was present in moderate concentrations, and VL was the major product. At pH 7.82, VL was the only product present in any significant concentration, and much of the vanadium was found as free vanadate and its oligomers. The large changes in product ratios reflect the proton requirements for product formation so that the pH independent formation constants can be obtained and product protonation states specified.

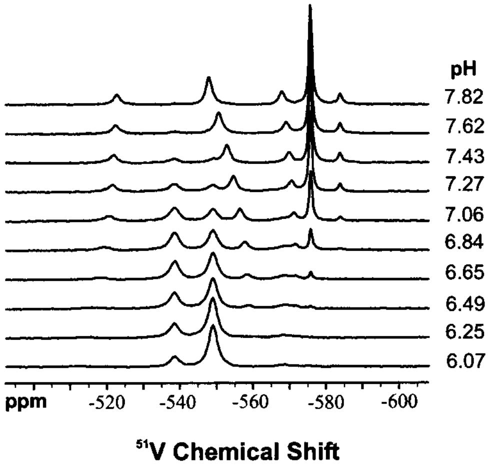

Figure 6. pH variation study for the interaction of vanadate with α-hydroxyisobutyric acid. For assignment of signals, see Figure 2. Conditions of the experiments: total vanadate, 3 mM; α-hydroxyisobutyric acid, 30 mM; and 1.0 M constant ionic strength (NaCl).

Observation of the ^{51}V chemical shift of the VL (−520 ppm) product as a function of pH revealed a systematic change in chemical shift with increase in acidity from pH 7.82. Such a variation is typical of a change in a protonation/deprotonation equilibrium, and the corresponding pK_a can be determined if it is assumed the variation of chemical shift derives solely from a protonation/deprotonation equilibrium. Unfortunately, the low pH chemical shift limit was not very well established by this study as the VL was converted into other products. However, a value for the low pH limit can be obtained because eq 8, which relates pH, pK_a, and chemical shifts,[23] requires a slope of 1. For this equation, δ_l is the low pH chemical shift limit, δ_h is the high pH limit, and δ_o is the observed value.

$$\mathrm{pH} = \mathrm{p}K_a + \log\,[(\delta_l - \delta_o)/(\delta_o - \delta_h)] \qquad (8)$$

Since a reasonable proportion of the full range of chemical shifts as a function of pH and the high pH limiting shift (−523 ppm) are known, the pK_a and low field limiting shift can be simultaneously be determined. The low pH limit was found to be −505 ppm and the pK_a was 6.2 ± 0.1. For the EHBA ligand, the corresponding value for the pK_a was determined to be 6.6 ± 0.1, with low and high pH chemical shift limits of −495 and −510 ppm, respectively. These measurements quantitate only the change in protonation state. The ionic state must be established by other means.

To establish the ionic state of the product from equilibrium studies, it is necessary to take into account the hydrogen ion concentration in the medium and the ionic states of the reactants and their pK_a's. Since the pK_a of the carboxylic acid ligand is well below the pH of the medium employed in this study, the ligand is monoanionic. Unfortunately, vanadate ($VO_4H_2^-$), which has a pK_{a2} of about 7.9 at 1 M ionic strength with NaCl (a value previously known[24] but also found here), has its NMR signal superimposed on that of a second VL product and thus

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(22) Tracey, A. S.; Li, H.; Gresser, M. J. *Inorg. Chem.* **1990**, *29*, 2267−2271.

(23) Tracey, A. S.; Gresser, M. J. *Can. J. Chem.* **1988**, *66*, 2570−2574.

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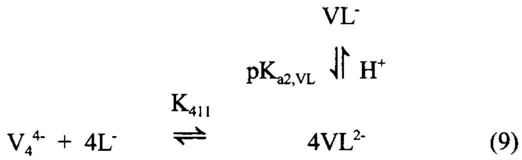
does not provide a suitable reference. However, over a wide pH range, both tetravanadate, $V_4O_{12}^{4-}$, ($V_4{}^{4-}$), and pentavanadate, $V_5O_{15}^{5-}$, (V_5^{5-}), carry a single negative charge per vanadium.[25,26] They therefore may be used to probe the protonation state of other products.

The formation of VL from V_4 can be written as described by eq 9,



$$\begin{array}{ccc} & & VL^- \\ & pK_{a2,VL} & \downharpoonleft\upharpoonright\ H^+ \\ V_4^{4-} + 4L^- & \overset{K_{411}}{\rightleftharpoons} & 4VL^{2-} \end{array} \qquad (9)$$

which can be reformulated as in eq 10. The results of the pH variation study, when plotted according to eq 10, showed that the product giving rise to the −523 ppm signal was dianionic.

$$(1 + [H^+]/K_{a2})\, K_{411}^{1/4} = c\mathrm{VL}/[V_4^{4-}]^{1/4}[L^-] \qquad (10)$$

Protonation then gives the monoanionic product at −505 ppm. The same conclusion was obtained when V_5^{5-} was utilized as the reference compound.

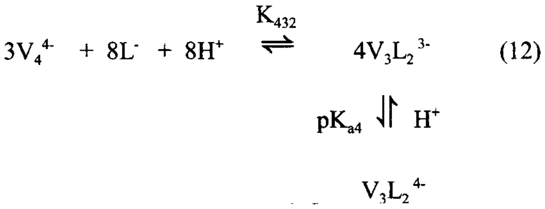
V_2L_2 requires protons for its formation and also might have a pK_a. When its formation was plotted according to eq 11, an excellent linear relationship was obtained (Supporting Information).

$$V_4^{4-} + 4L^- + 4H^+ \overset{K_{422}}{\rightleftharpoons} 2V_2L_2^{2-}$$

$$[V_4^{4-}]^{1/2}[L]^2[H^+]^2 K_{422}^{1/2} = [V_2L_2^{2-}] \qquad (11)$$

Therefore, like it does in the solid, V_2L_2 carries a doubly negative charge in aqueous solution. There was no indication that this product has a pK_a that influences its behavior within the range of pH of this study. If the structure of the compound in aqueous solution is the same as that found in the solid, then the product has no protons to release; therefore, the lack of a pK_a is consistent with that structure. Of course, there is the possibility of protonation under the mildly acidic conditions of this study, but that also was not observed.

In the solid, V_3L_2 is triply negative charged, as ascertained from the analytical data. However, the characterization of the charge state dependence of V_2L_3 proved to be difficult. Formation of this product from three $VO_4H_2^-$ and two α-HIBA ligands requires the incorporation of a minimum of two protons. The initial plot of the data (Supporting Information) showed a small amount of curvature. This suggested that $V_3L_2^{3-}$ has a pK_a, and this can be taken into account as expressed by eq 12. An appropriate plot of the experimental data was in accord with



$$\begin{array}{ccc} 3V_4^{4-} + 8L^- + 8H^+ & \overset{K_{432}}{\rightleftharpoons} & 4V_3L_2^{3-} \\ & pK_{a4} & \downharpoonleft\upharpoonright\ H^+ \\ & & V_3L_2^{4-} \end{array} \qquad (12)$$

eq 12 and suggested that pK_{a4} = 8.4 ± 0.3. This value is not well determined by this study, but the fact that V_3L_2 persists in solution longer than V_2L_2 with increase in pH (Figure 3, Figure 6) is in accord with such a pK_a. Table 1 summarizes various formation constants measured in this study.

^{51}V NMR and FTIR. Immediately after its dissolution into aqueous solution, the lactate complex, $[VO_2(OC(HCH_3)COO)]_2(NEt_4)_2$, gave a ^{51}V NMR signal at −533 ppm. Dissolving the complex in acetonitrile provided a signal at −509 ppm, a positive shift of 24 ppm. Similarly, large changes in chemical shifts (+ 26 ppm, α-HIBA; +28 ppm, EHBA) were observed for the other ligands of this study (Supporting Information). The question arises as to the source of this large change in chemical shift. Does it arise simply because of solvent effects, or is its source a change in coordination geometry about the vanadium center because of a coordinating solvent? Acetonitrile has, for instance, been shown to coordinate, to about a 50% extent, with a β-mercaptoethanol complex[27] that, even though it has a sulfur in the coordination sphere, has a geometry about vanadium that is similar to that of this lactate complex. However, in contrast to the situation here, where only one V═O stretch was observed in the IR spectrum, two V═O stretching bands were observed in the IR spectrum of the β-mercaptoethanol complex.[27] This suggests that, in the present situation, there is only one complex.

The V_2L_2 lactate complex with the large hydrophobic cation, $Ph_3P{=}N{=}PPh_3$, instead of Et_4N is quite soluble in many organic solvents. ^{51}V NMR spectra of this latter compound in both acetone and chloroform solutions were obtained. The chemical shift in acetonitrile solution was found to be similar to that for the same complex but with the tetraethylammonium cation, −509 ppm. The corresponding chemical shifts for acetone and chloroform solutions were −506 and −512 ppm, respectively (Supporting Information). This situation is different from that observed with the mercaptoethanol complex where, relative to the acetonitrile solution, the signal from the chloroform solution shifted to low field by 9 ppm as compared to a high field shift of 3 ppm for this complex.

When mixtures of acetonitrile and water, in different proportions, were used, a single signal but with a systematic change in chemical shift was observed for all ligands (Supporting Information). This could mean that there is no change in coordination, but does not exclude the possibility that there are two rapidly interconverting coordination geometries. In order for signal coalescence to occur, the rate of interconversion would be faster than the millisecond time scale of the NMR experiments. A low temperature study carried out with the appropriate mixed solvent concentrations to give the product chemical shift in the middle of its chemical shift range failed to reveal two signals for the α-HIBA complex.

Taken together, these observations suggest that the coordination geometry of the vanadium in water, in acetonitrile, and in acetone and chloroform is the same. Since the evidence also suggests that the solid-state coordination geometry (Figure 1) of the vanadium in V_2L_2 is preserved in acetonitrile, V_2L_2, therefore, has the same geometry in water. Some support for this conclusion is also provided by the vanadium chemical shifts of V_3L_2. The two NMR signals (−519 and −533 ppm) from the α-HIBA complex are downfield by 19 and 36 ppm compared to the water solution when the compound is dissolved in acetonitrile. This variation is comparable to that observed for V_2L_2, but it seems somewhat unlikely that all three vanadiums of V_3L_2 would undergo a chemical change that would influence all chemical shifts in a similar manner. Although this possibility cannot be ruled out, it seems more likely that there is no change in coordination of any of the vanadiums.

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(26) Larson, J. W. *J. Chem. Eng. Data* **1995**, *40*, 1276−1280.

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Table 2. ^{51}V NMR Chemical Shifts of Vanadium α-Hydroxy Carboxylic Acid Complexes in Aqueous 1.0 M Ionic Strength (NaCl) Solution

α-hydroxycarboxylate ligand	chemical shift (ppm)			
	VL^-	VL^{2-}	$V_2L_2^{2-}$	$V_3L_2^{3-}$
L-(+)-lactic acid		-517	-533	-533, -550
α-hydroxyisobutyric acid[a]	-505	-523	-549	-538, -569
2-ethyl-2-hydroxybutyric acid	-495	-510	-554	-538, -578

[a] Chemical shifts for the V_3L_2, α-HIBA complex in H_2O, -538, -569 ppm; CH_3CN, -519, -533 ppm.

The bisligand trivanadate species has not previously been reported. With lactate, where it is a minor product and the NMR signals overlap those of V_2L_2, the product was assigned to a mixed coordination bisvanadium product.[15] However, with the sidechain substitution of the other two ligands utilized here, the formation of the product is more highly favored. Additionally, the replacement of H in lactate by CH_3 to form α-HIBA causes a large change in the product chemical shift (Table 2). Not only does this simplify the analysis by improving spectral resolution but those changes also offer some clues as to what structure the product might have. It has previously been shown that substituents have a systematic influence on vanadium chemical shifts.[28] Additionally, alkyl group substitution patterns in vanadate alkyl esters have been found to have a clearly definable effect on chemical shifts,[23] as does the substitution pattern in methylated hydroxylamine complexes.[29] The products formed here apparently follow a similar pattern of dependency of chemical shift on alkyl substitution.

Since two signals in a 2:1 intensity ratio are observed, it can be inferred that the V_3L_2 product has two types of vanadium nuclei and two-fold symmetry. Additional information can be gleaned from Table 2. The products giving the signals in the region of -495 to -523 ppm are monoligand monovanadate compounds. The five-membered ring that is generated when the complex forms has the sidechains (H, CH_3 for lactate) across the ring from the vanadium and directed away from the vanadium oxo center (Scheme 1a). In this case, replacement of the H by a CH_3 has a small effect on the V chemical shift, changing it by about -5 ppm. Similarly, replacing each methyl by an ethyl residue had a total cumulative influence of about $+10$ ppm. For the bisligand bisvanadium product (Scheme 1b), replacement of the H by CH_3 causes a -15 ppm shift, with a further -6 ppm change by having ethyl instead of methyl sidechains. In this example, in each half of the dimeric complex, the sidechains are directed approximately parallel to the V oxo center of the adjacent vanadium of the dimer. Thus, the structural arrangements of the components of the compound have a definable influence on the vanadium chemical shift.

Exactly this pattern is observed with the V_3L_2 product. The signal at -533 ppm (lactate), corresponding to two vanadiums, moves only to -538 ppm when the H is substituted for methyl. Ethyl substitution has little or no incremental influence. On the basis of the above hypothesis, this means that these two vanadiums have a structural arrangement, with respect to the ligand, somewhat similar to that of the 1:1 complex. The remaining single vanadium of the complex undergoes a -19 ppm shift when CH_3 replaces H and an additional -9 ppm shift with ethyl substitution of the methyl groups. This suggests that the single vanadium has a structural arrangement, with respect to the remaining two vanadium centers and their attached ligands, similar to each of the individual vanadiums of the dimer and their ligands. Putting this information together allows a structure corresponding to that of Scheme 1c to be proposed. The analytical data for this compound (Experimental Section) gives a molecular formula that corresponds to the proposed structure. It is interesting that vanadiums of both pentacoordinate and hexacoordinate geometries occur in the proposed structure. Octahedral geometry does not appear to be a favored coordination mode for vanadate. Under nonforcing conditions, tetrahedral or pentacoordinate geometries seem to be preferred. Considering the charge state of this product, together with the fact that it can lose a proton, it is difficult to see how V_3L_2 could otherwise be put together and still satisfy the NMR and analytical data. If one starts with V_2L_2, it might be possible to bridge between the two vanadiums with a third one. This would generate two vanadiums of octahedral coordination and one with tetrahedral geometry. This does seem somewhat unlikely but such a coordination cannot be ruled out. The cis dioxo arrangement at the central vanadium, as depicted in Scheme 1c, is a favored arrangement for vanadium dioxo compounds, and without evidence for a different structure, it is retained here.

Scheme 1

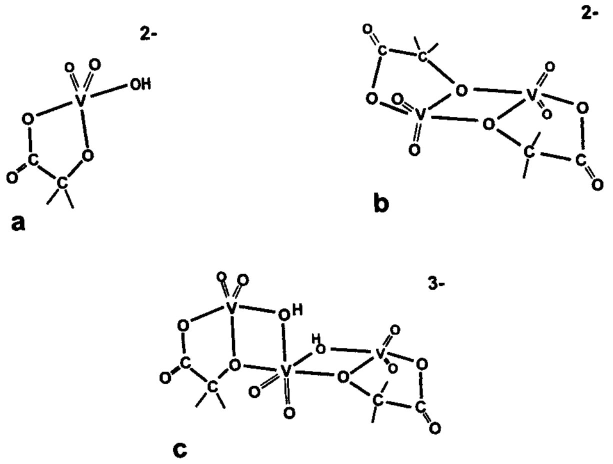

Table 3. IR Data for Various α-Hydroxycarboxylate Complexes from the Solid State and from Solution

compound	state	V=O stretch (cm^{-1})
$[VO_2(lac)]_2(NEt_4)_2$	solid	934
	CH_3CN	937.5
	CH_3CN/H_2O (4:1)	939.4, 914(sh)
	H_2O	938.4
$[VO_2(lac)]_2(Ph_3P{=}N{=}PPh_3)_2$	solid	932
	CH_3CN	937.5
	CH_3CN/H_2O (4:1)	939.4, 914(sh)
	CH_3COCH_3	936
	$CHCl_3$	932
$[VO_2(\alpha\text{-HIBA})]_2(NEt_4)_2$	solid	922, 945
	CH_3CN	934
	CH_3CN/H_2O (4:1)	936, 916(sh)
$[VO_2(\alpha\text{-HIBA})]_2[(C_6H_5)_4As]_2$	solid	932
	CH_3CN	934
$[\{VO_2(\alpha\text{-HIBA}\}_2V(OH)_2](NEt_4)_3$	solid	920, 934
$[VO_2(EHBA)]_2(NEt_4)_2$	solid	920, 937
	CH_3CN	932
	CH_3CN/H_2O (4:1)	934, 916(sh)
$[VO_2(EHBA)]_2[(C_6H_5)_4As]_2$	solid	930
	CH_3CN	932

Table 3 gives the frequencies observed in the V=O stretching region of the IR for theV_3L_2 α-HIBA complex and the various

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V_2L_2 compounds of this study. It is, perhaps, interesting to note that in acetonitrile solution there is a systematic decrease in the V_2L_2 V=O stretching frequency with increase in ligand size, going from 937.5 to 934 to 932 for the lactate, α-HIBA, and EHBA ligands, respectively. Addition of water (one part) to the acetonitrile solution (four parts) causes a 2 cm^{-1} increase in stretching frequency for all three complexes. These observations, like those of the NMR study, suggest that there are no selective changes in complexation, and, by inference, it seems unlikely that there is a change at all for any of the compounds when they are dissolved.

Conclusions

Reaction of lactate and related α-hydroxy carboxylic acids under moderate concentration of ligands and vanadate yield three major solution products and two crystalline compounds. There has been successful characterization of only one type of crystalline product, a dimeric complex of V_2L_2 stoichiometry, by X-ray crystallography. That coordination is found here for the lactate ligand (Figure 1, Scheme 1) and previously for a number of α-hydroxy carboxylic acids.[17−19] It did not prove possible to characterize the second crystalline compound, a trinuclear V_3L_2 product of mixed coordination, by X-ray diffraction studies. The structure proposed for this product was based on NMR and FTIR studies, and it consists of a central octahedrally coordinated vanadium substituted by two chemically indistinguishable trigonal bipyramidal vanadiums. These ligating groups could have either a cis or trans arrangement about the central vanadate. However, only one set of NMR signals was observed for this compound. Given that cis dioxo ligation is a favored arrangement, a cis coordination is assigned and depicted in Scheme 1. A third product of VL stoichiometry and its derivative with a VL_2 stoichiometry has previously been reported.[15] On the basis of the evidence presented here, and previously for lactate,[15] the previously assigned trigonal bipyramidal coordination is accepted for this product.

Both ^{51}V NMR and FT-IR studies of the aqueous coordination chemistry of vanadate in the presence of lactate, α-HIBA, and EHBA have strongly suggested that dissolution of the crystalline materials into aqueous solution does not lead to any significant change in coordination geometry about the vanadium. Because of this, reliable solution structures can be proposed. Adjustment of pH values and ligand and vanadium concentrations in a manner consistent with the equilibrium equations and formation constants allows selective enhancement of various components of the solution. This will be important when materials such as these are used as models for biochemical systems.

There is an overall tendency toward increased product formation with larger size of the ligand. Interestingly enough, formation of the trinuclear vanadium product is also increasingly favored over formation of V_2L_2 with increase in size of the ligand. Under comparable reaction conditions at a pH of about 7, V_3L_2 is a minor product with 2-hydroxypropanoate (lactate), similar to V_2L_2 for 2-methyl-2-hydroxylpropanoate (α-HIBA), and the major product with 2-ethyl-2-hydroxybutanoate (EHBA). The source of these effects may be a change in charge distribution within the ligating hydroxyl and carboxyl groups of the ligand as the ligand substitution pattern is varied.

Acknowledgment. Thanks are gratefully extended to NSERC Canada for its financial support of this work.

Supporting Information Available: Listing of X-ray structure crystal parameters, table of ^{51}V NMR solution study data, figure showing influence of total vanadate concentration on product distribution, two figures characterizing V_3L_2, and one figure characterizing V_2L_2. This material is available free of charge via the Internet at http://pubs.acs.org.

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