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Factors Affecting Solution Properties of Vanadium(V) Compounds: X-ray Structure of *β-cis*-$NH_4[VO_2(EDDA)]$[1]

Debbie C. Crans,* Anastasios D. Keramidas, Mohammad Mahroof-Tahir,
Oren P. Anderson, and Mary M. Miller

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523-1872

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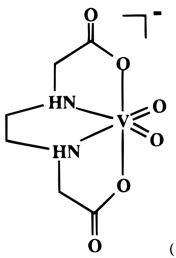
The solution properties of two isomeric forms of the V−EDDA complex (the symmetric α-cis and asymmetric *β*-cis) have been studied using multinuclear NMR spectroscopy. The isomerization constant of the aqueous equilibrium mixture expressed as [α-cis]/[*β*-cis] *increased* on the addition of organic solvents (methanol, formamide, and DMSO) and *decreased* on the addition of salts (NaCl, $NaClO_4$, and NH_4Cl). The isomerization constant and corresponding thermodynamic parameters were determined under a variety of conditions. The solution studies were consistent with the interpretation that solvation is the major contributor to isomer stability. Solid state characterization of the *β*-cis isomer of $NH_4[VO_2(EDDA)]$ confirmed this conclusion and allowed detailed examination of the role of hydrogen bonding in this complex. The structural parameters for this complex are triclinic, $P\bar{1}$, $a = 6.787(1)$ Å, $b = 7.272(1)$ Å, $c = 11.014(1)$ Å, $\alpha = 95.084(9)°$, $\beta = 92.805(8)°$, and $\gamma = 100.009(9)°$. The dynamic processes of these complexes were examined in water and in water−DMSO mixtures resulting in observation of an unknown intramolecular dynamic process. The extent to which this complex responds to the environment is discussed, and its implications for biological studies and the mechanism of action of vanadium compounds are briefly considered.

Introduction

It has been recognized for many years that the specific coordination geometry of metal complexes and their properties are affected by a number of factors including metal ion, ligand, solvation, temperature, and ion association (see, for example, ref 2). Vanadium complexes are particularly susceptible to external influences since the vanadium atom is small and readily accommodates several coordination geometries. In view of the current interest in vanadium compounds as oral insulin substitutes,[3−5] it is important to understand how various factors affect the structure and properties of vanadium complexes. The current paper probes the sensitivity of the structure and stability of isomeric aqueous vanadium(V) complexes to solvent and salt effects.

Vanadium(V) forms well-characterized complexes with ligands derived from EDTA.[6−12] Two EDTA complexes, differing in protonation states and counterions, have been characterized by X-ray crystallography; both show the vanadium atom in an octahedral geometry with a *cis*-dioxo unit.[7,8] Solution studies have convincingly shown that these complexes retain the solid state structure in solution.[9] In addition, solution studies have been carried out on complexes from ligands analogous to EDTA including those of *N*-(hydroxyethylamine)ethylenediamine-*N*,*N*′,*N*′-triacetic acid, *N*,*N*′-(dimethylethyl)ethylenediamine-*N*,*N*′-diacetic acid (H_2DMEDDA), and ethylenediamine-*N*,*N*′-diacetic acid (H_2EDDA).[9,12] The major DMEDDA complex in solution has similar spectroscopic properties to the EDTA complex and, accordingly, has been proposed to be structurally similar; the minor product (∼3%) observed in these solutions has not been characterized in detail.[9] Two complexes of similar stability form with EDDA as ligand.[9] The symmetric α-cis complex (**1**) is structurally similar to the EDTA complex, and the *β*-cis complex (**2**) is an asymmetric isomer. The geometry of **2** was deduced from spectroscopic studies in aqueous solution.[9]



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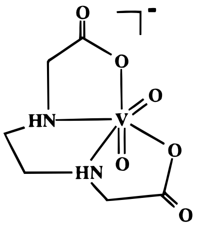

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In the present study we report solution and solid state characterization of the V−EDDA complexes. The extent to which the stability of the isomers is dependent on solvation and

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(1) Abbreviations: AN, acceptor number; DMEDDA, *N*,*N*′-dimethylethylenediamine-*N*,*N*′-diacetate; DMSO, dimethylsulfoxide; D_2O, deuterium oxide; DSS, sodium 3-(trimethylsilyl)-1-propanesulfonate; EDDA, ethylenediamine-*N*,*N*′-diacetate; EDTA, ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetate; H_2DMEDDA, *N*,*N*′-(dimethylethyl)ethylenediamine-*N*,*N*′-diacetic acid; H_2EDDA, ethylenediamine-*N*,*N*′-diacetic acid; H_4EDTA, ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid; IR, infrared; NMR, nuclear magnetic resonance; Oxal, oxalate; V−EDDA, the vanadium(V) complex(es) with EDDA; V−EDTA, the vanadium(V) complex with EDTA.

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ionic interactions is explored using solvent and salt mixtures. The effects of solvent and salt on the rapid interconversion is also examined because, in contrast to the corresponding cobalt(III) complexes, the vanadium(V) complexes interconvert in aqueous solution.[13,14] The solid state structure of the *β*-cis complex is determined and compared to that of the EDTA complex. We conclude that in vanadium(V) complexes of a ligand such as EDDA, where more than one stable isomer can form, environmental effects may even determine which isomer is predominant in the mixture. Should the biological effects of vanadium compounds be strictly related to their structure, information on model systems should be important to understanding the nature of the active vanadium species in biological systems.

Experimental Section

Materials and Methods. All chemicals obtained from Sigma or Aldrich were reagent grade and used without further purification. Stock solutions of $NH_4[VO_2(EDDA)]$, NH_4Cl, KCl, NaCl, and $NaClO_4$ were prepared by dissolving the crystalline material in water or D_2O and stored at ambient temperature. $K_3[VO_2(EDTA)]\cdot 4H_2O$,[6] $NH_4[VO_2(H_2\text{-}EDTA)]\cdot 3H_2O$,[15] and $NH_4[VO_2(Oxal)_2]\cdot 2H_2O$[16,17] were prepared as described previously. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR in KBr pellets. Microanalyses were performed by Desert Analytics, Tucson, AR.

Preparation of $NH_4[VO_2(EDDA)]$. NH_4VO_3 (0.58 g, 5.0 mmol) was dissolved in 15 mL of H_2O, and the pH was adjusted to 7.5 with a solution of NH_4OH (5 M). Solid H_2EDDA (0.95 g, 5.4 mmol) was added, and the suspension was stirred until dissolution was complete at which point the pH had decreased to 7.3 (if the pH of the solution was less than 7.3, it was increased to obtain better yields). This yellow solution was filtered to remove undissolved particles before adding 35 mL of ethanol. The resulting solution (a precipitate begins to form after 1 day) was kept at −15 °C for 5 days at which time a yellow crystalline material had precipitated. The precipitate was isolated by filtration and washed twice with 5 mL of ethanol. The isolated yield of $NH_4[VO_2(EDDA)]$ was 1.1 g (89%): ^{51}V NMR $\delta(D_2O)$ −503 (*β*-cis), −514 (α-cis); ^1H NMR $\delta(D_2O)$ 3.76 (4H, dd, AB), 2.97 (4H, dd, AB) (α-cis), 3.72 (2H, dd, AB), 3.70 (2H, dd, AB), 3.5, 3.1, 2.7 (4H, m, CDEF), (*β*-cis);[9] $^{13}C\{H\}$ NMR $\delta(D_2O)$ 186.1, 57.0, 56.8, 51.5 (α-cis), 185.9, 182.6, 60.7, 59.1, 50.1 (*β*-cis); IR (KBr) 3238 (s), 3130 (s), 1602 (s), 1451 (s), 1416 (m), 1392 (m), 1331 (s), 1306 (s), 1283 (m), 1259 (m), 1211 (w), 1151 (w), 1127 (m), 1090 (w), 1048 (m), 1018 (m), 1006 (w), 975.2 (m), 944 (m), 931 (s), 906 (s), 883 (s), 857 (s), 830 (s), 741 (m), 723 (m), 644 (m), 602 (m), 578 (m), 560 (w), 530 (m). Anal. Calcd for $C_6H_{14}N_3O_6V$: C, 26.19; H, 5.13; N, 15.27. Found: C, 26.31; H, 5.06; N, 15.12.

Preparation of NMR Samples. The samples were prepared from a 300 mM stock solution of crystalline $NH_4[VO_2(EDDA)]$ at pH 7.0 in water or D_2O. The use of deuterio or protio solvents depended on whether or not a particular sample was to be analyzed by ^{51}V NMR spectroscopy (normal solvents) or by both ^{51}V and ^1H NMR spectroscopy (deuterated solvents). Organic solvents (methanol (CH_3OH or CD_3OD), formamide, or DMSO (or DMSO-d_6)) and/or stock solutions of inorganic salts (NaCl, $NaClO_4$, or NH_4Cl) were added in the appropriate ratios to a solution of 0.100 mL of 300 mM V−EDDA using a 1.000 mL syringe. The final volume of each sample was adjusted to 1.000 mL by the addition of water or D_2O.

Samples used to measure the [α-cis]/[*β*-cis] ratio were prepared in triplicate typically containing from 10 to 30 mM $NH_4[VO_2(EDDA)]$ (although up to 100 mM solutions have been examined in this manner).

NMR Spectroscopy. NMR spectra were recorded on a Bruker ACP-300 spectrometer operating at 300 MHz for ^1H, 75 MHz for ^{13}C, and 79 MHz for ^{51}V. Routine parameters were used when recording the ^1H and ^{13}C NMR spectra and DSS (sodium 3-(trimethylsilyl)-1-propanesulfonate) was used as an external reference. The [α-cis]/[*β*-cis] ratio was determined by integration of ^1H NMR spectra using the C*H*$_2$COO signal for both isomeric complexes in solutions containing D_2O/CD_3OD and D_2O/DMSO-d_6. The accuracy in quantitation by ^1H NMR spectroscopy was significantly higher than the accuracy obtained by quantitation using ^{51}V NMR spectroscopy given the overlap of signals. However, in all cases, the results obtained by both methods were in close agreement.

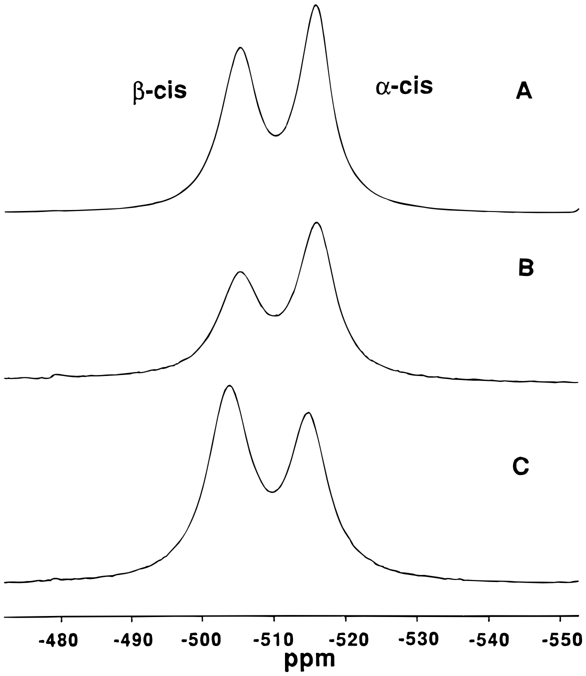

Figure 1. ^{51}V NMR spectra of 30 mM V−EDDA at pH 7.0 in (a) D_2O, (b) D_2O−DMSO-d_6 (1.4 M), and (c) 4.0 M NH_4Cl in water.

The ^{51}V NMR spectra were recorded using a sweep width of about 25,000 Hz, an accumulation time of 0.1 s, a pulse angle of 90°, a relaxation delay of 0.0 s, and approximately 1000 scans. No significant changes were observed when an increased relaxation delay was used during accumulation of the spectra. The ^{51}V NMR spectra are referenced to external $VOCl_3$. Using the known total vanadium concentrations (assuming all vanadium exists in oxidation state V) and the mole fraction of each vanadium species, the concentrations of each of the EDDA complexes and other oxovanadate species were calculated. An exponential line broadening of 15 was imposed on the accumulated data before Fourier transformation, at which point each ^{51}V NMR spectrum was phased, baseline corrected, and integrated. In light of the importance of spectral integration, we used several methods to ensure accuracy in our integrations. The ^{51}V NMR spectra were simulated using Glinfit and/or integrated by use of Bruker software or manual integration. Particular care was taken in the integration of ^{51}V NMR spectra at ambient temperature where significant resonance overlap is evident (see Figure 1). In addition the integrations of the ^{51}V NMR spectra were compared to the integrations of the ^1H NMR spectra where better signal resolution was obtained. The reported data represent the average value for the mole fractions of vanadium atoms in the respective vanadium complexes obtained from three different sample solutions. The indicated error limits reflect the deviations in these measurements (note, the accuracy in the experiments carried out by use of ^1H NMR spectroscopy was significantly higher than that reported in this manuscript).

When determining the thermodynamic parameters, the NMR spectrometer was calibrated within ±1° using an ethylene glycol sample. The NMR spectrometer was equilibrated for 10 min at each temperature before the first spectrum was recorded. To ensure that the temperature had stabilized, a second NMR spectrum was acquired and compared to the first spectrum. These measurements were initiated at ambient temperature, and then the higher temperatures were measured. Upon completion of a series, the temperature was reduced to ambient and the initial measurement redone to ensure that no redox chemistry had

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Table 1. Crystal Data and Structure Refinement for **2**

empirical formula	$C_6H_{14}N_3O_6V$
formula weight	275.14
temperature	−100 °C
wavelength	0.71073 Å
crystal system	triclinic
space group	$P\bar{1}$
unit cell dimensions	$a = 6.787(1)$ Å $\alpha = 95.084(9)°$ $b = 7.272(1)$ Å $\beta = 92.805(8)°$ $c = 11.014(1)$ Å $\gamma = 100.009(9)°$
volume	532.07(12) Å^3
Z	2
density (calculated)	1.717 mg/m^3
absorption coefficient	0.952 mm^{-1}
$F(000)$	284
crystal size	0.42 × 0.36 × 0.28
Θ range for data collection	2.0 − 25.0°
index ranges	$0 \leq h \leq 8, -9 \leq k \leq 9, -14 \leq l \leq 14$
reflections collected	2662
independent reflections	2453 [R(int) = 0.0202]
refinement method	full-matrix least-squares on F^2
data/restraints/parameters	2453/0/178
goodness-of-fit on F^2	1.081
final R indices [$I > 2\sigma(I)$]	$R1 = 0.0289$, $wR2 = 0.0801$
R indices (all data)	$R1 = 0.0324$, $wR2 = 0.0827$
extinction coefficient	0.019(4)
largest diff peak and hole	0.359 and −0.268 e A^{-3}

altered the sample under examination. When possible ^{1}H NMR spectroscopy was used for these experiments.

X-ray Structure Determination of $NH_4[VO_2(EDDA)]$), 2. Crystals of diffraction quality were obtained by slow diffusion of ethanol into a concentrated aqueous solution (approximately 0.3 M) of $NH_4[VO_2(EDDA)]$. A clear yellow crystal of **2** (0.42 × 0.36 × 0.28 mm^3) was used for X-ray data collection (see Table 1 for parameters). Intensity data were collected on a Siemens P4 diffractometer using Mo Kα ($\lambda = 0.7107$ Å) radiation. The unit cell constants were determined from a least-squares fit to the angles of 25 reflections. Data were collected ($\theta/2\theta$ scans) to $(\sin\theta)/\lambda = 0.595$ Å − 1 ($0 \leq h \leq 8, -9 \leq k \leq 9, -14 \leq l \leq 14$). The intensities of three standard reflections were examined every 97 reflections; no significant changes were noted. Lorentz and polarization corrections were applied, along with an empirical absorption correction based on intensities of selected reflections as a function of ψ ($T_{max} = 0.88$, $T_{min} = 0.72$). A total of 2453 unique reflections was observed; all of these reflections were employed during the full-matrix weighted least-squares refinement on F^2.

The structure was solved by using the direct methods routine TREF in the Siemens SHELXTL PLUS program library.[18] Hydrogen atoms of the ligand were placed in idealized positions, while the protons of the ammonium counterion were located in a difference Fourier map and refined independently with isotropic thermal displacement parameters. All non-hydrogen atoms were refined with anisotropic thermal displacement parameters; at convergence ($(\Delta/\sigma)_{max} = 0.001$ for the last cycle) $R = 0.0289$, and $wR = 0.0801$. Neutral atom scattering factors and anomalous dispersion corrections were used.[19]

Results and Discussion

Preparation of $NH_4[VO_2(EDDA)]$ (V−EDDA). The V−EDDA complex has previously been prepared from NH_4VO_3 and H_2EDDA at pH 6.0−6.5.[9] However, in view of the reported problems with reduction of the vanadium, this procedure was modified. We found that below pH 7.0 the V−EDDA complex will slowly reduce to generate a green solution. The lower the pH the faster the reduction occurs; at pH 5 the reduction will be noticeable in 4 h, whereas at pH 6−7 the reduction takes place over the course of 1−2 days. Above pH 8−8.5 the V−EDDA complex hydrolyzes to form vanadate, vanadate oligomers, and free EDDA ligand. It appears that isolation of the $NH_4[VO_2(EDDA)]$ may be best carried out in the pH range 7−8.5. Indeed, mixing NH_4VO_3 and H_2EDDA at pH 7.0−7.5 gave rise to $NH_4[VO_2(EDDA)]$ in 89% yield, free of the reported complicating redox reactions. In the following solution studies the isolated crystalline V−EDDA complex was used.

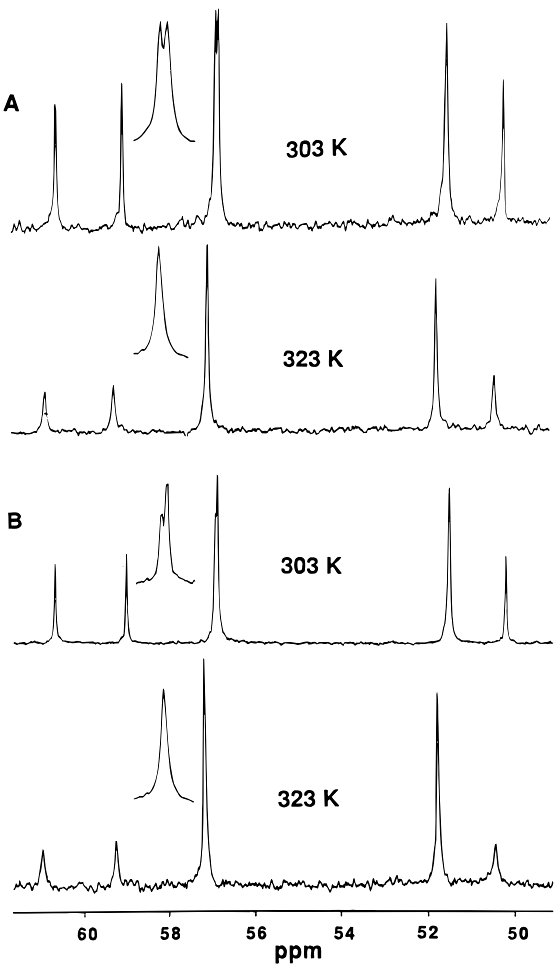

Figure 2. Variable temperature ^{13}C NMR spectra of 100 mM V−EDDA at pH 6.9 in (a) D_2O and (b) D_2O−DMSO-d_6 (1.3 M). The ^{13}C resonances for the α-isomer are at about 57 and 52 ppm, respectively.

Stability of α-cis and β-cis Isomers in Aqueous Solution. The exact concentrations of the approximately 1:1 mixture of α-cis and β-cis isomers can conveniently be monitored by ^{1}H,[9] ^{13}C,[9,12] and ^{51}V[12] NMR spectroscopy. The previous careful analysis of the ^{1}H NMR spectrum, combined with the observed temperature dependence,[9] allows unambiguous assignment of the resonance at higher field in the ^{51}V NMR spectrum to the α-cis isomer (Figure 1) and the ^{13}C resonances in the ^{13}C NMR spectrum (Figure 2). The equilibrium between the β-cis and α-cis isomers (1) is expressed by the ratio [α-cis]/[β-cis] (2).

$$\beta\text{-cis} \rightleftharpoons \alpha\text{-cis} \qquad (1)$$

$$K = [\alpha\text{-cis}]/[\beta\text{-cis}] \qquad (2)$$

Most of the results described here were carried out using a stock solution of the V−EDDA complex. In addition, a series of spectra were examined over the pH range from 5.5 to 9.0 which did not reveal any significant changes in the magnitude of the [α-cis]/[β-cis] ratio. Below pH 6.0 significant reduction of the complex is observed even though the fraction remaining as α-cis and β-cis V−EDDA complexes maintains an essentially unchanged [α-cis]/[β-cis] ratio (within experimental error). As anticipated the [α-cis]/[β-cis] ratio did not change as a function of concentration from 10 to 100 mM V−EDDA complex.

Stability of α-cis and β-cis Isomers in Mixed Solvent Systems. Given the insolubility of $NH_4[VO_2(EDDA)]$ in organic solvents and the fact solvent mixtures are known to

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Table 2. Stability of α-cis and *β*-cis [VO_2EDDA]$^-$ Isomers at pH 7.0 (Before Addition of Organic Solvent) in Mixed Solvent Systems at 18 °C[a–d]

solvent	concentration of organic solvent in H_2O/M	stability [α-cis/*β*-cis] ratio
H_2O		1.1(±0.1)
H_2O/CH_3OH[b]	4.9(±0.1)	1.5(±0.1)
	9.9(±0.1)	1.8(±0.1)
	15(±1)	2.0(±0.1)
	19(±1)	2.3(±0.1)
H_2O/H_2NCHO[c]	5.0(±0.1)	1.3(±0.1)
	10(±1)	1.3(±0.1)
	15(±1)	1.9(±0.1)
	20(±1)	2.1(±0.1)
H_2O/DMSO[d]	2.8(±0.1)	1.5(±0.1)
	5.6(±0.1)	2.8(±0.1)
	8.4(±0.1)	4.1(±0.1)
	11(±1)	7.0(±0.1)

[a] The reported errors in the [α-cis]/[*β*-cis] ratio are the average deviation from the mean value of three experiments (analyzed in triplicate). [b] The concentrations of [α-cis] and [*β*-cis] isomers were measured in 30 mM solutions prepared from solid $NH_4[VO_2(EDDA)]$ using ^{51}V NMR and ^1H NMR spectroscopy. See Experimental Section for further details. Neat CH_3OH/CD_3OD corresponds to 24.5 M; the latter was used for the ^1H NMR experiments. [c] The concentrations of [α-cis] and [*β*-cis] isomers were measured in 30 mM solutions prepared from solid $NH_4[VO_2(EDDA)]$ using ^{51}V NMR spectroscopy. See Experimental Section for further details. Neat formamide corresponds to 25.2 M. [d] The concentrations of [α-cis] and [*β*-cis] isomers were measured in 30 mM solutions prepared from solid $NH_4[VO_2(EDDA)]$ using ^{51}V NMR and ^1H NMR spectroscopy. Above 5 M DMSO the ^{51}V NMR resonances of α-cis and *β*-cis merge complicating measurements by ^{51}V NMR spectroscopy. See Experimental Section for further details. Neat DMSO-d_6 corresponds to 15.2 M.

induce solvent effects in a manner similar to pure solvents (see, for example, ref 20), solvent mixtures were used to quantitatively examine the changes in the [α-cis]/[*β*-cis] ratio as a function of solvent composition. Three solvents, methanol (CH_3OH or CD_3OD), formamide (H_2NCHO), and dimethyl sulfoxide (DMSO or DMSO-d_6), were chosen because of their properties and the solubility of $NH_4[VO_2(EDDA)]$ in these solvents. In some experiments with DMSO-d_6 and CD_3OD, both ^{51}V NMR and ^1H NMR were employed to measure the stability ratio in D_2O–organic solvent mixtures. In Figure 1 the ^{51}V NMR spectra are shown of 30 mM crystalline $NH_4[VO_2(EDDA)]$ dissolved in D_2O and 1.5 M DMSO-d_6 and in Figure 2 the ^{13}C NMR spectra of 100 mM crystalline $NH_2[VO_2(EDDA)]$ dissolved in D_2O and 1.3 M DMSO-d_6. Comparing these two spectra (and others) shows that the ratio of [α-cis]/[*β*-cis] has increased upon addition of DMSO-d_6 (from 1.1- to 1.4-fold excess).

As shown in Table 2, the [α-cis]/[*β*-cis] ratio gradually changed from 1.1 to 2.3 when increasing the CH_3OH (or CD_3OD) concentration from 0 to 19 M. Despite the similarity of methanol to water, its presence favors the α-cis isomer by more than a factor of 2. A similar effect is observed on the addition of formamide. The [α-cis]/[*β*-cis] ratio increases from 1.1 to 2.1 when the formamide concentration increases from 0 to 20 M. At only 11 M DMSO the α-cis isomer is in 7-fold excess over the *β*-cis isomer demonstrating that this solvent is much more effective in stabilizing the α-cis isomer than either methanol or formamide.

All three organic solvents show that the stability of the *β*-cis isomer decreases as the amount of organic solvent increases. The size of the effects on the stability ratio is less obvious since the stability ratio decreases in the following order: DMSO > CH_3OH ∼ formamide > water. Since the dielectric constant, ϵ, for these solvents decreases in the following order: formamide > water > CH_3OH > DMSO, the dielectric constant of the solvents does not show a pattern consistent with the observed stability pattern of the [α-cis]/[*β*-cis] ratio in the mixed solvent systems. Alternative solvent properties such as dipole moment (formamide > CH_3OH ∼ DMSO > water) or polarizability (DMSO > formamide > CH_3OH > water) also do not show a simple correlation with the observed stability patterns; although the solvent polarizability does come closer than the dielectric constant or dipole moment. The possibility that hydrogen bonding is important to the stability of either the α-cis or the *β*-cis isomer suggests that a correlation may exist with these solvents' abilities to donate electron density to electron-deficient centers or accept electrons from electron-rich centers. Using Gutmann's scale to describe the property acceptor number (AN),[21] we find the order water > CH_3OH ∼ formamide > DMSO. This is exactly the order that was observed for the increasing stability of the α-cis isomer. Thus, it is plausible that the [α-cis]/[*β*-cis] stability pattern is a result of a less favorable solvent interaction with the *β*-cis isomer. This would be in agreement with the suggestion by Amos and Sawyer that the two isomers have different solvation spheres.[9] Perhaps the addition of a component that competes effectively with the solvent will favor the *β*-cis isomer and decrease the [α-cis]/[*β*-cis] ratio. This possibility is explored in the following.

Table 3. Stability of α-cis and *β*-cis [VO_2EDDA]$^-$ Isomers at pH 7.0 in the Presence of Various Salts at 18 °C[a,b]

additive	concentration of the sal in H_2O/M	stability [α-cis/*β*-cis] ratio
no salts		1.1(±0.1)
NaCl	4.0(±0.1)	1.0(±0.1)
	5.3(±0.1)	0.92(±0.06)
$NaClO_4$	4.0(±0.1)	1.0(±0.1)
	5.3(±0.1)	0.90(±0.06)
NH_4Cl	3.0(±0.1)	0.86(±0.07)
	4.0(±0.1)	0.80(±0.04)
	5.3(±0.1)	0.74(±0.06)
	6.3(±0.1)	0.65(±0.06)

[a] The errors in the [α-cis]/[*β*-cis] ratio are the average deviation from the mean value of three experiments (analyzed in triplicate). [b] The concentrations of [α-cis] and [*β*-cis] isomers are measured in 30 mM solutions prepared from solid $NH_4[VO_2(EDDA)]$ using ^{51}V NMR spectroscopy. See Experimental Section for further details.

Stability of α-cis and *β*-cis Isomers in Salt Solutions. The effects of NaCl, $NaClO_4$, and NH_4Cl on the [α-cis]/[*β*-cis] ratio was determined by ^{51}V and/or ^1H NMR spectroscopy. As shown in Table 3 a gradual increase in NaCl and $NaClO_4$ concentration is accompanied by a decrease in the [α-cis]/[*β*-cis] ratio. This effect is even more dramatic when NH_4Cl is added, since the addition of 6.3 M NH_4Cl decreases the ratio from 1.1 to 0.65. The ^{51}V NMR spectrum of a solution containing the V–EDDA complex and 4.00 M NH_4Cl is shown in Figure 1c. Clearly the *β*-cis isomer becomes the dominant isomer in the presence of 4.00 M NH_4Cl.

The decreased [α-cis]/[*β*-cis] ratio at high salt concentrations is consistent with the interpretation that solvation of the α-cis isomer is disrupted and/or solvation of the *β*-cis isomer is increased. The observation that NH_4Cl is significantly better than NaCl in stabilizing the *β*-cis isomer could be attributed to the higher ability of this salt to hydrogen bond to the *β*-cis isomer of the vanadium(V) anion. It is possible that one isomer must form slightly stronger interactions than the other; a VO_2 unit and one carboxylate group in the α-cis isomer may be slightly better hydrogen bond acceptors than two carboxylate

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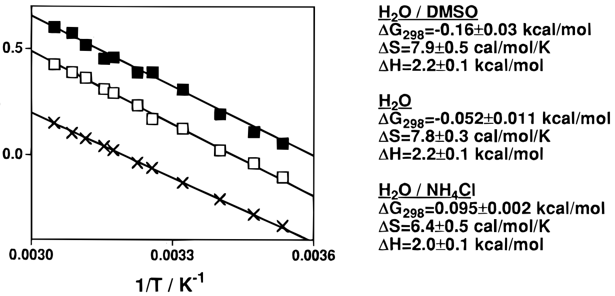

Figure 3. Plots of ln K_{eq} as a function of $1/T$ in water (□), 1.3 M DMSO (■), and 2.0 M NH_4Cl (×). The points are the experimental data, and the solid line is that calculated with the indicated thermodynamic parameters. The calculated parameters are shown with experimental uncertainties (obtained as standard deviation on the resulting line in a spreadsheet simulation).

groups and one oxovanadium group in the *β*-cis isomer.[22] Hydrogen bonding between solvent and complex would be consistent with the large entropic term contributing to the stability of the V−EDDA complex.[23] To further probe the importance of hydrogen bonding we pursued two lines of inquiry, solution studies further exploring the nature of the stabilization by solvents and salts and solid state characterization of the *β*-cis isomer.

Thermodynamic Parameters for the Isomerization Reaction Between *β*-cis and α-cis V−EDDA Isomers. As described previously by Amos and Sawyer, higher temperatures favor the α-cis isomer.[9] Within the limited temperature range (283−328 K) available to us due to the limited stability of the V−EDDA complexes, we determined the changes in the [α-cis]/[*β*-cis] ratio in water, a water−DMSO (1.3 M) mixture, and 2.0 M NH_4Cl. The data are shown in Figure 3 in a ln K_{eq} plot as a function of $1/T$. The parameters in water agree with those previously reported by Amos and Sawyer[9] and allow comparison of thermodynamic parameters in three solvent systems.

Although the [α-cis]/[*β*-cis] ratio is higher in the water−DMSO mixture, the parameters for ΔS and ΔH are indistinguishable within experimental error. Since an increasing [α-cis]/[*β*-cis] ratio is observed with increasing concentration of DMSO and decreasing concentration of H_2O, the changes in the [α-cis]/[*β*-cis] ratio presumably reflect some destabilization of the *β*-cis isomer at the lower H_2O concentrations. This is consistent with hydrogen bonding to the *β*-cis isomer or a destabilizing solvation effect as the H_2O concentration decreases on the *β*-cis isomer.

The thermodynamic parameters obtained in a solution containing 2.0 M NH_4Cl were slightly different from those obtained in water and mixed water−DMSO solutions (see Figure 3). Of particular interest was the slightly lower ΔS term (6.4 cal/mol K compared to 7.8/7.9 cal/mol K). Perhaps this difference supports the interpretation that the addition of salt decreases the need for solvent organization around the *β*-cis isomer; it is possible that the salt is able to take the place of some of the H_2O molecules, thus stabilizing this isomer. However, if NH_4^+ simply takes the place of the H_2O molecule in a hydrogen bond, no or small differences in the entropy term would also have been anticipated. As shown in Table 3, salts other than NH_4Cl, less capable of hydrogen-bonding to the V−EDDA isomers, also significantly decreased the [α-cis]/[*β*-cis] ratio. These salt effects are consistent with the interpretation that solvent organization and not hydrogen bonding is the most important contributor to determination of the [α-cis]/[*β*-cis] ratio.

Table 4. Stability of α-cis and *β*-cis $[VO_2EDDA]^-$ Isomers in the Presence of Various Concentrations of DMSO in 3.0 M NH_4Cl Solution in H_2O at 18 °C[a,b]

additive	concentration of DMSO in H_2O/M	stability [α-cis/*β*-cis] ratio
NH_4Cl (3.0 M)	0.0(±0.1)	0.86(±0.07)
	1.4(±0.1)	0.95(±0.06)
	2.8(±0.1)	1.1(±0.1)
	4.2(±0.1)	1.5(±0.1)

[a] The errors in the [α-cis]/[*β*-cis] ratio are the average deviation from the mean value of three experiments (analyzed in triplicate). [b] The concentrations of [α-cis] and [*β*-cis] isomers are measured in 30 mM solutions prepared from solid $NH_4[VO_2(EDDA)]$ using ^{51}V NMR spectroscopy. The pH of the solutions were adjusted to 7.0 before DMSO was added to the solutions. See Experimental Section for further details.

Stability of α-cis and *β*-cis Isomers in Combined Salt and Mixed Solvent Systems. Adding a salt to a solution of the V−EDDA complex in a mixed solvent system should explore the effectiveness of possible hydrogen bonding and solvation in stabilizing the α-cis and *β*-cis isomers. If solvation is the dominant factor affecting the stability pattern, the salts should enhance the effects of solvent on the [α-cis]/[*β*-cis] ratio in the mixed solvent system compared to water. On the other hand, if the hydrogen bonding (both intra- and intermolecular) with the *β*-cis isomer is the dominating factor in determining the stability of the two isomers, the [α-cis/][*β*-cis] ratio should change less in the water−DMSO series as compared to the pure water series.

As shown in Table 4 a series of studies of the V−EDDA complex in the presence of 3.00 M NH_4Cl began at a [α-cis]/[*β*-cis] ratio of 0.86. The addition of DMSO to this solution (maintaining salt and V−EDDA complex concentrations constant) raised the [α-cis]/[*β*-cis] ratio. At 2.8 M DMSO the original decrease in the [α-cis]/[*β*-cis] ratio has been overcome, resulting in a [α-cis]/[*β*-cis] ratio of 1.1. Increased addition of DMSO continues to increase the [α-cis]/[*β*-cis] ratio at a rate significantly faster than that observed in aqueous solution. These results support the interpretation that the solvation of the α-cis and/or *β*-cis isomers is more important to the overall [α-cis]/[*β*-cis] ratio than hydrogen bonding.

Lability of the α-cis and *β*-cis Isomers of the V−EDDA Complex. The rates of the interconversion of the two isomers in aqueous solutions are complete within a few minutes. In no case was it possible to observe anything but the equilibrium mixture of the two isomers even though the starting point was 100% *β*-cis isomer. The second order rate constant for V−EDDA complex formation (pH range 2−3) was determined to be 10^8 M^{-1} s^{-1} and attributed to the reaction between VO_2^+ and HEDDA.[24] The reactions between $H_2VO_4^-$ and H_2EDDA or $H_2VO_4^-$ and H_3EDDA were reported to be significantly slower (no further information was provided).[24] Attempts to observe the conversion between the α-cis and *β*-cis isomers in the neutral pH range using variable temperature ^1H, ^{13}C, and ^{51}V NMR spectroscopy were carried out in this work. Close examination of the ^{51}V NMR spectra of V−EDDA isomers in Figure 1 in water, in a water−DMSO mixture, and in the presence of 4.0 M NH_4Cl show little, if any, differences in the respective line widths. Thus, no exchange between α-cis and *β*-cis isomers is occurring on the ^{51}V NMR time scale. This conclusion is also supported by variable temperature ^{51}V NMR spectra showing no changes in line width attributable to exchange processes (data not shown).

Evidence for some dynamic process in these solutions was found in the ^{13}C NMR spectrum (Figure 4). The spectra of

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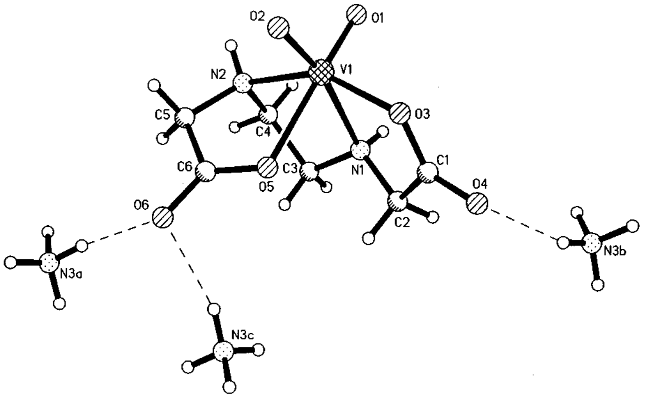

Figure 4. Structure and labeling scheme for **2**. Three different NH_4^+ ions (obtained through three different symmetry operations of the unit cell) and their interactions with **2** are shown: the three N···O distances (and the corresponding O···H distances) are 2.792 Å (1.900 Å), 2.874 Å (2.090 Å), and 2.845 Å (2.014 Å), respectively.

solutions containing 100 mM V−EDDA at pH 7.0 in the presence and absence of 1.3 M DMSO-d_6 and D_2O are shown in Figure 4. The line widths of the methylenes adjacent to the carboxylate in the β-cis isomer increase at elevated temperatures, both in D_2O and in D_2O−DMSO-d_6 mixtures, indicative of a dynamic process in this temperature range. The corresponding methylene group in the α-cis isomer shows different behavior; this signal is a doublet at 303 K which is coalesced at 323 K. The possibility that this process reflects formation of a square-pyramidal complex equilibrating with the α-cis isomer is less likely since the ^{51}V NMR spectra failed to show a distinct resonance for such a vanadium complex. Given the structural difference and the time scale of ^{51}V NMR spectroscopy, such a new complex should give an additional NMR resonance. Presumably the doublet indicates some structural differences in the α-cis isomer, perhaps two forms of α-cis isomer, one symmetric and the other asymmetric. ^{13}C NMR spectra recorded below 301 K support this possibility. ^{1}H NMR spectra also support the interpretation that such an intramolecular process exists in the α-cis isomer. Further information requires a more detailed analysis, including consideration of the slow redox reaction that occurs at elevated temperatures in these mixtures during extended spectral accumulations. We conclude that the behavior of both methylene groups adjacent to the carboxylate in the α-cis and β-cis isomers is indicative of new intramolecular dynamic processes. Furthermore, our results show that although the α-cis and β-cis complexes equilibrate within a few minutes, their rates of isomerization are slower than the rates of formation and/or hydrolysis of other complexes such as the V−EDTA complex,[10,25] the V−Tricine complex,[26] and other vanadium(V) complexes with aminocarboxylate ligands.[27,28]

In the past, hydrogen bonding has been deemed important for the formation of the solid state structure of several vanadium complexes[29−32] and less important in others.[15] The following studies were aimed at exploring whether a hydrogen-bonding contribution exists in the solid state.

Table 5. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **2**

	x	*y*	*z*	*U*(eq)[a]
N3	3482(3)	6672(3)	9134(2)	32(1)
V1	881(1)	3294(1)	6544(1)	20(1)
O1	1286(2)	2301(2)	5214(1)	31(1)
O2	1950(2)	5522(2)	6553(1)	29(1)
O3	2749(2)	2407(2)	7674(1)	29(1)
O4	3316(2)	594(2)	9125(1)	38(1)
O5	−503(2)	4066(2)	8216(1)	26(1)
O6	−2732(2)	5701(2)	8958(1)	37(1)
N1	−855(2)	555(2)	7007(1)	24(1)
N2	−2075(2)	3553(2)	5967(1)	23(1)
C1	2189(3)	1076(2)	8360(2)	26(1)
C2	−5(3)	127(3)	8175(2)	32(1)
C3	−3020(3)	582(2)	6900(2)	28(1)
C4	−3386(3)	1671(3)	5819(2)	29(1)
C5	−2824(3)	4932(2)	6805(2)	26(1)
C6	−1978(3)	4901(2)	8100(2)	24(1)

[a] *U*(eq) is defined as one-third the trace of the orthogonalized U_{ij} tensor.

Characterization of Solid State $NH_4[VO_2(EDDA)]$. Infrared Spectroscopy. The properties of the solid material were examined using IR spectroscopy. Two bands, one symmetric and one asymmetric,[33] at 905 and 857 cm^{-1} arise from the V=O bonds in the VO_2^+ group in $NH_4[VO_2(EDDA)]$. The frequencies for V=O bonds in other *cis*-dioxovanadium(V) complexes were measured for comparison; at 935 and 900 cm^{-1} for $K[VO_2(DMEDDA)]\cdot H_2O$,[9] at 923 and 866 cm^{-1} for $NH_4[VO_2(Oxal)_2]\cdot 2H_2O$, at 935 and 895 cm^{-1} for $K_3[VO_2(EDTA)]\cdot 4H_2O$, and at 928 and 892 cm^{-1} for $NH_4[VO_2(H_2EDTA)]\cdot 3H_2O$. The locations of the stretches for the V−DMEDDA complex are very similar to those of the stretches in the potassium V−EDTA complex, neither of which enjoys significant stabilization by intermolecular hydrogen bonding. However, the differences in the locations of absorbance bands are very small compared to the ammonium V−EDTA complex which does show an intermolecular hydrogen-bonding framework. Although such considerations are encouraging, larger differences were also observed in the absorbance bands of the ammonium V−Oxal complex. Furthermore, it has been shown that, although stretching frequencies are sensitive to formation of hydrogen bonds, variation in angles and other factors, such as counterions, will also affect the stretching frequency.[34] We conclude that not only the ligand but also the counterion affect the precise location of the absorbance band, and suffice it to say that the differences in the absorbance bands for the V−EDDA complex compared to the V−EDTA complex suggest that the structures are somewhat different or that the force constant in the V−EDDA complex is different than in the EDTA complex.[35]

Characterization of Solid State $NH_4[VO_2(EDDA)]$. X-ray Crystallography. Figure 4 shows the structure and the labeling scheme of the V−EDDA anion and the closely interacting NH_4^+ cation as characterized by X-ray crystallography. Tables 5 and 6 list the atomic coordinates and metric parameters, respectively. A figure of the anion drawn with 50% thermal ellipsoids is included in the Supporting Information. The anion was found to be the β-cis isomer of the V−EDDA complex (structure **2**).

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Table 6. Bond Lengths (Å) and Angles (deg) for **2**

Bond Angles			
V1−O1	1.6324(13)	C1−C2	1.525(3)
V1−O2	1.6549(13)	C2−H2A	0.96
V1−O3	1.9611(13)	C2−H2B	0.96
V1−N2	2.120(2)	C3−C4	1.521(3)
V1−O5	2.1815(12)	C3−H3A	0.96
V1−N1	2.245(2)	C3−H3B	0.96
O3−C1	1.297(2)	C4−H4A	0.96
O4−C1	1.225(2)	C4−H4B	0.96
O5−C6	1.265(2)	C5−C6	1.515(2)
O6−C6	1.244(2)	C5−H5A	0.96
N1−C2	1.465(2)	C5−H5B	0.96
N1−C3	1.472(2)	N1−H11	0.73(2)
N3−H31	0.90(3)	N2−C5	1.475(2)
N3−H32	0.87(3)	N2−C4	1.488(2)
N3−H33	0.83(3)	N2−H21	0.83(3)
N3−H34	0.93(4)		
Bond Angles			
O1−V1−O2	105.18(7)	N1−C2−C1	109.48(14)
O1−V1−O3	103.55(6)	N1−C2−H2A	110.74(10)
O2−V1−O3	100.88(6)	C1−C2−H2A	109.59(10)
O1−V1−N2	92.77(6)	N1−C2−H2B	109.23(10)
O2−V1−N2	98.20(6)	C1−C2−H2B	109.55(10)
O3−V1−N2	150.53(6)	H2A−C2−H2B	108.2
O1−V1−O5	163.15(6)	N1−C3−C4	106.80(14)
O2−V1−O5	88.27(6)	N1−C3−H3A	109.65(9)
O3−V1−O5	83.33(5)	C4−C3−H3A	110.01(10)
N2−V1−O5	74.99(5)	N1−C3−H3B	110.86(9)
O1−V1−N1	90.04(6)	C4−C3−H3B	110.83(9)
O2−V1−N1	164.69(6)	H3A−C3−H3B	108.7
O3−V1−N1	76.58(5)	N2−C4−C3	110.48(14)
N2−V1−N1	79.08(6)	N2−C4−H4A	109.21(9)
O5−V1−N1	76.46(5)	C3−C4−H4A	109.22(10)
C1−O3−V1	122.85(11)	N2−C4−H4B	109.76(9)
C6−O5−V1	116.54(11)	C3−C4−H4B	109.94(10)
C2−N1−C3	117.5(2)	H4A−C4−H4B	108.2
C2−N1−V1	108.32(11)	N2−C5−C6	110.58(14)
C3−N1−V1	110.09(11)	N2−C5−H5A	109.54(9)
C2−N1−H11	109(2)	C6−C5−H5A	109.57(9)
C3−N1−H11	108(2)	N2−C5−H5B	109.49(9)
V1−N1−H11	104(2)	C6−C5−H5B	109.55(9)
C5−N2−C4	113.45(14)	H5A−C5−H5B	108.1
C5−N2−V1	110.67(10)	O6−C6−O5	124.8(2)
C4−N2−V1	109.75(11)	O6−C6−C5	119.2(2)
H31−N3−H32	109(2)	C5−N2−H21	108(2)
H31−N3−H33	109(3)	C4−N2−H21	106(2)
H32−N3−H33	110(3)	V1−N2−H21	108(2)
H31−N3−H34	104(3)	O4−C1−O3	123.4(2)
H32−N3−H34	116(3)	O4−C1−C2	120.7(2)
H33−N3−H34	109(3)	O3−C1−C2	115.9(2)

The vanadium atom is found in a distorted octahedral geometry coordinated to the tetradentate EDDA ligand and to two oxo ligands. The VO_2 group is in the cis configuration, with an O1−V1−O2 angle of 105.18(7)° and with V1−O1 and V1−O2 distances of 1.6324(13) and 1.6549(13) Å, respectively. These V−O bonds are sufficiently short to imply substantial double bonding. Long bonds extend from the vanadium atom to a carboxylate ligand group (V1−O5 = 2.1815(12) Å) and an amine ligand group (V1−N1 = 2.245(2) Å) trans to the oxo ligands. The remaining carboxylate (V1−O3 = 1.9611(3) Å) and amine (V1−N2 = 2.120(2) Å) ligand moieties in the EDDA ligand are also coordinated to the vanadium atom.

The V═O bond lengths for **2** are very similar to those previously reported for related complexes with oxygen and nitrogen ligands trans to oxo groups, including $Na_3[VO_2EDTA]\cdot 4H_2O$ (1.639(2)/1.657(1) Å),[7] $NH_4[VO_2H_2EDTA]\cdot 3H_2O$ (1.623(2)/1.657(2) Å),[15] and $(NH_4)_3[VO_2(Oxal)_2]\cdot 2H_2O$ (1.635(2)/1.648(2) Å).[8] The bond lengths of the vanadium to the other functionalities are also very similar to those reported previously in the α-cis isomer of the EDTA complex, in the oxalate complex, and in other related complexes.[7,8,15,31,36,37] Perhaps the most interesting feature here is the long V1−O5 bond, which is among the longest bond lengths observed for a vanadium atom bound to a carboxylate ligand.[31]

The structure of the EDDA ligand is basically the same as reported previously in both α-cis and *β*-cis complexes of EDDA with other metal ions.[38−40]

The interaction between **2** and the NH_4^+ ion was examined in detail by locating the hydrogen atoms (see Figure 4). Additional parameters associated with, and derived from, the structure determination, including hydrogen atom coordinates and thermal displacement parameters, are reported in the Supporting Information. Figure 4 shows the NH_4^+ ion in its symmetry related positions. Three major types of hydrogen-bonding interactions with the carboxylate groups in the V−EDDA complex are identified. Careful inspection of the crystal lattice also reveals very weak hydrogen-bonding interactions between the N1−H11 and O2 of a second molecule of **2** and between N1−H21 and the O1 of a second molecule of **2**. Intermolecular hydrogen-bonding interactions have previously been invoked to explain elongated V═O bond lengths outside the range from 1.56 to 1.61 Å in which most VO and *cis*-VO_2 bond lengths fall.[29−31] However, the reported structural changes in the V═O bond lengths in all cases are small. Since the V═O bonds in **2** are very similar to the related EDTA complexes that do not have the possibility for stabilization by intramolecular hydrogen bonding, we conclude that intramolecular hydrogen bonding is negligible and that, although an intermolecular hydrogen-bonding pattern can be identified, the strength of the intermolecular hydrogen bond between the V═O and the non-ammonium ion N−H is very weak even in the solid state.

Comparison of Structural Features for the α-cis and *β*-cis V−EDDA Isomers. The structural data for the symmetric α-cis isomer of the EDDA complex are likely to be very similar to those of the EDTA complex, thus making a detailed comparison between various structural parameters for the α-cis and *β*-cis isomers possible. Studies with Co(III) complexes of EDDA and related ligands have shown that the conformation in each of the three five-membered rings formed upon complexation is important to the overall stability as well as the crystal lattice that forms.[14,39,41,42] Specifically Weakliem and Hoard labeled the three different types of rings as the R, E, and G rings in which the ideal conformation had angle sums of 538.4°, 538.4°, and 527.9°.[41] The nomenclature is shown in Figure 5 as well as the angle sums for both the α-cis and *β*-cis geometries.

On the basis of this type of analysis, the *β*-cis isomer resembles the ideal geometry more than the α-cis isomer for all three ring systems. In the event that the α-cis isomer has the larger and/or more organized solvation sphere, its solvation must be such that DMSO or methanol can easily be substituted for water.

Why is only one isomer observed for the EDTA complexes? Although steric hindrance is a possibility, and substitution of the nitrogen with an acetate or a methyl group will increase steric bulk, the distances to the nearest oxygen in the VO_2 unit are significantly larger (2.7 Å) than the van der Waals radii and thus not likely to destabilize the complex significantly.

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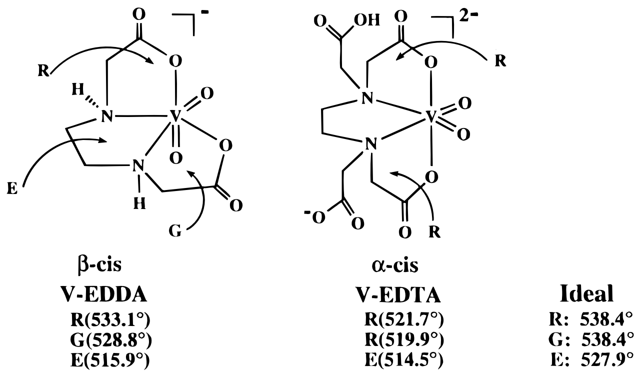

Figure 5. A schematic drawing showing the three different types of chelating rings (R, G, and E) with the vanadium and their respective angle sums for α-cis and *β*-cis isomers.

Studies of EDTA complexes have documented the importance of the contribution from the Δ*S* term. Thus, the differences in solvation of various complexes are essential to the stabilization of these complexes.[43] The studies presented here clearly show that similar effects can also determine the isomer ratio and that mixed solvent systems and salts can assist in characterizing the important parameters in these systems.

Implications to Biological Studies with Vanadium(V) Compounds. The structure, stability, and lability of vanadium(V) compounds are all important to the mechanism(s) by which these compounds act in biological systems and in part have contributed to the elusive mechanism(s) by which vanadate mimics insulin action.[25] In view of the current proposals regarding vanadium compounds, mimicking the phosphate ester/phosphate anhydride hydrolytic transition state/high-energy intermediate, it is important to understand the extent to which the environment may modify the structure of a particular vanadium compound. The recently discovered lability of many well-known vanadium(V) compounds[44,45] further complicates these matters when attempting to elucidate which species is responsible for the majority of the biological response. The work described here illustrates that, in addition to oxidation state, ligands, pH, and temperature, *subtle changes in solvation can contribute to the structure* of a vanadium complex such as the V−EDDA complex. These findings provide additional evidence explaining why some vanadium compounds can act in a multifaceted manner with various enzymes. Since very few studies have been successful in identifying the exact form of the vanadium that is exerting a particular biological response (see, for example, ref 46) little is known concerning the specific structural properties of active vanadium complexes. Such biological studies can benefit from the identification of vanadium complexes that remain intact under the *in vitro* or *in vivo* conditions of biological studies, and some progress has recently been made in this area.[47,48] Furthermore, significant information has been gained on X-ray crystallographic data of phosphoryl group protein transfer vanadium complexes and examples are now accumulating where the vanadium is coordinated as a tetrahedral anion,[49,50] as a trigonal bipyramidal anion,[51] and as a distorted five-coordinate anion.[52] The need for fundamental information on the solution structure and lability of vanadium complexes, such as those described in this work, is increasing if the modes of action of vanadium compounds are to be elucidated.

Conclusion

The V−EDDA complex forms two isomeric complexes containing octahedral vanadium and a tetradentate EDDA ligand in solution. The complexes differ in the manner in which the carboxylate is coordinated: the symmetric α-cis isomer has the two carboxylates coordinated trans to each other, and the *β*-cis isomer has the carboxylates coordinated trans to an oxo and an amine functionality. In this work solution studies of the α-cis/*β*-cis equilibrium mixture of the V−EDDA complex have revealed that *organic solvents increase* the [α-cis]/[*β*-cis] ratio, whereas *salts decrease* this ratio. Studies were conducted to examine the extent of the effects and probe the role of complex solvation and hydrogen bonding, both of which were consistent with the observations made in solution on this system. The spectroscopic properties support the interpretation that differential solvation of the two isomers is the major contributor to the exact location of the [α-cis]/[*β*-cis] ratio. This conclusion was further explored by structural characterization of the solid state asymmetric *β*-cis isomer of the V−EDDA complex. Structural comparison of the two isomers allows examination of the importance of hydrogen bonding in the solid state and the inherent ideality of the geometry of this isomer. We conclude that although hydrogen-bonding patterns were apparent in the solid state, none of these seemed appropriate to explain the observations made in solution.

The studies presented here illustrate the *structural* effects of environmental factors on selected and particularly responsive vanadium(V) complexes. Although these types of effects can be approximated in *in vitro* studies, the effects in *in vivo* studies are much more difficult to predict, since the environmental factors are dependent on the specific compartmentalization of the vanadium compound in the biological system. However, as increased information on the active vanadium species is obtained in biological systems, knowledge of the effects of environmental factors may assist in the identification of the site of action of these compounds. In addition, it is possible that environmental factors can extend the lifetime or facilitate the conversion of a particular isomer to an isomer with greater potency.

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Supporting Information Available: A drawing of the *β*-cis V−EDDA monoanion with 50% thermal ellipsoids and tables listing hydrogen coordinates and isotropic displacement parameters for **2** and anisotropic displacement parameters for **2** (3 pages). Ordering information is given on any current masthead page.

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