Characterization of Vanadium(V) Complexes in Aqueous Solutions: Ethanolamine- and Glycine-Derived Complexes†,1

Debbie C. Crans* and Paul K. Shin

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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Abstract: The preferred coordination geometry of vanadium(V) in aqueous solution with nitrogen- and oxygen-containing multidentate ligands has been determined. The ligands all contain at least two oxygen functionalities and one amine functionality and are derived from diethanolamine (DEA), glycine, and ethylenediaminetetraacetic acid (EDTA). The complexes of 17 ligands have been examined using a combination of ^{1}H, ^{13}C, ^{51}V, and ^{17}O NMR spectroscopy and IR and UV–vis spectrophotometries. When possible, correlations with solid-state structures have been made, although in several cases the structure in the solid state deviates from that observed in aqueous solution. Five coordinate vanadium complexes form when the complex contains chelating hydroxylate and amine functionalities, whereas the coordination of carboxylate groups results in complexes with six-coordinate vanadium. The tetradentate ligands chelate the vanadium center with three or four functionalities. At high pH, four functionalities chelate vanadium when at least one of them is also a carboxylate. Only three functionalities in these ligands are tightly bound to the vanadium in complexes at low pH, while the last functionality is either loosely bound or pendent. The potentially hexadentate ligands form complexes with four functionalities chelating vanadium. An empirical correlation is observed for the ^{51}V NMR inverse line width at half-height as a function of chemical shift and the coordination around the vanadium. The flexibility and modulation in ligand coordination observed in this work could be important for the function of vanadium in biological systems.

The interest in the aqueous coordination chemistry of vanadium has recently been enhanced by vanadium's potent insulin mimetic effects[2a–c] and its activity as cofactor in the haloperoxidases.[2d] The interactions of vanadate with amino acids, peptides, and proteins remain less defined since many of these complexes have only been characterized by ^{51}V NMR spectroscopy.[3–5] Nevertheless, the major complexes formed from dipeptides and vanadate have the amino group, the amide nitrogen, and the carboxylate group chelated.[5] When the dipeptide contained an amino acid with a functionality in the side chain such as serine, additional complexes were found to form involving the hydroxyl chain.[3,5] A variety of related complexes with both oxygen and nitrogen chelating functionalities have also been described using ^{51}V NMR spectroscopy and other methods for characterization of solution complexes including NMR spectroscopic techniques, UV spectroscopy, and potentiometry.[6–9] Most of the studies were concerned with the stability of the complexes, two studies explored their rates of formation,[8,10] but little information is available concerning the solution structure of these complexes.

A few related vanadium(V) compounds were characterized in the solid state by X-ray crystallography.[11–13] These included the vanadium(V) complexes with ethylenediaminetetraacetate (EDTA)[11] and *N*-[1-(2-pyridyl)ethyl]iminodiacetate[12] and recently with triethanolamine (TEA)[13] and tri-2-propanolamine (TPA).[13a] In the first two complexes the vanadium atom was found to contain a cis-dioxo unit with the vanadium in an octahedral geometry and the ligands chelating in a tetradentate manner. In the case of the V–EDTA complex, solution studies showed the structure of this complex in solution mirrored that observed in the solid state.[9] In the case of the V–TEA and the V–TPA complexes, the vanadium atom was pentacoordinate.[13] Upon dissolution of the V–TEA and the V–TPA complexes in methanol, their structures observed in the solid state were maintained.[13a] However, upon dissolution into aqueous solution, both complexes were found to hydrolyze to the aqueous complexes in which the ligand chelated the vanadium with three functionalities.[7,13a] The differences between the V–TEA and V–TPA complexes in the solid state and the aqueous solution suggest that solid-state characterization of these types of complexes may not be sufficient.[13a]

A detailed solution-phase spectroscopic examination of a series of related complexes has been carried out to determine the coordination preferences of aqueous vanadium(V) with nitrogen- and oxygen-containing ligands. During this study, an empirical relationship was observed between the inverse line width at half-height ($\Delta\nu^{-1}$) and the coordination number of vanadium with the ^{51}V NMR chemical shift. In short, this work presents information

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(1) Abbreviations: ADA, *N*-(2-acetamido)iminodiacetic acid; bicine, *N,N*-bis(2-hydroxyethyl)glycine; DEA, 2,2′-iminodiethanol (diethanolamine); EDDA, *N,N*′-ethylenediaminediacetic acid; EDDE, *N,N*′-bis(2-hydroxyethyl)-ethylenediamine; EDTA, (ethylenedinitrilo)tetraacetic acid; EDTE, *N,N,N*′,*N*′-tetrakis(2-hydroxyethyl)ethylenediamine; EDTP, *N,N,N*′,*N*′-tetrakis(2-hydroxypropyl)ethylenediamine; glygly, glycylglycine; HEDT, *N*-(2-hydroxyethyl)ethylenediaminetriacetic acid; HIDA, *N*-(2-hydroxyethyl)iminodiacetic acid; MIDA, methyliminodiacetic acid; NTA, nitrilotriacetic acid; PDEA, 1-[*N,N*-bis(2-hydroxyethyl)amino]-2-propanol; TEA, 2,2′,2″-nitrilotriethanol (triethanolamine); TPA, 1,1′,1″-nitrilotri-2-propanol (triisopropanolamine), tricine, *N*-[tris(2-hydroxymethyl)methyl]glycine).

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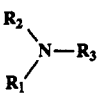
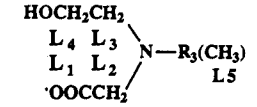
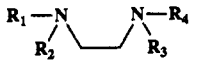
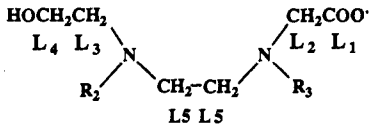
Table 1. Oxygen- and Nitrogen-Containing Ligands and the Abbreviations and Numbering System Used in This Study





ligand	R_1	R_2	R_3
DEA	CH_2CH_2OH	CH_2CH_2OH	H
TEA	CH_2CH_2OH	CH_2CH_2OH	CH_2CH_2OH
PDEA	CH_2CH_2OH	CH_2CH_2OH	$CH_2CH(CH_3)OH$
TPA	$CH_2CH(CH_3)OH$	$CH_2CH(CH_3)OH$	$CH_2CH(CH_3)OH$
bicine	CH_2CH_2OH	CH_2CH_2OH	$CH_2CO_2^-$
HIDA	CH_2CH_2OH	$CH_2CO_2^-$	$CH_2CO_2^-$
MIDA	$CH_2CO_2^-$	$CH_2CO_2^-$	CH_3
NTA	$CH_2CO_2^-$	$CH_2CO_2^-$	$CH_2CO_2^-$
ADA	$CH_2CO_2^-$	$CH_2CO_2^-$	CH_2CONH_2
tricine	$CH_2CO_2^-$	$C(CH_2OH)_3$	H
glygly	$CH_2CO_2^-$	$COCH_2NH_2$	H





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ligand	R_1	R_2	R_3	R_4
EDDE	CH_2CH_2OH	H	CH_2CH_2OH	H
EDTE	CH_2CH_2OH	CH_2CH_2OH	CH_2CH_2OH	CH_2CH_2OH
EDTP	$CH_2CH(CH_3)OH$	$CH_2CH(CH_3)OH$	$CH_2CH(CH_3)OH$	$CH_2CH(CH_3)OH$
EDDA	$CH_2CO_2^-$	H	$CH_2CO_2^-$	H
EDTA	$CH_2CO_2^-$	$CH_2CO_2^-$	$CH_2CO_2^-$	$CH_2CO_2^-$
HEDT	$CH_2CO_2^-$	CH_2CH_2OH	CH_2CO_2	CH_2CO_2

on the coordination of aqueous vanadium(V) with a large series of ligands, spectroscopic methods of analysis of vanadium(V) complexes, and chemical shift information which eventually should assist in the interpretation and analysis of biological studies of vanadium(V) with multidentate peptidic ligands.

Experimental Section

General Methods. Reagent grade chemicals were obtained from Sigma or Aldrich, except for ethylenediamine-*N,N,N',N'*-tetraacetic acid (EDTA, Mallinckrodt) and triethanolamine (TEA, Eastman Kodak). All reagents were used without further purification. Distilled and deionized (DDI) water was used for preparation of stock solutions and samples. Vanadate stock solution was prepared by dissolving vanadium pentoxide (V_2O_5) with a minimal amount (≤2 equiv) of sodium hydroxide in DDI water to maintain low pH. It was stored in polyethylene bottles at 4 °C. Concentration of the stock solution was determined at pH 13 by UV–vis spectroscopy at 260 nm with a molar extinction coefficient of 3.55×10^3 M^{-1} cm^{-1}.[14] No concentration changes were observed over a 6-month period.

NMR Sample Preparation. All NMR samples were prepared at room temperature and contained 10% (v/v) D_2O. Constant ionic strength was maintained at 0.40 M with 4.0 M KCl. Vanadate and ligand concentration was varied as needed. No significant changes in pH were observed for each solution measured before and after the NMR spectra were acquired.

1D NMR Spectroscopy. ^{51}V NMR spectra were acquired on a Bruker WPSY spectrometer (4.7 T) at 52.6 MHz and a Bruker ACP-300 NMR spectrometer (7.0 T) at 78.9 MHz. A spectral window of 150 ppm, a 90° pulse angle, and an acquisition time of 0.25 s with no relaxation delay was used. A 15-Hz line-broadening factor was typically applied before Fourier transformation. Chemical shifts are reported with respect to the external reference $VOCl_3$ (0 ppm). Complex and oligomeric vanadate concentrations were determined using the Bruker integration software. Mole fractions of each of the oligomers were calculated from the integration of the spectra. Using the known total vanadate concentration, the oligomer concentrations were subsequently calculated after assuming that all the vanadium present in solution was in the form of vanadium(V).

^{17}O NMR spectra were acquired on a Bruker ACP-300 NMR spectrometer (7.0 T) at 41 MHz. A spectral window of 2000 ppm, a 90° pulse angle, a 0.017-s acquisition time, and a 0.07-s relaxation delay were employed. No line broadening was applied before Fourier transformation, and water was used as an internal reference at 0 ppm. Samples were made as described above, although they were enriched to 3–5% with ^{17}O-labeled water. Samples were incubated overnight at ambient temperature to allow equilibration of the ^{17}O label.

^1H and ^{13}C NMR spectra were acquired on a Bruker ACP-300 NMR spectrometer (7.0 T) using standard parameters. ^{13}C NMR spectra were acquired with a 200 ppm spectral window, a 90° pulse, and a relaxation delay ot 700 ms. A 2-Hz exponential line broadening was applied to the FID before Fourier transformation. Chemical shifts are reported with respect to the external standard, DSS, at 0 ppm.

2D NMR Spectroscopy. Phase-sensitive COSY and HETCOR spectra were acquired on a Bruker ACP-300 NMR spectrometer (7.0 T) using standard parameters; the mixing time for the ^{13}C 2D EXSY experiment was 0.3 s.

Variable Temperature NMR. All variable temperature data were acquired on the Bruker ACP-300 NMR spectrometer (7.0 T). The probe was calibrated before each experiment using a methanol standard as previously described.[15] At most, there is a ±1 °C experimental error throughout the 273–333 K range.

Results and Discussion

Aqueous Vanadium Complex Formation. In aqueous solution vanadate and multidentate ligands readily form complexes. We systematically explored the coordination preferences of vanadium(V) as the functionalities in the ligand are varied. Table 1 summarizes the 17 ligands used in this work, their structures, abbreviations,[1] and the numbering system used. The vanadium(V) complexes were first examined using ^{51}V NMR spectroscopy. The multidentate ligands form very stable complexes with vanadate which lead to low concentrations of vanadate oligomeric anions, even at high total vanadium concentrations.[3-8] The ^{51}V NMR studies show how many complexes form and their concentrations in solution. These studies also allow the determination of the nuclearity of the complexes in solution, as described in detail elsewhere.[7] Most of the complexes described in Tables 2 and 3 were mononuclear and contain one ligand. Two complexes exist for the V–MIDA complex; the studies reported here were

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Table 2. ^{51}V NMR Chemical Shift, Full Line Widths at Half-Height, and Experimental Conditions for Observation of a Series of Vanadium(V) Complexes

complex	^{51}V NMR[a] chemical shift/ppm	$\Delta\nu$[b] (fwhh)/Hz	$[V_i]$:[L][c]/mM:mM	[complex][c]/mM	stability ratio[d] [complex]/$[V_1]$	exptl[c] pH
V–TEA	–483	142	400:600	250	34	8.99
V–bicine 1	–484	177	200:500	90	4	9.95
V–PDEA[e]	–487	175	200:300	96	38	7.95
V–TPA	–488	150	500:1500	420	9	9.50
V–DEA	–488	135	200:600	136	16	9.01
V–EDTE	–489	464	450:200	56	66	8.00
V–EDDE	–493	442	10:100	1	0.2	9.01
V–EDTP	–496	470	450:200	17		6.11
V–HEDT 1	–497	560	150:150	65	2	10.02
V–HIDA 1	–499	349	300:150	36	22	8.53
V–glygly	–504	353	250:250	6		6.92
V–NTA	–507	497	300:300	276	521	5.48
V–tricine	–507	303	412:500	385	571	7.18
V–ADA	–506	529	100:200	89	98	6.84
V–bicine 2	–508	370	200:500	126	7	7.00
V–EDDA 1	–510	492	250:250	108	64	8.23
V–MIDA	–513	333	5:200	2	6	6.99
V–EDTA	–516	774	125:167	125	832	7.00
V–HIDA 2	–520	472	100:300	100	121	5.03
V–HEDT 2	–520	710	150:150	127	296	7.65
V–EDDA 2	–521	454	250:250	110	62	8.23

[a] The measured ^{51}V NMR chemical shift is rounded off and reported as integers. [b] The line widths ($\Delta\nu$) were measured after a 15-Hz line broadening was applied. The results indicated are the measured fwhh after 15 Hz have been subtracted. They are accurate within ±15 Hz. [c] The total vanadate and ligand ratio used in the sample at the indicated pH results in the complex concentration as measured by ^{51}V NMR spectroscopy. [d] Stability of the complex is reflected by the ratio of complex concentration to monomeric vanadate concentration. This value was measured from a series of spectra with total vanadate or ligand concentrations varied (as reported in ref 7) or from a single ^{51}V NMR spectrum at 298 K unless otherwise specified in Table 3. [e] This data was obtained at 273 K.

Table 3. ^{13}C NMR CIS Values for a Series of Vanadium(V) Complexes[a]

complex	CIS value[b] C1	C2	C3	C4	C5[c]	exptl pH	^{51}V NMR δ (ppm)
V–TEA			4.6(b) –3.9(f)[e]	12.1(b) –1.2(f)[e]		9.99	–483
V–bicine 1	–2.2	–4.7	4.7	11.5		9.99	–484
V–PDEA[d]			4.6(b_1) 6.1(b_2) –3.8(f)[e]	13.8(b_1) 14.5(b_2) 1.3(f)[e]	 –0.2	7.95	–487
V–TPA			4.2/3.5(b) –4.3(f)[e]	11.4/10.8(b) –1.1(f)[e]	2.4(b) 0.0(f)	9.50	–488
V–DEA			5.5	14.3			–488
V–HEDT 1	3.4(b) –0.8(f_1) –1.0(f_2)	5.5(b) 2.1(f_1) 2.7(f_2)	–0.9	14.0	0.9 3.3	10.02	–495
V–HIDA 1	5.7	5.6	5.2	11.2		8.50	–499
V–tricine	11.3	3.0	2.3	17.9(b) 3.6(f_1) 1.5(f_2)		7.18	–507
V–bicine 2	10.5	5.8	4.1	7.4		7.00	–508
V–EDDA 1	7.4(b_1) 4.2(b_2)	7.2(b_1) 3.4(b_2)			10.8 1.9	8.23	–510
V–HIDA 2	10.1	6.6(b)	3.8	2.4		5.03	–516
V–EDTA	5.1(b) –1.4(f)	5.3(b) 3.4(f)			2.6	8.02	–516
V–HEDT 2	5.0(b_1) 5.5(b_2) 1.0(f)	4.4(b_1) 4.9(b_2) 3.1(f)	4.6	0.0	2.4 2.3	7.65	–520
V–EDDA 2	7.6	3.4(b)			3.2	8.23	–521

[a] Labeling is defined in Table 1. [b] The CIS values obtained from 75-MHz ^{13}C NMR spectra by subtracting the chemical shift of the ligand from that of the complex. The chemical shift differences are reported to one-tenth of a part per million. Spectral parameters are detailed in the experimental section. Multiple CIS values for a single carbon type are distinguished by the subscripts 1 and 2 (except at C5 carbons). [c] These carbons correspond to those in the ethylene backbone except for the PDEA and TPA ligand, where C5 is the methyl carbon in the isopropyl arm(s). [d] This data was obtained at 273 K. [e] Assignments for C3f and C4f reported in ref 13a in complexes V–TEA, V–PDEA, and V–TEA were incorrect (reversed).

carried out in a concentration range where the 1:1 complex dominates.[16] The stoichiometries of the major V–HIDA complexes are unclear since a 2:2 complex has been isolated and characterized by X-ray crystallography (Crans and Mahroof-Tahir, unpublished).

The stability of these complexes varies with ligand and reaction conditions, particularly with pH. The ratio of complex concentration to monomeric vanadate concentration [complex]/$[V_1]$ has been used to compare complex stability for several vanadate complexes.[7] This ratio is pH-dependent. The experimental pH values at which the complexes are described in Table 2 were used to calculate the ratio. The experimental conditions were chosen such that sufficient signals for each species (free ligand as well as complexed ligand) were observable by the NMR methods employed. The pH used for the [complex]/$[V_1]$ calculation may not correspond to the optimum [complex]/$[V_1]$ ratio, but they

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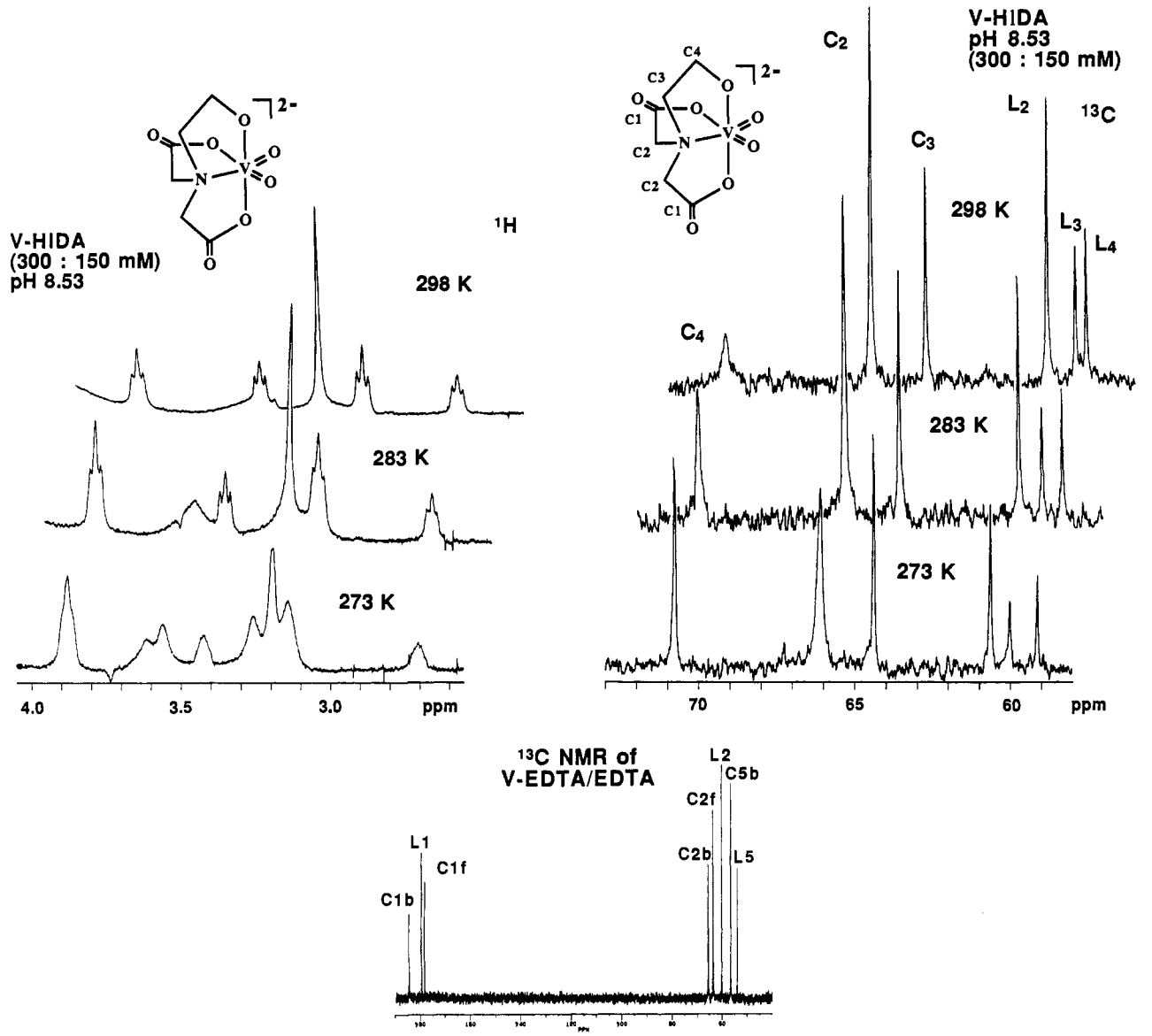


Figure 1. ^{1}H and ^{13}C NMR spectra of the V–HIDA 1 complex (a and b, top) at variable temperatures and the ^{13}C NMR spectrum of the V–EDTA complex (c, bottom).

are useful to give the reader a qualitative comparison of relative complex stabilities.

One or more complexes form depending on the functionalities in the ligand, the concentrations, the vanadium to ligand ratio, and the pH. Table 2 summarizes the complex ^{51}V NMR chemical shift, the full line width at half-height, the vanadium to ligand concentration ratio, the complex concentration, the complex stability ratio ([complex]/[V_i]), and the pH of the solutions examined in this work. The complexes are listed in the order of decreasing ^{51}V NMR chemical shift. In the case of bicine, HIDA, HEDT, and EDDA two complexes were observed, and the conditions used to study each one are given in Table 2. Two major complexes are also observed with glygly, as previously reported.[3-5] The complex formation between vanadate and ligand is rapid, with no observed change in the equilibria upon storage of the sample for reasonable periods at 4 °C. The nature of the complex and the concentration of ligand will affect the stability of the solution. Most of these complexes were unchanged in the course of 2 weeks, and several complexes were stable up to several months at 4 °C.

Application of CIS Analysis to Determine Coordinating Functionalities in Oxovanadium(V) Complexes. ^{1}H and ^{13}C NMR spectroscopy were used to determine the number and type of coordinating moieties in vanadium(V) complexes with multidentate ligands with oxygen- or nitrogen-containing functionalities. Both spectroscopic methods are sensitive to complexation, because the net change in the electronic environment of a ^{1}H or a ^{13}C nucleus changes the chemical shift of the nucleus. The coordination-induced shift (CIS) for a given nucleus is defined as the difference between its chemical shift in the complex versus that in free ligand, CIS = $\delta_{BOUND} - \delta_{FREE}$.[17] Figure 1a,b illustrates the effect of complexation in the V–HIDA 1 complex (at high pH) and shows the spectra at various temperatures. A ^{13}C spectrum for the V–EDTA complex is also shown (Figure 1c). The spectra in Figure 1 contain signals for both free ligand and complex. The carbons in the free ligand are referred to as Lx, while the carbons in a complex are referred to as Cx, where x refers to the corresponding atom (Figure 1b). If the functionality is bound to the vanadium, the letter b follows the Cx designation (Cxb), whereas atoms in a pendent arm will be marked by an f (Cxf). For example, a carboxylate carbon will be labeled C1b if bound to vanadium and C1f is unattached (see Figure 1c). Large CIS values are indicative of the number of moieties that are directly attached to the vanadium atom and are used to describe the solution structure of these complexes.

The ^{13}C NMR CIS values are shown for 15 complexes in Table 3. The experimental pH and the ^{51}V NMR chemical shifts are

(17) Jacobson, R. R. Ph.D. Dissertation, State University of New York, Albany, 1989, and references therein. All CIS values are reported in parts per million units.

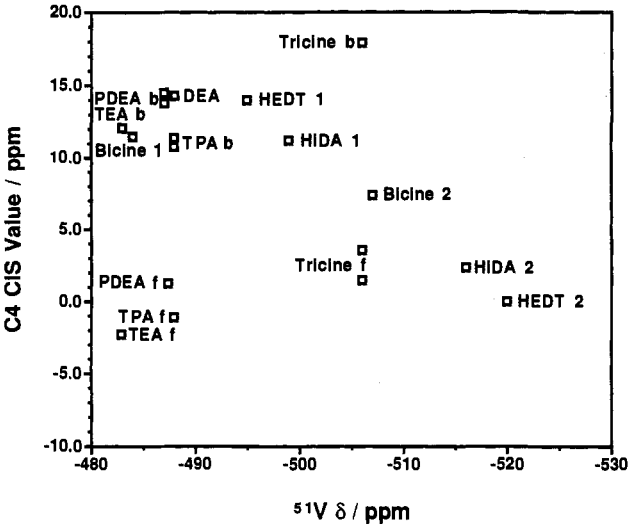


Figure 2. C4 CIS values plotted as a function of ^{51}V NMR chemical shifts.

also listed. A table with the ^{13}C NMR chemical shifts for these complexes is provided in the supplemental material (Table S1). ^{1}H NMR data were also obtained with similar results; since the ^{1}H spectra in general were more complex due to overlapping resonances, this information is not summarized here. Before we discuss the results for each complex we can make the following general observations that will assist in assigning the spectra.

The C1 (carboxylate carbon) ^{13}C NMR CIS values range from −2.2 to 11.3 ppm. The larger positive values indicate coordination of the carboxylate moiety (C1b), while the smaller positive and negative values indicate carbons in noncoordinating arms (C1f). Vanadium(V) complexes with bound carboxylate arms (CIS ≥ 4.5) have ^{51}V NMR chemical shifts in the −500 to −520 ppm range. Complexes with free carboxylate arms (CIS ≤ 0) are distributed over the entire ^{51}V NMR spectral range of this study. A smaller effect is observed for the C2 and C3 CIS values upon complexation. With one exception (V–bicine 1), the C2 CIS values range from 2.1 to 7.2 ppm. The C3 CIS values range from −4.3 to 6.1 ppm. In general, CIS values greater than 3.5 for the C2 and C3 carbons are observed if they are found near both a coordinating amine moiety and a coordinating oxygen atom. Smaller CIS values are observed if C2 or C3 is adjacent to a weakly interacting or pendent arm.

The C4 (carbon adjacent to a hydroxyl group) CIS values span the range −1.2 to 17.9 ppm, as illustrated in Figure 2, where the C4 CIS value was plotted as a function of the ^{51}V NMR chemical shift. The complexes form three clusters in this figure; the complexes with CIS values from −4.0 to −1.1 ppm, from 1.5 to 7.4 ppm, and from 11.5 to 17.9 ppm. The lowest CIS values clearly illustrate the unattached and pendent hydroxyl arm, giving CIS values around −2 ppm. The strongly associated hydroxylate arms with CIS values above 11 ppm are also convincing. The central cluster with CIS values between 1.5 and 7.4 ppm span the range from complexes containing ligands with pendent arms to covalently bound arms. The CIS values describe the structural variations or exchange reactions in specific complexes. Analysis of the CIS data for individual complexes will explore these possibilities.

The CIS values for the C5 carbons, with the exception of V–EDDA 1, are in the range −0.2 to 3.3 ppm. The mean CIS value of 2.6 ppm shows that most of these types of complexes coordinate a ligand via the ethylenediamine nitrogens loosely to the vanadium(V) center. The low CIS value of these types of interactions presumably reflects the nature of the coordinative bond between the nitrogen and the vanadium.

In summary, the CIS values are very sensitive probes to determine whether a functionality is coordinated without limiting the nature of the carbon atom or its adjacent functionalities. It appears that strong interaction of vanadium to oxygen is evidenced by CIS values of 10 ppm or more, whereas smaller CIS values around 5 ppm may reflect signal averaging on the NMR time scale or weaker coordination. CIS values of +2 ppm or less indicate that this ligand is not coordinated. These generalizations are restricted to C_1 and C_4 carbon atoms, and we will now describe specific studies of several complexes.

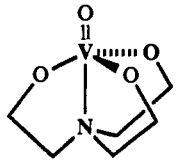
V–EDTA Complex. The reaction of 125 mM vanadate with 167 mM EDTA at pH 8.02 forms a 125 mM 1:1 V–EDTA complex with a broad ^{51}V NMR resonance at −516 ppm. X-ray determinations of V–EDTA complexes have been reported with two symmetrically coordinated carboxylates, two free carboxylates, and two coordinated amine groups.[11] The ^{1}H NMR spectrum shows an AB pattern consistent with two symmetrically coordinating carboxylates in the α-cis conformation as described previously.[9] The five ^{13}C NMR resonances of this complex are consistent with a six-coordinated cis-dioxo vanadium(V) center with symmetrical carboxylate coordination (α-cix configuration). The low C1b CIS value of 5.1 ppm (Table 3) presumably reflects long oxygen–vanadium bonds in these complexes. We conclude that a C1 CIS value around 5 ppm in a complex with a ligand containing the ethylenediaminediacetic acid backbone is to be expected when the carboxylates are coordinated trans to each other.

V–Tricine Complex. The 1:1 V–tricine complex (398 mM) forms in a solution containing 412 mM vanadate and 500 mM tricine at pH 7.12.[7,8] The large C1 CIS value of 11.3 ppm is indicative of strong coordination by the carboxylate moiety in this complex. The exceptionally large CIS value of 17.9 for the C4 carbon also indicates strong coordination of the alcohol arm to the vanadium(V) center. The methylene (C2) and methine (C3) carbons in the alcohol arms also have positive CIS values, 3.0 and 2.3 ppm, respectively, which supports a coordinated amine. The two free alcohol methylenes ($C4f_1$ and $C4f_2$) have positive, albeit smaller, CIS values (3.6 and 1.5 ppm, respectively), which most likely reflect the observed intramolecular exchange occurring in this complex.[8] The V–tricine complex contains a coordinated carboxylate, an alkoxylate, an amine, and two oxo groups, totaling a minimum of five substituents. It is possible that water could also be coordinated to vanadium, and then the complex would be six-coordinate. No structural information is currently available for this complex, and the above data and those reported previously[8] support either a five- or six-coordinate structure.

V–DEA Complex. The 1:1 V–DEA complex (136 mM) forms in a solution of 200 mM vanadate and 300 mM DEA at pH 9.01.[7] A C4 CIS value of 14.3 ppm indicates that the alcohol arms are strongly coordinated to the vanadium(V) center, while a 5.5 ppm C3 CIS value indicates that the amine is also tightly coordinated. Since only one peak is observed for both of the C3 and C4 carbons, the two alcohol arms must be symmetrically coordinated or rapidly exchanging. If the V–DEA has kinetic properties similar to the V–tricine complex, the former is more likely.[8] Tridentate DEA chelates the cis-dioxo vanadium(V) center to form a five- or six-coordinate complex. No other structural information is available to support either coordination geometry, although related studies of the V–TEA complex would favor a pentacoordinate complex (see below and ref 13a).

V–TEA Complex. The reaction of 400 mM vanadate with 600 mM TEA at pH 9.00 forms a 173 mM 1:1 V–TEA complex. The CIS values for C4b and C3b in this complex are 12.1 and 4.6 ppm, respectively. C4f has a CIS value of −1.2 ppm, and that of C3f is −3.9 ppm. The C4b and C3b resonances are approximately twice as intense as those of C4f and C3f, suggesting two ethanol arms are bound and one is free. This data is consistent with a tridentate TEA ligand, where the central amine and two alcohol arms chelate the vanadium center with the third arm pendent. Structural studies of a V–TEA complex isolated from organic solvents have demonstrated that the TEA ligand can also coordinate in a tetradentate manner.[13] This complex is different from that observed in aqueous solution since all three arms chelate

vanadium (1). Dissolution of 1 in methanol or acetonitrile gives CIS values supporting the coordination of all three arms. Aqueous solution studies of ther V–TEA complex using ^{17}O-labeled water shows an ^{17}O NMR spectrum that is consistent with pentacoordinate vanadium with the structure shown in 2.[13]



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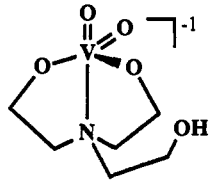

2

V–PDEA Complex. The reaction of vanadate (200 mM) with PDEA (300 mM) was examined at pH 9.00. The ^{13}C NMR CIS data were obtained from the sample at 273 K, where the resonances were clearly observable; the ambient temperature spectra gave a much poorer signal to noise ratio. The ^1H NMR spectra showed only slightly better resolution at lower temperature. Seven ^{13}C NMR resonances were assigned to the complex, indicating asymmetric chelation of the vanadium(V) center by the PDEA ligand. Only one complex was observed even though more than one type of complex could form. The 13.8 ppm $C4b_1$ CIS value and the 14.5 ppm $C4b_2$ CIS value indicate coordination via one ethyl and the isopropyl arm. The central amine is coordinated as evidenced by the $C3b_1$, C3f, and $C3b_2$ CIS values of 4.6, –4.0, and 6.1 ppm, respectively. The 1.5 ppm C4f CIS value indicates that the second ethanol arm is pendent. Based on the analogy of these CIS values with the CIS values of the aqueous V–TEA complex, we expect the V–PDEA complex to contain pentacoordinate vanadium(V) like the aqueous V–TEA complex.[13]

V–TPA Complex. The reaction of vanadate with TPA is complicated by the fact that the commercially available TPA is a mixture of the two sets of racemic ligands (*R,R,R* and *S,S,S*) and (*R,R,S* and *S,S,R*). These sets of diastereomers have different ^1H and ^{13}C NMR spectra, and two ^{51}V NMR signals are observed when the vanadium complex forms with each diastereomer of the ligand (both ligands form complexes with vanadium(V)).[13a] As described previously, the V–TPA complex that crystallizes out of organic solvents contains the *R,R,R* and *S,S,S* ligand.[13a] Aqueous dissolution of the crystal has made it been possible to assign the CIS shifts for one set of the racemic ligands in a solution containing 500 mM vanadate and 1.50 M TPA at pH 9.50. As seen in Table 3, the aqueous complex contains two types of bound arms with C4 CIS values of 10.8 and 11.4 ppm and one pendent arm with a C4 CIS value of 1.1 ppm. The ^{17}O NMR spectrum was also acquired with ^{17}O-labeled H_2O where the two oxo moieties were labeled in the complex.[13a] The observed spectrum is most consistent with a complex containing pentacoordinate vanadium with two arms coordinated and one pendent arm (analogous to 2 for the V–TEA complex).

V–Bicine Complexes. Bicine contains both carboxylate and hydroxyl functionalities in addition to an amine group and thus has the potential to form different types of vanadium complexes. One complex forms in the pH range 8–12 (V–bicine 1) and another at lower pH (V–bicine 2). A ^{13}C NMR spectrum was acquired on a sample containing 200 mM vanadate and 500 mM bicine at pH 9.99 in a solution containing the 90 mM V–bicine 1 complex. Only one C4 resonance is observable, and it has a CIS value of 11.5 ppm. The C3 carbons are also observed as a single peak with a CIS value of 4.7 ppm. The carboxylate arm has C1 and C2 CIS values of –2.2 and –4.7 ppm, respectively. This data indicates that the V–bicine 1 complex is coordinated through the two hydroxylate groups and the amine group. This complex is likely to be structurally similar to the V–DEA, V–TEA, and V–TPA complexes based on similar ^{51}V NMR chemical shifts and CIS data.

Bicine, at lower pH ($5 \leq pH \leq 9$), forms a complex with vanadate that is observable at –507 ppm in the ^{51}V NMR. The V–bicine 2 complex (140 mM) at pH 7.11 was observed in a solution prepared from 500 mM bicine and 200 mM vanadate. The 10.5 ppm C1 CIS value indicates coordination by the acid moiety, and the 5.8 and 4.1 ppm downfield shifts for C2 and C3, respectively, indicate coordination by the central amine. The 7.4 ppm CIS value for C4 is too low to suggest strong chelation but too high to indicate a pendent arm. The data would be consistent with the alcohol arms coordinating the vanadium(V) atom via longer and weaker V–OR bonds than those found in other alkoxide-coordinated complexes. Since only a single broadened peak was observed for C4 in the ^{13}C NMR spectrum, the possibility of intramolecular exchange between bound and free alcohol arms with a rate on the order of the NMR time scale was also considered. VT ^1H NMR studies show that at lower temperature some dynamic processes are frozen out and render the two hydroxyethyl arms nonequivalent. The dynamic process that makes the two hydroxyethyl arms nonequivalent by ^1H NMR shows no change in the chemical shift of C4 by ^{13}C NMR. If the dynamic process in question involved freezing out a complex with a pendent arm, a much larger difference in the chemical shift of C4 would have been observed in this temperature range. The chemical shift is inconsistent with one pendent hydroxyethyl arm but consistent with two differently coordinated (in a cis fashion) hydroxyethyl arms. We conclude that the solution structure of the V–bicine 2 complex chelates all four functionalities in the bicine ligand. The low C4 CIS value presumably reflects a longer and weaker bond to the vanadium atom.

The apparent difference in number and type of chelating moieties in the two V–bicine complexes may be due to either the vanadium(V) metal preference for coordination environment or completition between potentially coordinating functional groups on the ligand or both. Below pH 2 vanadium(V) in aqueous solution is found as the appropriately hydrated VO_2^+ cation. From pH 2 to 6 six-coordinate vanadium(V) in the form of decamer forms showing the preference for the octahedral coordination in the oxoanionic arrangement. Four-coordinate species, or possibly five-coordinate species, have been suggested for vanadium species that exist under these conditions.[5] The preferences of vanadium(V) for the various geometries other than octahedral is not understood, although the analogy of vanadium(V) with phosphorus under such conditions is well-documented (see refs 6 and 8 and references therein). The preferential coordination geometry of the vanadium is therefore not obvious; will it act as a metal or as a phosphorus analog?

The coordination geometry in these complexes may be driven by the nature of the potentially coordinating functionalities. The ability to form stronger bonds requires overlap of similar molecular orbitals. The preference in the five-coordinate V–TEA complex and its analogs (e.g. V–bicine complex) for coordinating alkoxo moieties could reflect the better overlap of the alkoxo sp^3 hybridized orbitals with the equatorial orbitals (sp_xp_y or $d_{z^2}p_z$) on the vanadium. The relatively high s-character in both of these orbitals should support a strong bond. The d^2sp^3 orbitals in the octahedral complex can form a stronger bond with a carboxylate group if an appropriate unhybridized d orbital is available to overlap with the delocalized p–π orbitals in the carboxylate moiety. Since the two unhybridized d orbitals in the octahedral complex are directed along the bonding axis, octahedral geometry favors this type of bonding over trigonal bipyramidal geometry. These considerations are furthermore substantiated when recognizing that the alkoxo group deprotonates at high pH, whereas at low pH it is protonated. Thus, at high pH the alkoxo and carboxylate functional groups compete, while at lower pH the hydroxylate and carboxylate functional groups compete to coordinate the vanadium(V) center. Since the deprotonated alkoxo group forms a stronger bond than the protonated hydroxyl group, it is reasonable that the former functionality competes more favorably against the carboxylates and would bind preferentially as described above in the absence of carboxylate group coordination. Coordination of alkoxo groups should favor five-coordinate vanadium

as presumably observed for V–bicine 1. The observed interactions in the V–bicine 2 complex correlate well with formation of a complex containing octahedral vanadium, suggesting that these ligand–metal interactions are more stabilizing there than in a complex following the vanadium(V) phosphorus analogy.

V–HIDA Complexes. The HIDA ligand contains an amine, a hydroxyl, and two carboxylate functionalities. It forms two complexes with vanadate (V–HIDA 1 and V–HIDA 2); the V–HIDA 1 complex forms in the pH range 7–10. In a sample containing 300 mM vanadate and 150 mM HIDA at pH 8.50, 54 mM complex is observed. Direct coordination by the alkoxo moiety is supported by the 11.2 ppm C4 CIS value. However, only one sharp resonance is observed for the C1 carbons, with a CIS value of 5.7 ppm. Such a CIS value would be reasonable if the coordination indicated a weak bond to the vanadium or if this signal was the result of averaging between a pendent and coordinated arm. Therefore, VT studies of the V–HIDA 1 complex were undertaken.

The broad ^{1}H resonance attributed to the protons on C2 at 298 K was found to sharpen at lower temperature and freeze out at 278 K. The AB pattern centered at 3.4 ppm at 273 K is similar to the AB pattern observed at 273 K for the V–tricine complex.[8] This shows that the two carboxylates are distinguishable at low temperature. As the temperature increases to 298 K the two carboxylate groups exchange rapidly, and accordingly, only one resonance is observed. This interpretation is supported by the ^{13}C NMR spectra, where a broadening of the C2 resonance is observed at lower temperatures. Since very little change is observed in the chemical shift for C2, the two carboxylate groups must be very similar. The latter point is inconsistent with one free and one pendent carboxylate group but consistent with two coordinated carboxylate groups (in a cis geometry to make them nonequivalent). We conclude that this complex is chelated through the amine, the alkoxo, and both carboxylate groups.

The V–HIDA 2 complex forms in the pH range from 4 to 8. ^{13}C NMR CIS analysis was carried out on a spectrum of a sample prepared from 100 mM vanadate and 300 mM HIDA at pH 5.03 (containing 100 mM V–HIDA 2 complex). The single resonance observed for both C1 carbons is shifted downfield by 10.1 ppm, suggesting both carboxylate arms are coordinated to the vanadium. The signle resonance for the C2 CIS value is 6.6 ppm, indicating the central amine is coordinated. The relatively small C4 CIS value (3.8 ppm) and C3 CIS value (2.6 ppm) indicate that this arm is pendent or, at most, coordinated very weakly to the vanadium. These results suggest that the HIDA ligand coordinates via both carboxylates and the amine group in the V–HIDA 2 complex and that the hydroxyl arm is either pendent or coordinated weakly to the vanadium.

Both V–HIDA complexes contain coordinated carboxylate groups and consequently both complexes contain octahedral vanadium. The differences in these complexes are the strengths of each chelated bond to the metal. In the V–HIDA 1 complex the alkoxo group is strongly coordinated to the vanadium and the two carboxylates less tightly. In contrast, the V–HIDA 2 complex contains carboxylates that are bound more tightly, whereas the hydroxyl group is only weakly associated. These observations follow the expected effectiveness in interaction of the alkoxo, the carboxylate, and the hydroxyl groups. Further studies using techniques other than NMR spectroscopy will determine whether the stoichiometries of these complexes are 1:1 since we have recently isolated a 2:2 V–HIDA complex (Crans and Mahroof-Tahir, unpublished).

V–NTA Complex. The 1:1 V–NTA complex (280 mM) forms in a solution containing 300 mM vanadate and 300 mM NTA at pH 7.17. The solution equilibria, structure, and complexation mechanism have previously been investigated using potentiometry and spectrophotometry, leading to a structural proposal of a hexacoordinate vanadium complex containing a tetradentate NTA ligand with a nitrogen trans to an oxo group (in the cis-dioxo unit).[18,19] Based on the X-ray structure of the vanadium(IV,V)–NTA_2 dimer complex[20] combined with kinetic studies, a similar structure was proposed.[21] The CIS analysis of the V–NTA complex shows two types of chelated carboxylates with C1b_1 and C1b_2 CIS values of 10.0 and 8.5 ppm, respectively. Since one carboxylate has a lower CIS value than the other two, it is chelated less strongly to the vanadium. A complex containing a carboxylate trans to an oxo group and two carboxylates trans to each other should give such CIS values. The possibility that one carboxyl group is pendent is inconsistent with the high CIS value and VT ^{1}H and ^{13}C NMR studies. High-temperature ^{1}H and ^{13}C NMR spectra revealed exchange between the carboxylate groups. The anticipated chemical shift changes reflecting the intramolecular exchange between a coordinated and pendent arm were not observed. The CIS values of 8.4 and 6.7 ppm for the C2 carbons suggest strong coordination of the amine atom. We conclude that the NTA ligand is tetradentate in the aqueous complex. Two carboxylate groups are strongly coordinated to the vanadium and the third carboxylate is coordinated more weakly to the vanadium since it is trans to one of the oxo groups.

V-EDDA Complexes. The EDDA ligand forms two 1:1 complexes (V–EDDA 1 and V–EDDA 2) that coexist in a solution made with 250 mM vanadate and 250 mM EDDA at pH 8.23. ^{1}H NMR studies, but not ^{13}C or ^{51}V NMR studies, of these complexes have been reported previously.[9] The two complexes are distinguished by the arrangement of carboxylates around the vanadium in the α-cis or β-cis conformations.[9] The V–EDDA 2 complex (α-cis) is similar to the V–EDTA[11] complex with respect to the ^{51}V NMR chemical shifts and CIS values.

The ^{13}C NMR resonances for the V–EDDA 1 complex were obtained from a spectrum recorded of a solution containing both complexes by subtracting the resonances assigned to the V–EDDA 2 complex. The six ^{13}C resonances of equal intensity suggest that the EDDA ligand is unsymmetrically chelating the vanadium(V) center as expected if the complex has the β-cis conformation. CIS values for the C1b_1, C1b_2, C2b_1, and C2b_2 carbons (7.4, 4.2, 7.2, and 3.4 ppm) indicate coordination by the carboxylate and amine moieties, supporting the β-cis conformation. The two different C5b CIS values (10.8 and 1.9 ppm) are particularly noteworthy. The latter value is similar to the C5b value for the V–EDTA complex and reflects the effect on C5 when the adjacent amine nitrogen is trans to an oxo. The former CIS value (10.8 ppm) is, however, much larger and reflects the much stronger interaction between the other amine and the vanadium center, presumably induced by the trans carboxylate group.

V–HEDT Complexes. The HEDT ligand forms two complexes with vanadate. One complex, V–HEDT 1, forms from pH 7 to 11, and the other, V–HEDT 2, from pH 5 to 9. A solution containing 65 mM V–HEDT 1 was made with 150 mM vanadate and 150 mM HEDT at pH 10.02. The C4 carbon is shifted downfield by a CIS value of 14.0 ppm, suggesting strong coordination to the vanadium(V) center by the alkoxo group. The C3 and C5 carbons, however, have CIS values of –0.9 and 0.0 ppm, respectively, suggesting that one of the nitrogen atoms is weakly coordinated to the vanadium(V) center. The carboxylate arm attached to this nitrogen atom is not bound to the vanadium, as evidenced by its negative CIS value (C1f_2 CIS value of –1.0 ppm). The CIS values for the C5 (3.3 and 0.9 ppm), C2b (5.5 ppm), and C2f (2.7 and 2.1 ppm) carbons support the chelation of the metal center by both nitrogen atoms. Two more resonances, C1b and C1f_2, are observed for the pendent C1 carbon, with CIS values of 3.4 and –0.8 ppm, respectively, and indicate coordination of one carboxylate group to the vanadium(V) center. The smaller CIS value of C1 in this complex, compared to the V–EDTA complex, presumably reflects the trans coordination of the alkoxide

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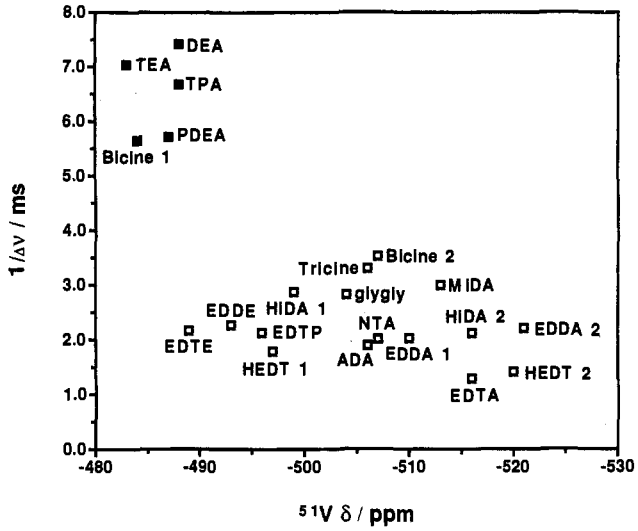

Figure 3. Inverse line width, $\Delta\nu^{-1}$, plotted as a function of the ^{51}V NMR chemical shift for vanadium(V) complexes.

to this carboxylate group. The aqueous solution studies are consistent with the interpretation that two amine groups, one carboxylate group, and one hydroxylate group chelate the vanadium in the V–HEDT 1 complex. Furthermore, these results suggest this complex only forms the α-cis complex, as found in the V–EDTA and V–EDDA 2 complexes.

The ^{13}C NMR data for the V–HEDT 2 complex (127 mM) were obtained from a solution containing 150 mM vanadate and 150 mM HEDT at pH 7.65. The ^{1}H and ^{13}C NMR spectra of this complex were identical to those of the V–EDTA complex with the exception that one pendent acetate arm is replaced by an alcohol arm. This CIS analysis is therefore consistent with two coordinated amines and two coordinated carboxylate groups in the V–HEDT 2 complex in an α-cis arrangement (i.e. trans carboxylates).

Empirical ^{51}V NMR Chemical Shift and Line-Width Correlation. The ^{51}V NMR chemical shift and the full width at half-height line width, $\Delta\nu$, were measured for vanadium(V) complexes (21 complexes) formed from 17 ligands. The results are listed in Table 2. Plotting the inverse line width, $\Delta\nu^{-1}$, as a function of the chemical shift, we discovered two distinct clusters (Figure 3). The first cluster occupies the quadrant defined by the inverse line-width values of 5–8 and the chemical shift range –480 to –490 ppm. The second cluster occupies the quadrant defined by the inverse line-width values of 1–4 and a chemical shift range –490 to –526 ppm. In examining the structures of complexes that are located in each cluster, it appeared that this plot may visually illustrate whether the coordination number for the vanadium atom is five or six in a particular complex.

Two compounds with known solution structures are located in the first cluster: V–TEA and V–TPA complexes.[13a] Both of these aqueous complexes contain pentacoordinate vanadium(V) with tetradentate ligands chelated through three functionalities (the central amine and two hydroxylate groups). The additional complexes located in this cluster V–DEA, V–PDEA, and V–bicine 1 all have the potential to similarly coordinate through two hydroxylate groups and one amine group. The CIS analysis presented above suggests that all these complexes are very similar to the V–TEA and V–TPA complexes. It appears that all the compounds found in this cluster contain a chelated tridentate ligand. Pentacoordinate vanadium(V) compounds have been reported that are not located in this cluster. However, such complexes do not contain a cis-dioxo vanadium center or a ligand containing similar amine and oxygen functionalities.[13,22,23] This correlation presented here appears to be specific for complexes with both nitrogen and oxygen functionalities chelating a cis-dioxo vanadium(V) center.

The second cluster contains a variety of different types of complexes. It includes the V–EDTA complex, which has been characterized by X-ray crystallography and spectroscopic studies.[9,11] Similar complexes include V–EDDA 1 and EDDA 2, and these have also been characterized previously.[9] This group of complexes spans the chemical shift range from –510 to –521 ppm and also includes V–HEDT 2. A second group of complexes has substituted the carboxylate groups in EDTA with hydroxyl groups. This group of complexes (V–EDTE, V–EDDE, V–EDTP, and V–HEDT 1) have chemical shifts from –488 to –498 ppm. This chemical shift range is similar to that observed for the first cluster; however, their inverse line-width values are very different. It is of interest that the coordination of the second amine group does not significantly change the chemical shift of the complex but only affects the inverse line-width value. The presence of the V–HEDT 1 complex in this group is surprising, since this complex contains a coordinated carboxylate group. The chemical shift range from –498 to –509 ppm contains complexes derived from three types of ligands. Complexes formed from ligands containing a minimum of one coordinating hydroxylate, one carboxylate, and one amine group include V–HIDA 1, V–tricine, V–bicine 2, and V–HEDT 1. Complexes containing a minimum of two chelating carboxylates and one amine group include V–NTA, V–ADA, MIDA, and V–HIDA 2. The last complex having a somewhat higher chemical shift than other members in this group may reflect the interaction of the hydroxyl group with the vanadium center. Last, the V–glygly complex represents complexes formed between vanadate and small peptides. These vanadium–peptide complexes have been described as six-coordinate in the literature,[3,5] although no X-ray crystallographic data is currently available for a vanadium–peptide complex. A related system has been examined with X-ray spectroscopy, namely, the vanadium-*N*-[1-(2-pyridyl)ethyl]iminodiacetate complex.[20] Although this ligand was not included in the series shown in Table 2 and 3, it does contain two carboxylate groups and an additional functionality such as in the ligands NTA, ADA, and HIDA. The X-ray structure showed an octahedral vanadium atom with a cis-dioxo unit and the nitrogen trans to an oxo group.[20]

Most of the complexes in the second cluster contain six-coordinate vanadium(V). The only complexes that might contain five-coordinate vanadium are in the series including V–HIDA 1, V–tricine, and V–bicine 2. V–tricine has previously been described as containing five-coordinate vanadium; however, as pointed out, no evidence was available to rule out a six-coordinate vanadium-(V) complex.[8] Additional experimental information on these complexes is desired. Complexes with other ligands containing oxygen and nitrogen functionalities include the SALEN-type ligands, which do not have chemical shifts in this range.[24] Some similarity in ligand structure and functionalities are presumably a requirement for application of this correlation. Nevertheless, it appears that the second cluster contains exclusively complexes with six-coordinate vanadium and that a correlation may exist between ^{51}V NMR chemical shift line width and the coordination number.

The line widths of NMR spectra are sensitive to exchange reactions. Should such exchange occur on the time scale of the NMR experiment, the observed line width and chemical shift of a complex may be very sensitive to the sample conditions. However, previous studies suggest that the formation rate constants for these complexes are fairly similar and that intermolecular exchange processes will not be observable on the ^{51}V NMR time scale.[8,10,14b] The VT NMR studies described above for the V–bicine 2 and both of the V–HIDA complexes

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support this expectation. The correlation described above should be used carefully with due care for other possible effects (such as exchange) on the line widths of the vanadium complexes.

Several correlations have previously been made between ligand type (oxygen and nitrogen donor) and number and the g and A values for vanadium(IV) complexes.[25] A relationship between the ^{51}V NMR chemical shift and the sum of the ligand electronegativities[26a] and the steric effects[26b] has been observed. An empirical relationship has been used to suggest coordination around the vanadium in aqueous vanadate esters.[27] Recently, various terms contributing to the chemical shift in innocent and noninnocent ligands have been examined in six-coordinate vanadium complexes.[28] Various attempts to obtain structural information for complexes in solution have been used, and some studies suggest these approaches may be essential because aqueous vanadate complexes have different structures than those isolated in the solid state.[13a] The empirical relationship shown here, albeit limited with respect to the type of ligands, does provide several advantages. First, the correlation is defined for ligands naturally present in mammalian and other biological systems and should assist in studies with peptides and other biogenic ligands. Second, the involvement of the line width in this correlation allows the distinction between complexes in which the coordinating groups are similar, but where the coordination of the vanadium changes. An example of this is seen in the V–DEA (–487 ppm) and V–EDTE (–489 ppm) complexes, where the former contains five-coordinate vanadium and the latter contains six-coordinate vanadium but their chemical shifts are similar. Given the quadrupolar nature of vanadium, ^{51}V NMR line widths are sensitive to the symmetry of the complex and thus the coordination geometry. It is possible that this empirical relationship may have some theoretical basis.[29] Third, the experimental information needed to provide a rapid guess whether the complex may contain a five-coordinate or six-coordinate vanadium atom is simple to obtain. Furthermore, the correlation is very simple to use and can be easily obtained from a single ^{51}V NMR spectrum.

To probe our empirical correlation further, we turned to ^{17}O NMR spectroscopy and IR and UV spectrophotometry to obtain additional experimental information on the few complexes in which the coordination geometry had not been unequivocally determined as six-coordinate (V–HIDA 1, V–tricine, and V–bicine 2).

^{17}O NMR Studies of Vanadium(V) Complexes. ^{17}O NMR spectroscopy can provide further detail concerning the oxo substitution on the vanadium(V) atom. The cis-dioxo unit is conserved in aqueous complexes, but easily exchanges with water such that the addition of ^{17}O-labeled water will label this functionality.[8,13] The ^{17}O NMR resonances were measured for the V–HIDA 1, V–HIDA 2, V–EDDA 1, V–EDDA 2, and V–EDTA complexes and are listed in Table 4. These resonances have line widths (~500 Hz) consistent with terminal oxo coordination.[23]

A single 1106 ppm resonance for the V–EDTA complex was observed since equivalent amines are both trans to the oxo atoms in the α-cis conformation. The V–EDDA 2 complex, analogous to the V–EDTA complex, has a single resonance at 1099 ppm. In contrast, the V–EDDA 1 complex in the β-cis conformation has two inequivalent oxo moieties; one is trans to an amine and the other trans to a carboxylate. The 1114 and 1087 ppm resonances found for this complex show that such a change in the trans effect gives a 27 ppm difference in the ^{17}O NMR chemical shift.

Two different resonances for the V–HIDA 2 complex were observed with chemical shifts of 1141 and 1085 ppm. The 1085 ppm resonance is very similar to one of the resonances in the V–EDDA 1 complex, but very different from that observed in a pentacoordinate system.[13] Furthermore, the CIS values of the V–HIDA 2 complex indicate that both carboxylates, the central amine, and the hydroxyl group chelate the cis-dioxo vanadium center. Even though the hydroxyl group interacts less than the carboxylates in this complex, any interaction of this residue requires a six- and not a five-coordinate, trigonal bipyramidal environment around the vanadium(V) center. The 56 ppm that separates these two resonances in the V–HIDA 2 complex is considerably larger than for the V–EDDA 1, V–TEA, or V–TPA complexes. A significant difference in the trans substituents is therefore likely in this complex, and five reasonable six-coordinate structures for a 1:1 V–HIDA 2 complex are illustrated in structure **A** through **E**. Structures **C**, **D**, and **E** all contain a pendent arm, and accordingly, three oxygen atoms should yield an ^{17}O signal in the ^{17}O NMR spectrum. Since a 1:1 ratio between the two signals is observed in the spectrum and structures **C**, **D**, and **E** require one oxygen to be significantly different than the other two, one of these oxygen atoms must not be observable in the ^{17}O NMR spectrum. If one, and only one, oxygen was exchanging rapidly with water on the NMR time scale, this could be consistent with the observations, although this is less likely, given the nature of these complexes. In contrast, the ^{17}O NMR spectrum is consistent with an amine and a carboxylate being trans to the two oxo substituents, as in structures **A** and **C**. The oxo group at 1085 ppm is likely to correspond to the oxo group trans to the

Table 4. ^{17}O NMR Data for Seven Vanadium Complexes

complex	chemical shift (ppm)	$\Delta\nu$ (Hz)	$[V_i]$:[L] (mM:mM)	exptl pH	temp (K)
V–EDTA	1106	406	1000:1000	5.80	298
V–EDDA 1	1114	260	500:500	7.47	298
	1087	480			
V–EDDA 2	1099	366	500:500	7.47	298
	1099	366			318
V–HIDA 1	1038	321	300:600	8.58	298
	1038	321			273
V–HIDA 2	1140	488	300:600	5.50	298
	1085	557			
V–TEA[a]	980	275[a]	50:250	9.50	298
	954	305[a]			
V–TPA[a]	985	434[a]	200:600	9.50	298
	940	434[a]			

[a] These results were reported in ref 13a. Line-width values for these complexes are reported here after subtracting the 50 Hz used for line broadening.

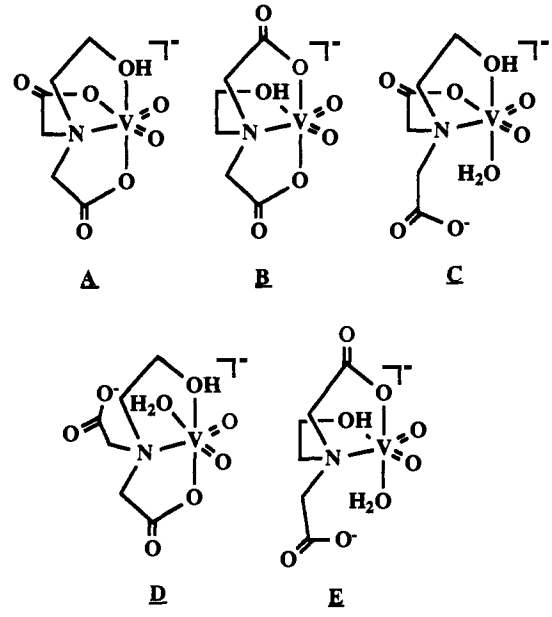

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Table 5. IR[a] and UV-Vis[b] Data for Selected Vanadium(V) Complexes

complex	IR $\Delta\nu_{V=O}$ (cm^{-1})	UV-vis λ_{max} (nm)	^{51}V NMR chem shift, δ (ppm)	exptl pH
vanadate	921	367		8.90
V-TEA	904	395	-485	9.07
V-bicine 1	907	384	-487	9.95
V-HIDA 1	893	417	-499	8.52
V-tricine	893	408	-507	7.18
V-bicine 2	889	429	-508	7.00
V-EDTA	894	427	-519	7.00
V-HIDA 2	890	432	-520	5.05

[a] The resolution in these measurements was ±2 cm^{-1}. [b] The resolution in these measurements was ±5 nm.

amine since a similar resonance is observed for the V-EDDA 1 complex. Differences in orientation of the carboxylate arm and concomitant orbital overlap in the V-HIDA 2 and V-EDDA 1 complexes could explain differences in the chemical shift of the second resonance (1140 and 1114 ppm, respectively). A cis-dioxo group in the same plane as the amine–carboxylate chelate ring, as illustrated in structures **A** and **C**, would be different than the cis-dioxo group in the V-EDDA 1 complex. In conclusion, a V-HIDA 2 complex with an oxo group trans to an amine and the other oxo group trans to a carboxylate group is consistent with the observed ^{17}O NMR spectrum.

The V-HIDA 1 complex produces only one resonance at 1038 ppm. The possibility that the oxygens are exchanging on the time scale of the ^{17}O NMR experiment was examined by VT studies. The spectra were recorded at 318, 298, and 273 K, but no evidence for a change in line width or decoalescence was observed in this temperature range. Three reasonable structural possibilities are consistent with all this information for a 1:1 complex. First, a five-coordinate complex with only one type of oxygen would be a possibility for this complex (with a nitrogen in the equatorial plane in contrast to the axial nitogen found in the V-TEA complex).[13] A second possibility would be an octahedral complex in which inequivalent oxo groups exchange rapidly. Third, the oxo groups are trans to an amine and an alkoxo group, and these affect the bond strengths of the oxo groups similarly such that only one signal is observed in the ^{17}O NMR spectrum. Based on the available evidence, we expect the V-HIDA 1 complex to be octahedral, perhaps with a stoichiometry other than 1:1.

IR and UV-Vis Spectroscopic Studies of Vanadium(V) Complexes. IR spectroscopy is a sensitive method for examining the nature of the V=O functionality, and differences are likely to be observed in five-coordinate and six-coordinate complexes. As reported in Table 5, the V=O strength for the aqueous V-TEA complex was found to be 904 cm^{-1} and that of the V-EDTA complex 894 cm^{-1}. The V-bicine 1 complex has a V=O stretch at 907 cm^{-1}, supporting the CIS analysis that this complex is similar to the V-TEA complex. In analogy, the V-HIDA 2 complex has a V=O strength at 890 cm^{-1}, supporting the conclusion that this complex contains six-coordinate vanadium, as in the V-EDTA complex. The three complexes under consideration, V-HIDA 1, V-tricine, and V-bicine 2, have stretches at 893, 893, and 889 cm^{-1}, respectively. These observations are consistent with these complexes containing six-coordinate vanadium atoms. Similar arguments can be made for the λ_{max} from the UV-vis absorption maxima. The results are also summarized in Table 5. Both V-TEA and V-bicine 1 have higher energy transitions associated with V=O stretches and ligand to metal charge-transfer bands from the IR and UV-vis data, respectively, compared to the other complexes shown in Table 5. The differences between complexes characterized as five- and six-coordinate are, however, apparent. In conclusion, IR and UV spectroscopy support the assignments of the five-coordinate complexes in one cluster and six-coordinate complexes in the second cluster (Figure 3).

Comparison of Solution Structures of Vanadium(IV) and Vanadium(V) Complexes. EDTA chelates vanadium as a pentadentate ligand in the V(IV)–EDTA complex in the solid state[30] and in solution,[31] whereas the V(V)–EDTA complex only involves four functionalities from EDTA.[9,11,31] Both vanadium(IV) and -(V) form complexes with *N*-[1-(2-pyridyl)ethyl]-iminodiacetate that have all four functionalities of the ligand chelated to the metal center.[21] In the mixed valent V(IV,V)–NTA_2 complex the NTA ligands chelate vanadium through four functionalities at each metal center.[20] This is in contrast to the aqueous V-TEA complex that only utilizes three functionalities, whereas the solid-state form chelates all four ligand functionalities to the metal.[13] Aqueous vanadium(V) thus seems to exhibit more structural variety than is seen in the vanadium(IV) complexes.

The complexes examined that have all possible functionalities chelated to the vanadium include V-NTA, V-EDDA 1, V-EDDA 2, V-EDDE, V-bicine 2, V-HIDA 1, and perhaps V-HIDA 2. All the other compounds from tetradentate ligands described in Table 3 form complexes with less than the maximum number of coordinated functionalities to the vanadium(V) center. Vanadium(V) has a great affinity for maintaining the cis-dioxo unit intact. However, the remaining four coordination sites in a six-coordinate complex could easily accommodate a fourth chelated functionality. The preference of vanadium(V) to coordinate fewer functionalities is thus not related to maintaining the intact cis-dioxo unit. The fact that V-bicine 1 and perhaps V-HIDA 2 have one pendent arm is of interest because, in both cases, an aqueous complex forms at a different pH with all four functionalities chelated to the vanadium(V) center. In the complexes with all functionalities chelating, the CIS values are smaller than in analogous complexes containing pendent arms, suggesting that each of the bonds in such complexes are weaker than bonds in complexes with only three functionalities chelating. Vanadium(IV) complexes of amino acids have been described as having pendent arms; however, no crystallographic information on such complexes is available.[32] The existence of vanadium(V) complexes with pendent arms could be of great potential in preparation of materials for medicinal purposes.

The vanadium(V) complexes that form with no pendent arms bear more resemblance to the vanadium(IV) complexes. The V-NTA, V-EDDA 1, V-EDDA 2, and V-EDDE complexes also chelate with all four functionalities in the neutral pH range. Vanadium(IV) complexes tend to be chelated by more functionalities and often form both monomers and dimers in solution.[20,33] Dimeric mixed vanadium(IV,V) systems have also been reported in solution and in the solid state.[20,21] Vanadium(V) in the form of vanadate and vanadate esters form dimeric species;[34] however, such systems are very labile and do not enjoy the stability of the vanadium(IV) systems. Evidence for dimeric species was observed by isolation and characterization of a dinuclear V-HIDA complex (Crans and Mahroof-Tahir, unpublished).

Vanadium(V) Complex Formation in Biological Systems. The studies presented here provide a library of information on the aqueous coordination chemistry of vanadium(V). If the vanadium(V) metal in a biological system surrounded by oxygen and nitrogen donors is five-coordinate, it is likely to have only one carboxylate group in the vicinity. However, the vanadium atom can bind as a complex, and in this case the structure and stability of this complex will determine its fate. Five-coordinate vanadium has been reported inside ribonuclease A as a vanadate–uridine

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complex.[35] In this case, the X-ray structure was not trivial to solve in part because of the low occupancy of the uridine–vanadate complex.[35] Lysine-25 in the vicinity of the active site could potentially move over and interact with the vanadate–uridine complex. Is it interacting through ionic interactions, or is it close enough for covalent interactions? For the latter to occur, the lysine must first be deprotonated. Nevertheless, our studies suggest that the vanadium can easily expand its coordination sphere and include another coordinating amine without significantly changing the ^{51}V NMR chemical shift.

The correlation presented in Figure 3 currently is limited since it has not yet been tested with other important functionalities such as the tyrosine and imidazole groups. These two groups are essential to many proteins, and most predictions and considerations should await further experimentation. However, a few points can be made at this time.

Vanadium–protein complexes with two or more carboxylate functionalities are likely to contain six-coordinate vanadium. Chemical shifts of vanadium–protein complexes such as those observed for vanadium(V)–protein complexes in bromoperoxidase from *Ascophyllum nodosum* (–1070 ppm)[36] are very unusual, and the binding environment of the vanadium is likely to involve peroxide and noninnocent ligands, as described in model studies.[28] On the other hand, chemical shifts in the range of –560 ppm as observed for the vanadium complex with SOD[37] and 3-phosphoglycerate mutase[38] are more likely to involve the more traditional functionalities found in proteins. In the cae of SOD, two lysines were targeted as functionalities interacting with the vanadium atom, and in 3-phosphoglycerate mutase three histidines and one tryptophan residue were identified as likely candidates to interact with the bound vanadium. The studies performed here could be interpreted to suggest that the vanadium may be six-coordinate.

The $V(V)_2$–human transferrin complex contains two types of vanadium, with chemical shifts of –530 and –531 ppm.[39] These types of chemical shifts are close to those observed for the complexes studied in this work and would suggest that the sites may contain one or two coordinating nitrogen atoms and a minimum of two coordinating oxygen atoms (one in the form of a carboxylate group). The ligands of the Fe(II) in transferrin are two tyrosines, a bidentate carbonate, one aspartate, and one histidine.[40] If a vanadium(V) atom were to bind at the active site, its ^{51}V NMR chemical shift may be expected to be in the range predicted based on this work even though neither the tyrosine nor the imidazole functionalities have been considered at this time. This expectation is based on the fact that phenol–vanadate complexes have roughly similar chemical shifts as alcohol–vanadate complexes.[34,41] Chemical shifts for imidazole–vanadate complexs have not been reported because no new resonance is observed in vanadate solutions containing imidazole where an imidazole–vanadate complex clearly forms.[34] However, related pyridine–vanadate complexes both with pyridine as monodentate and polydentate ligands show similar chemical shifts as the ethanolamine-derived complexes.[42] Accordingly, similar studies are likely to indicate that complexes of ligands containing tyrosine and imidazole functionalities have chemical shifts in the range discussed here.

Conclusions

The preferred coordination geometry of vanadium(V) in aqueous solution with nitrogen- and oxygen-containing multidentate ligands has been determined. Spectroscopic characterization of aqueous solution complexes is essential because recent studies have shown that the structures in the solid state and aqueous solutions may not be identical. Five-coordinate complexes result when the complex contains chelated alkoxo and amine functionalities, whereas in general, coordination of carboxylate groups results in complexes with six-coordinate vanadium. Six-coordinate vanadium(V) complexes often have one more pendent arm than similar vanadium(IV) complexes. An empirical correlation was observed for the inverse line width and coordination number with the ^{51}V NMR chemical shifts of these complexes. The flexibility and modulation in ligand coordination observed in this work could be important in the function of vanadium(V) in biological systems.

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Supplementary Material Available: Table of ^{13}C NMR chemical shift values for a series of vanadium complexes (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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