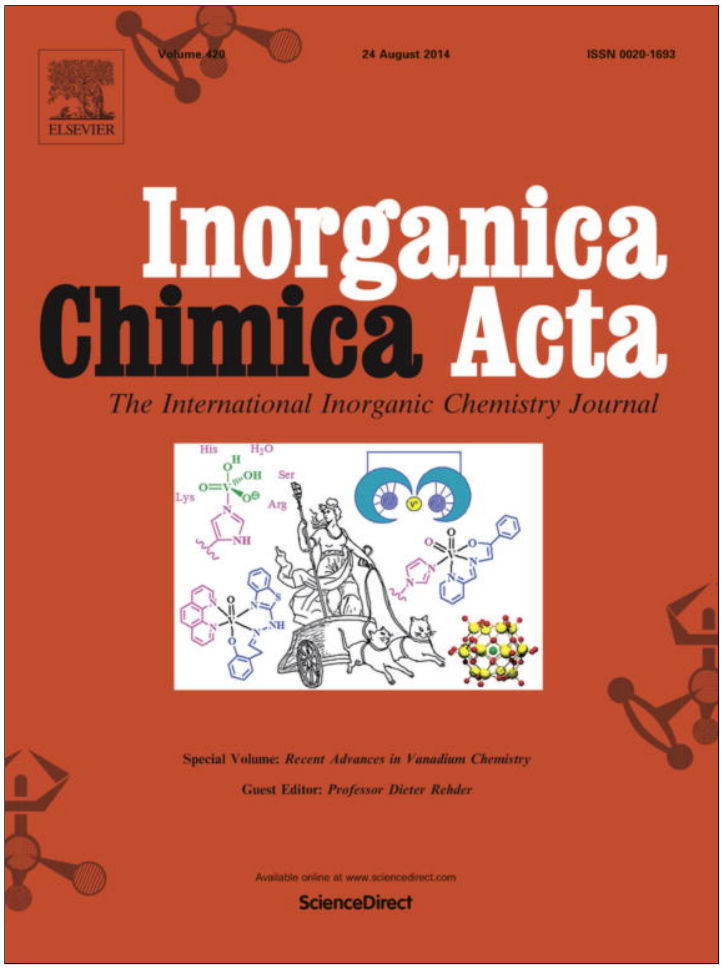

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Spectroscopic Characterization of *L*-ascorbic Acid-induced Reduction of Vanadium(V) Dipicolinates: Formation of Vanadium(III) and Vanadium(IV) Complexes from Vanadium(V) Dipicolinate Derivatives

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ABSTRACT

A Br-substituted dioxidovanadate dipicolinate complex was prepared and structurally characterized by X-ray crystallography. The counter ion in the solid state is the ammonium cation in a monoclinic crystal cell with, *P*2(1)/*c*. The X-ray structure is similar to the structure generated from the analogous nitro substituted dipicolinate ligand. When exploring reactions of this and other dipicolinate-containing compounds with *L*-ascorbic acid, both vanadium(IV) and vanadium(III) species were formed under acidic conditions; then identified by conventional (X-band) and high-frequency and -field electron paramagnetic resonance (EPR) spectroscopy. A reaction with half an equivalent of *L*-ascorbic acid led to the formation of vanadium(IV) species, and addition of substituents (X = H, Cl, Br, OH, and NH_2) in the para position of dipicolinic acid did not have a major effect on the vanadium(IV) species formed. In a reaction with excess *L*-ascorbic acid and vanadium(V)dipic-X complexes (where X = H, Cl, Br, OH, and NH_2), vanadium(III) species were observed, thus proving that vanadium(III) species can be formed under acidic conditions resembling those in biological systems.

1. Introduction

Vanadium-containing compounds have been reported with insulin-like activities and anti-cancer properties through structure-activity relationships [1–26]. The mode of action remains less defined [3,9,11,21,23,24,27], although many researchers believe that inhibition of protein tyrosine phosphatases and cellular redox metabolism are important aspects of how these compounds exert their action. Many insulin-like compounds contain V(IV) and V(V) metal centres, where the +4 and +5 oxidation states are found in known biological systems as reported in the literature [28]. This is consistent with redox cycling that is either biological or chemical. Recently Melchior et al. [29] reported the first insulin-like effects of a tris(maltolato)vanadium(III) compound and a few years later Buglyó et al. [30] reported the insulin-like activity of vanadium(III) dipicolinate. However, redox cycling in nature involving V(III) has been reported only in sea squirts (also referred to as tunicates (*Ascidia ceratodes*)) [31,32]. Although the speciation and location of the V(III) have been controversial, the existence of V(III) in living organisms is now accepted [31–34].

The toxicity of vanadium salts and complexes in mammals is well known [35–37]. Although vanadium treatment reduced the level of hyperglycemia in diabetic rats, serious signs of its toxicity were also described [36,37] which limit the use of vanadium salts and coordination complexes as therapeutic agents in the treatment of diabetes. For example, the vanadium complex bis(ethylmaltolato)oxovanadium(IV) (BEOV) failed to complete Phase II clinical trials [21,38]. Treatment of rats with vanadium-containing species markedly reduced glutathione and *L*-ascorbic acid concentrations in blood and certain tissues [23,39,40]. Redox cycling is inferred because regardless of whether V(IV) or V(V) compounds are administered as insulin-like agents, where +4 and +5 oxidation states are observed in the same fashion as for vanadium(IV) and vanadium(V) protein complexes which are found in serum as reported by Chasteen et al. [28]. Here, EPR data revealed the presence of *L*-ascorbic acid in fresh serum that quantitatively convert vanadate(V) to vanadyl(IV), resulting in formation of specific VO^{2+}-

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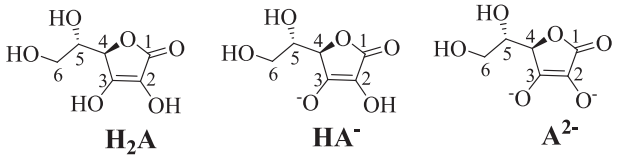
albumin and $(VO^{2+})_2$-transferrin complexes [28]. In contrast, different effects are observed when V(III), V(IV) or V(V)-dipic compounds are administered as insulin-like agents to streptozotocin-induced diabetic rats, suggesting that there are some differences in the metabolism of each complex [30]. In the study as reported by Buglyó et al. [30], it was implied that redox processes must be important factors for the biological action of the vanadium-containing compounds, where it was observed that the V(V)-dipic complex was the most effective insulin-like agent, in contrast to previous studies in which the V(IV)-maltol complex was the most effective. It was concluded that the effectiveness of coordination complexes of vanadium is both ligand and oxidation state dependent.

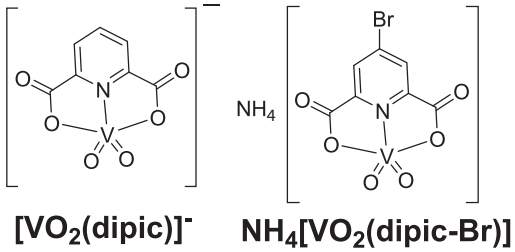
V(III) ions in aqueous solution have been reported to undergo a series of speciation reactions [41,42]. Since V(III) readily oxidizes in the presence of oxygen in neutral pH, this oxidation state is often stabilized by complexation with coordinating ligands. Originally, V(III) ions in tunicates were believed to be coordinated to dopamine derivatives [43,44], but since then it has been shown that dopamine and V(III) were not located in the same cells. Currently, it is believed that the V(III) in the blood cells of tunicates are in an acidic environment, where this environment helps stabilize the +3 oxidation state so that it can be observed naturally in these organisms [45]. Due to the ease of oxidation V(III) compounds, such compounds have not been studied as extensively as V(IV) and V(V) compounds. Chatterjee et al. [46] reported the synthesis, structure determination and reactivity of a highly air stable V(III) complex of dipicolinic acid. It must also be stressed that it was reported that a V(III)-dipic complex [30] was found to have anti-diabetic properties. Formation of V(III) species were also reported in the presence of NADH by researchers [47–49], an observation which was called in question because of the redox potentials of these compounds [50,51]. Evidence for formation of V(III) under biological conditions is thus important in understanding the role of vanadium-containing compounds as anti-diabetic agents [30] and in tunicates [52–54].

L-ascorbic acid (vitamin C, H_2A) is a biological reductant. Its properties are pH-dependent in aqueous solutions and as pH increases its reducing power increases [55,56]. The ascorbate dianion, A^{2-}, is more readily oxidized than the monoanion, HA^-, which in turn is more reactive than *L*-ascorbic acid.



Several years ago, Wilkins et al. [57] reported the reduction of V(V) by *L*-ascorbic acid at low and neutral pH values, where *L*-ascorbic acid was found to form three different coordination complexes of V(IV) arising from inner- and outer-sphere electron-transfer pathways: two complexes containing V(IV)-ascorbate, and one containing a V(IV)-dehydroascorbic acid complex. Ferrer and Baran [58] were able to isolate one complex having the composition $K_{1.5}Na_{0.5}[VO(HA)(OH)_3]$ and containing *L*-ascorbic acid as a monodentate ligand. They also isolated two complexes, K[VO(diketo)(OH)]·H_2O and $Na_3[VO(diketo)_2(OH)]$, where the enolized form of an oxidation product, 2,3-diketogulonic acid acted as a bidentate ligand [58]. In another section of the literature, it was suggested that the reaction between *L*-ascorbic acid and V(V) could be involved in biotransformations of vanadium-containing compounds that behave as insulin-like agents [59].

The mode of action of vanadium-containing compounds is closely linked to the reactions that they can undergo in cellular media and thus it is important to learn about the mode of action of these compounds. The formation of $[VO_2(dipic)]^-$ and $[VO_2(dipic\text{-}OH)]^-$ was investigated both by kinetic studies and EXSY spectroscopy showing rapid transformation both in direction of formation and hydrolysis [3,60–66]. Since the reaction of vanadate with *L*-ascorbic acid/ascorbate was found to involve both inner-sphere and outer-sphere processes, spectroscopic characterization of the species that are formed are desirable [57,59]. Detailed information characterizing the solution species that forms in redox reactions with *L*-ascorbic acid is important to understand how vanadium complexes work in biological systems. In this work we spectroscopically characterized the species that form in the reaction of the $[VO_2(dipic)]^-$ anion and its derivatives with *L*-ascorbic acid, while including the report of a new vanadium(V) complex, $NH_4[VO_2(dipic\text{-}Br)]$.



2. Experimental

2.1. Materials

All reagents were of analytical grade from Sigma–Aldrich Chemical Company.

2.2. Synthesis of the complexes

$[V(dipic)(H_2O)_2F]\cdot 1.5H_2O$ and $[V(dipic)(Hdipic)(H_2O)]\cdot 3H_2O$ were synthesized as reported previously [67]. $NH_4[VO_2(dipic\text{-}Cl)]\cdot H_2O$, $Na[VO_2(dipic\text{-}NH_2)]\cdot H_2O$, $NH_4[VO_2(dipic\text{-}OH)]\cdot H_2O$, and $NH_4[VO_2(dipic)]$ were synthesized as reported in the literature [61–63]. $NH_4[VO_2(dipic\text{-}Br)]$ was synthesized using a procedure analogous to that of potassium (4-carboxypyridine-2,6-dicarboxylato) dioxidovanadium (V) monohydrate, which was reported by Holder and VanDerveer [68], but using 4-bromopyridine-2,6-dicarboxylic acid ($H_2dipic\text{-}Br$) [69] instead of 4-carboxypyridine-2,6-dicarboxylic acid and NH_4VO_3. The synthesis was as follows: deionized water (20 ml) was added to solid NH_4VO_3 (1.74 g, 14.9 mmol) and $H_2dipic\text{-}Br$ (3.67 g, 14.9 mmol). The mixture was stirred while heated at 80–90 °C until the supernatant became yellow in color. While hot, the pH of the solution was lowered to 1.1 with 2.0 M HCl at which point the reaction mixture was heated for 15 min with stirring. The reaction mixture was filtered while hot; then the filtrate was cooled to room temperature whereupon a yellow-white solid was precipitated. The solid was filtered under vacuum and air-dried. Yield = 2.54 g (49%). Single crystals of $NH_4[VO_2(dipic\text{-}Br)]$ were obtained after recrystallization of the crude product from hot water.

2.3. Solid state characterization of $NH_4[VO_2(dipic\text{-}Br)]$ by X-ray crystallography

Intensity data were collected using a Rigaku Mercury CCD detector and an AFC8S diffractometer. Data reduction including the application of Lp and absorption [70] corrections used the CRYSTALCLEAR [71] program. The structure was solved by direct methods and subsequent Fourier difference techniques, and refined anisotropically,

Table 1
Crystal data and structure refinement for $NH_4[VO_2(dipic\text{-}Br)]$.

Identification code	vo2dipicbr
Empirical formula	$C_7H_6BrN_2O_6V$
Formula weight	344.99
T (K)	153(2)
λ (Å)	0.71073
Crystal system	monoclinic
Space group	$P2(1)/c$
Unit cell dimensions	
a (Å)	5.6346(17)
b (Å)	18.654(6)
c (Å)	10.532(3)
α (°)	90
β (°)	101.516(12)
γ (°)	90
V (Å^3)	1084.7(6)
Z	4
Calculated density (Mg m^{-3})	2.113
Absorption coefficient (mm^{-1})	4.617
$F(000)$	672
Crystal size (mm)	0.26 × 0.24 × 0.22
θ (°)	3.83–26.05
Limiting indices	$-6 <= h <= 5$, $-23 <= k <= 22$, $-12 <= l <= 12$
Reflections collected/unique (R_{int})	7714/2111 (0.0271)
Completeness to θ = 26.05 (%)	99.2
Absorption correction	REQAB (multi-scan)
Maximum and minimum transmission	0.4299 and 0.3799
Refinement method	full-matrix least-squares on F^2
Data/restraints/parameters	2111/0/158
Goodness-of-fit (GOF) on F^2	1.008
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0313, wR_2 = 0.0735
R indices (all data)	R_1 = 0.0398, wR_2 = 0.0777
Largest difference in peak and hole (e Å^{-3})	1.341 and −1.022

by full-matrix least squares, on F^2 using SHELXTL 6.10 [72]. Hydrogen atom positions in the ligand were calculated from ideal geometry with coordinates riding on the parent atom. Ammonium hydrogen coordinates were determined from a difference Fourier and fixed at those values. A summary of the data collection and refinement for the complex is presented in Table 1.

2.4. Ambient temperature solution X-band EPR spectroscopy

X-band EPR spectra were recorded on a Bruker BioSpin EMX^{micro} spectrometer. The spectra were recorded using the following parameters: modulation frequency = 100 kHz, modulation amplitude = 5.0 G, center field = 3238 G, sweep width = 2000 G, resolution = 2048 points, conversion time = 82.0 ms, time constant = 40.96 ms, sweep time = 168 s, microwave frequency = 9.85 GHz, microwave power = 19.2 mW, and number of scans = 1.

2.5. Solid state and frozen solution characterization by high-frequency and -field EPR (HFEPR) spectroscopy

HFEPR spectra were recorded at the National High Magnetic Field Laboratory (NHMFL, Tallahassee, FL, USA). The spectrometer employs a Virginia Diodes (Charlottesville, VA, USA) source operating at a base frequency of 12–14 GHz and multiplied by a cascade of multipliers in conjunction with a 15/17 T superconducting magnet [73]. Detection was provided with an InSb hot-electron bolometer (QMC Ltd., Cardiff, UK). The magnetic field was modulated at 50 kHz. A Stanford Research Systems SR830 lock-in amplifier converted the modulated signal to DC voltage. Low temperature was provided by an Oxford Instruments (Oxford, UK) continuous flow cryostat with temperature controller. $[V(dipic)(H_2O)_2F]\cdot 1.5H_2O$ and $[V(dipic)(Hdipic)(H_2O)]\cdot 3H_2O$ were used in the solid state while the vanadium(III)-containing solutions were prepared *in situ* with stoichiometric amounts of *L*-ascorbic acid and the respective V(V) parent complexes.

3. Results

3.1. Synthesis and structural characterization of $NH_4[VO_2(dipic\text{-}Br)]$

The synthesis of $NH_4[VO_2(dipic\text{-}Br)]$ was carried out using a procedure similar to those previously reported [65,68,74]. Crystals of $NH_4[VO_2(dipic\text{-}Br)]$ were grown by recrystallization from water. The structure of $NH_4[VO_2(dipic\text{-}Br)]$ was determined by X-ray crystallography and is shown in Fig. 1, together with the atomic numbering scheme. A summary of the data collection and refinement for the complex is presented in Table 1. In Table 2 the selected bond lengths and angles are presented in comparison with other complexes reported previously. Supplemental crystallographic data for $NH_4[VO_2(dipic\text{-}Br)]$ are also given. The coordination geometry of all but $K[VO_2dipic\text{-}NO_2]$ are approaching the trigonal bipyramidal geometry; however the geometries are distorted and as such merging the square pyramidal and trigonal pyramidal geometries. In this complex the two largest angles around the V atom are ∠O1–V–O2, 147.46(9)° and ∠O6–V–N1, 134.15(11)°. Since the O5 atom is not involved in either of these two angles and these two angles are used to define τ [75], O5 becomes the apical ligand by which we calculate the $\tau = (147.46–134.15)/60 = 0.222$ [75]. Since the τ value is closer to 0 than to 1, the coordination geometry for this complex is approaching square-pyramidal rather than trigonal pyramidal. This is interesting, because only one complex previously showed such asymmetry and twisting of the VO_2 unit in the direction of opening up the coordination environment for an additional ligand ($K[VO_2(dipic\text{-}NO_2)]$) [66].

Comparison of the structural parameters (Table 2) shows that these complexes are very similar in nature, but subtle differences are shown therein. Interestingly, the structure that it is closest to the $NH_4[VO_2(dipic\text{-}Br)]$ complex is the $[VO_2(dipic\text{-}OH)]^-$ anion which is crystallized with the $[Me_4N]^+$ cation [74]. The V=O and V–O bond lengths are very similar. However, an interesting difference is observed for the V–N bond length which is found to be longer than any of the previously reported complexes except for the $K[VO_2(dipic\text{-}NO_2)]$ complex [66]. The effect of the Br-substitution is thus to reduce the bonding between the V and

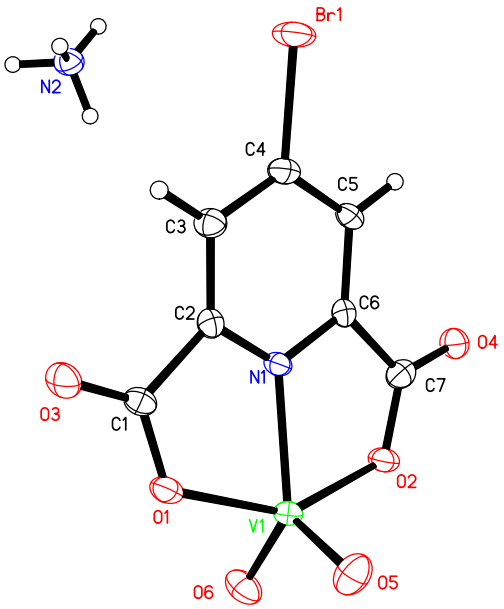


Fig. 1. Structure of $NH_4[VO_2(dipic\text{-}Br)]$ showing labeling scheme with thermal ellipsoids.

Table 2
Comparative bond lengths and angles for $NH_4[VO_2(dipic\text{-}Br)]$ and other known dipicolinatooxovanadium(V) complexes.

	$Cs[VO_2(dipic)]\cdot H_2O$	$Na[VO_2(dipic\text{-}OH)]\cdot 2H_2O$	$K[VO_2(dipic\text{-}OH)]\cdot H_2O$	$[Me_4N][VO_2(dipic\text{-}OH)]\cdot H_2O$	$NH_4[VO_2(dipic\text{-}Br)]$	$Na[VO_2(dipic\text{-}NH_2)]\cdot 2H_2O$	$K[VO_2(dipic\text{-}NO_2)]$
$V–N_{py}$	2.089(6)	2.0770(19)	2.089(6)	2.077(4)	2.099(3)	2.050(3)	2.1019(17)
V=O	1.610(6), 1.615(6)	1.6264(17), 1.6290(17)	1.606(5), 1.616(5)	1.615(3), 1.626(3)	1.611(2), 1.620(2)	1.620(3), 1.627(3)	1.6253(15), 1.6293(14)
$V–O_{carb}$	2.001(5), 1.982(5)	1.9945(16), 2.0011(16)	2.033(5), 1.990(5)	1.998(4), 2.022(3)	1.992(2) 2.000(2)	1.990(3), 1.991(3)	1.9910(14), 1.9953(15)
C–Br					1.880(3)		
$O_{carb}–V–O_{carb}$	149.4(2)	149.42(7)	148.0(2)	148.88(14)	147.46(9)	149.99(12)	148.81(6)
$O_{oxo}–V–N_{py}$	122.0(3), 128.2(3)	124.48(8), 125.71(8)	123.1(3), 127.4(3)	123.37(17), 125.92(18)	117.33(12) 134.15(11)	124.92(13), 126.05(13)	118.59(7), 131.85(7)
$O_{carb}–V–N_{py}$	74.6(2), 75.9(2)	74.96(7), 74.47(7)	73.3(2), 74.7(2)	74.41(14), 74.48(14)	74.08(10) 74.30(9)	75.15(11), 74.85(11)	74.75(6), 74.62(6)
Refs.	[88]	[74]	[61]	[74]	This work	[77]	[77]

the N atom. Based on this structural analysis, one would anticipate that the properties of this complex would resemble that of the $K[VO_2(dipic\text{-}NO_2)]$ complex more than the other complexes previously reported.

Fig. 2 shows the packing diagram showing the H-bonding network. Two $[VO_2(dipic\text{-}Br)]^-$ anions are coordinated through the V=O groups to an NH_4^+ cation in a diamond core arrangement. The NH_4^+ cation extends this network by associating with a second $[VO_2(dipic\text{-}Br)]^-$ anion through the O-atoms associated with the carboxylic acid group. This H-bonding network emphasizes the fact that the $[VO_2(dipic\text{-}Br)]^-$ anion is unsymmetrical because only one of the V=O bonds are involved in H-bonding. Although at first glance the bond lengths of both V=O bonds appear similar, a difference in V=O bond length of 0.0089 Å is large and is undoubtedly contributing to some of the asymmetry observed for this anion.

3.2. Spectroscopic identification of vanadium(V)-containing complexes upon reduction by L-ascorbic acid

3.2.1. Addition of low concentration of L-ascorbic acid: formation of V(IV) species

The nature of the species formed between the reaction of vanadium(V)-containing complexes with *L*-ascorbic acid was investigated using EPR spectroscopy. The product of the green solution which was formed from the reaction of 100 mM vanadium(V)-containing species and a half equivalent of *L*-ascorbic acid (50 mM) was subjected to analysis by ambient temperature X-band EPR spectroscopy, Fig. 3. The solutions were prepared by dissolution of solid complexes ($NH_4[VO_2(dipic)]$, $NH_4[VO_2(dipic\text{-}OH)]\cdot H_2O$, $NH_4[VO_2(dipic\text{-}Cl)]\cdot H_2O$, $NH_4[VO_2(dipic\text{-}Br)]$, and $Na[VO_2(dipic\text{-}NH_2)]\cdot H_2O$) in an aqueous solution of *L*-ascorbic acid, whereby and the reaction was completed in seconds under acidic conditions. The spectra shown in Fig. 3 demonstrate that the VO_2dipic-derivatives were all reduced to form vanadium(IV)-containing species under acidic conditions. Two different forms of vanadium(IV)-containing species can be identified by X-band EPR spectra as reported previously for the V(IV)-dipic^{2-} and V(IV)-dipic-OH^{2-} species [64] even though three species are expected to exist in these solutions: the 1:1 dipic-X/V(IV), 1:2 dipic-X/V(IV), and dipic-X "free" VO^{2+} species, where X = H and OH. The respective spectra of the vanadium(IV)-containing species in aqueous media at room temperature gives signals for the 1:1 species and VO^{2+} species, suggesting that these species overlap for the entire series of V(V)-dipic complexes in aqueous solutions containing *L*-ascorbic acid.

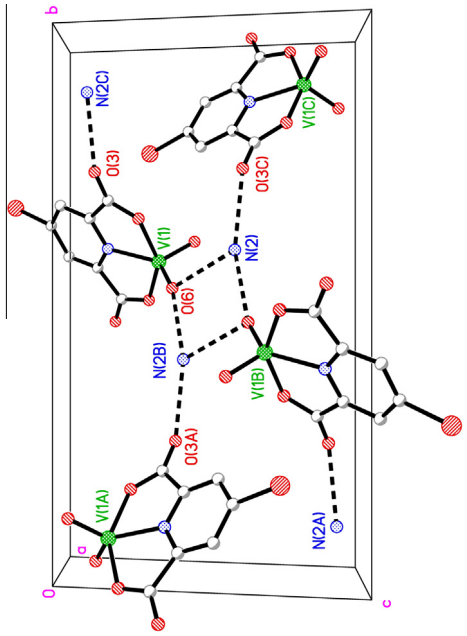


Fig. 2. Packing diagram of $NH_4[VO_2(dipic\text{-}Br)]$ viewed down the *a* axis showing hydrogen bonds to the ammonium cations.

3.2.2. Addition of high concentration of L-ascorbic acid: V(III) species

The formation of V(III) species from reacting $NH_4[VO_2(dipic)]$ with excess *L*-ascorbic acid was investigated by HFEPR spectroscopy. The HFEPR spectra of vanadium(III)-containing species prepared *in situ* were compared to HFEPR spectra of two V(III) complexes in the solid state: $[V(dipic)(Hdipic)(H_2O)]\cdot 3H_2O$ and $[V(dipic)(H_2O)_2F]\cdot 1.5H_2O$.

We begin by describing the spectra obtained with the solid $[V(dipic)(Hdipic)(H_2O)]\cdot 3H_2O$ [67]. This complex has been structurally characterized and is known to contain six-coordinate vanadium with two dipic ligands completing the coordination sphere. It generated high-quality HFEPR spectra that were very close to ideal spin-triplet powder patterns (Fig. 4). The spectra indicated a zero-field resonance near 168 GHz (not shown), corresponding to the *D*-value of about 5.6 cm^{-1}. Simulations of the individual spectra allowed one to refine that value, and obtain the full set of spin Hamiltonian parameters: $D = +5.42\ cm^{-1}$, $|E| = 0.150\ cm^{-1}$; $g_{x,y} = 1.96$, $g_z = 2.00$; spin Hamiltonian parameters for this and related V(III) complexes are summarized in Table 3. Anticipating the discussion, these parameters are consistent with a distorted six-coordinate vanadium(III) complex and thus in agreement with the structural information available on this compound.

Since the $[VO_2(dipic\text{-}X)]^-$ (where H, OH, Cl, Br, and NH_2) samples under investigation contained only one dipicolinate or its analogues ligand, we investigated by HFEPR a model compound containing similarly one ligand, $[V(dipic)(H_2O)_2F]\cdot 1.5H_2O$. The $[V(dipic)(H_2O)_2F]\cdot 1.5H_2O$ prepared as described previously re-

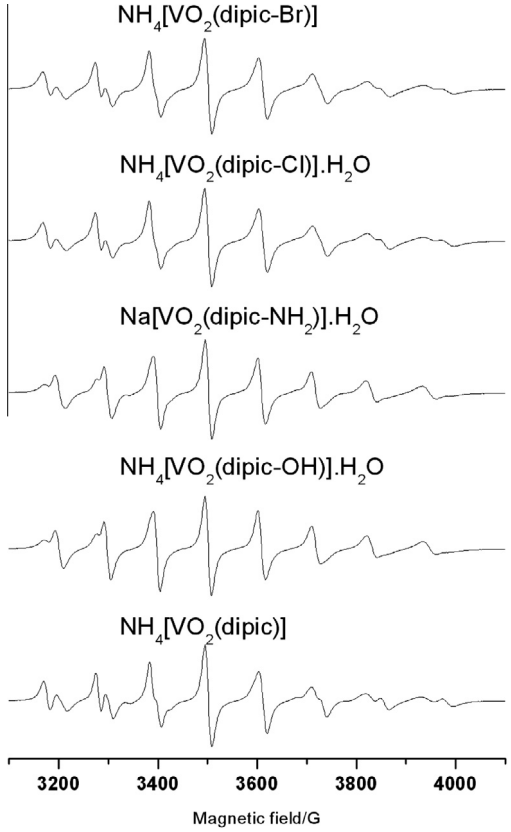


Fig. 3. X-band EPR spectra of 100 mM V(V) complexes reduced by *L*-ascorbic acid to form V(IV) species in aqueous solution. [complex]/[*L*-ascorbic acid] = 2:1. The spectra were recorded using the following parameters: center field = 3238 G, sweep width = 2000 G, conversion time = 82.0 ms, time constant = 40.96 ms, sweep time = 168 s, microwave frequency = 9.85 GHz, microwave power = 19.2 mW, and number of scans = 1.

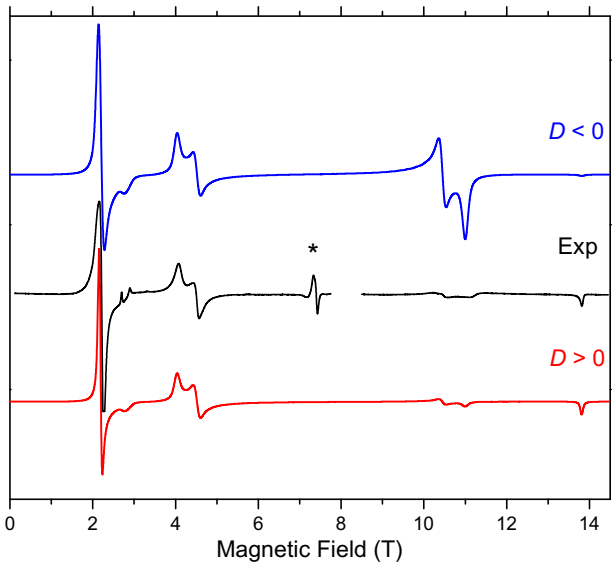


Fig. 4. HFEPR spectrum of polycrystalline [V(dipic)(Hdipic)(H_2O)]·3H_2O recorded at 10 K and 224 GHz (black or middle trace) accompanied by its simulations (color traces) using the following spin Hamiltonian parameters: $S = 1$, $|D| = 5.42\ cm^{-1}$, $|E| = 0.150\ cm^{-1}$, $g_{x,y} = 1.96$; $g_z = 2.00$. Blue or upper trace: negative zfs; red or lower trace: positive zfs. The latter reproduces the experimental intensities of some turning points better. The $g \sim 1.95$ spectral region containing V(IV) resonances was omitted in the spectrum shown. The origin of the signal marked with asterisk is unknown.

sulted in spectra of imperfect powder EPR patterns. The data could nevertheless be analyzed using a spin triplet ($S = 1$) Hamiltonian (Fig. 5). A near-zero field transition was found again at 168 GHz (not shown; but similar to that for [V(dipic)(Hdipic)(H_2O)]·3H_2O), which allowed one to estimate the zfs parameter $|D|$ as 5.6 cm^{-1}. Simulations of the individual spectra allowed one to refine that value, and obtain the full set of spin Hamiltonian parameters: $|D| = 5.56\ cm^{-1}$, $|E| = 0.056\ cm^{-1}$; $g_{x,y} = 1.92$, $g_z = 2.00$. Note that no parallel ($B_0 \parallel z$) turning points were observed in the spectra, thus the $g_z = 2.00$ value is approximate only, and set to accommodate the spectral position of the "half-field" ($\Delta M_S = \pm 2$) resonance. Although the simulations seem to suggest a negative sign of D, the spectra are so far from being perfect powder patterns that the sign remains undetermined. The [V(dipic)(H_2O)$_2$F]·1.5H_2O sample also contained a fair amount of a V(IV) species, most probably in a form of a vanadyl (VO^{2+})-containing species, which is a common impurity in V(III) systems. These V(IV) resonances were left out of the experimental trace shown in Fig. 5. The spin Hamiltonian parameters are very similar to those of [V(dipic)(Hdipic)(H_2O)]·3H_2O and consistent with a distorted six-coordinate vanadium(III) complex.

The reaction of high concentrations of $[VO_2(dipic\text{-}X)]^-$ (where X = H, OH, Cl, Br, and NH_2) with excess *L*-ascorbic acid follows a different path that than the reaction of less than one equivalent of *L*-ascorbic acid with the V(V)dipic derivative. Specifically, the V(V)-containing species (100 mM) was reduced quickly to form V(IV) complexes upon addition of either 1 or 5 equivalents of *L*-ascorbic acid. However, on standing for additional 2–4 weeks under acidic conditions at ambient temperature, the solutions of 100 mM V-dipic complexes in the presence of *L*-ascorbic acid formed the V(III)-containing species (see below). This reaction of *L*-ascorbic acid was carried out with $[VO_2(dipic\text{-}X)]^-$ (where X = H, Cl, Br, OH, and NH_2). The HFEPR spectra are shown in Fig. 6 for the reaction of $NH_4[VO_2(dipic)]$ with *L*-ascorbic acid. For both 1:5 and 1:1 concentrations the sample produced good-quality spin-triplet spectra, with a major species described by the following spin Hamiltonian parameters: $D = +5.05\ cm^{-1}$, $|E| = 0.373\ cm^{-1}$, $g_{x,y} = 1.9$; $g_z = 2.1$. (The g_z value is very approximate since no parallel turning points were observed in the spectra.) A presence of a different, minor V(III) species was also observed, as is a common occurrence in V(III) in aqueous solutions [76]. We conclude that *L*-ascorbic acid at one equivalent and excess levels reduced all the V(V)-dipic complexes tested to V(III) species in aqueous solution upon standing several weeks under acidic conditions at ambient temperature. As shown by the presence of "minority species" in the spectrum shown in Fig. 6, the resulting solutions contain more than one six coordinate V(III) species as can expected because of mass balance and the fact the compounds tested contained only one ligand. Since currently no structural data are available on these systems, further information on the nature of the solution structure of these compounds must await solid state structural data detailing the coordination environment around the V(III) metal center. In the discussion section, we will propose the structure of the vanadium(III) species.

4. Discussion

The $[VO_2(dipic)]^-$ complex and its derivatives are a class of vanadium-containing compounds that have been thoroughly characterized with regard to chemical, physical, biological and anti-diabetic properties [3,60–66,74,77]. These compounds are special, as to our knowledge, these are the first V(V) coordination complexes that were found to have insulin-like properties [63], and as a result we and others have been interested in characterizing the chemistry of this class of compounds.

Table 3
HFEPR spectra of V(III)dipic and comparable V(III) complexes in the solid state and in aqueous solution.

Complex	D (cm^{-1})[a]	E (cm^{-1})[a]	g	Refs.
$[V(dipic)(Hdipic)(H_2O)]\cdot 3H_2O$ (solid)	+5.42	+0.150	$g_{x,y} = 1.96$, $g_z = 2.00$	this work
$[V(dipic)(H_2O)_2F]\cdot 1.5H_2O$ (solid)	5.56	0.056	$g_{x,y} = 1.92$, $g_z = 2.00$	this work
$NH_4[VO(dipic)]$ with 5 equivs. of *L*-ascorbic acid aqueous solution	+5.05	+0.373	$g_{x,y} = 1.9$, $g_z \sim 2.1$	this work
$Na[V(trdta)]\cdot 3H_2O$ (solid) where trda = trimethylenediamine-N,N,N′,N′-tetraacetate	5.60[b]	0.85	$g_{iso} = 1.95$	[76]
$[V(trdta)]^-$ (aqueous solution)	+0.87[c]	0	$g_{x,y} = 1.98$,	[76]
	+0.62	0	$g_z = 1.95$	
$[V(acac)_2(N–N)]ClO_4$ (solid), where N–N = dipyrido[3,2-*a*: 2′,3′-*c*]phenazine	+4.20	+0.46	$g_{x,y} = 1.910$ $g_z = 1.980$	[53]
$[V(III)(phen)(Ox)]ClO_4$ (solid), where Ox = oxalate	+4.39	+0.20	$g_{x,y} = 1.900$ $g_z = 1.900$	[87]

[a] The sign of D is given where determined while the sign of E is assumed to be same as that of D.
[b] Another triplet state with somewhat smaller zfs and of lower concentration has been also identified from the field/frequency map with $|D| \cong 5.15\ cm^{-1}$, $|E| \cong 0.23\ cm^{-1}$, $g_{iso} \cong 1.95$.
[c] In addition to the two triplet species listed here, another triplet state with larger zfs has been also identified in the spectra with $|D| \cong 2.35\ cm^{-1}$, $|E| \cong 0$, $g_{iso} \cong 1.95$.

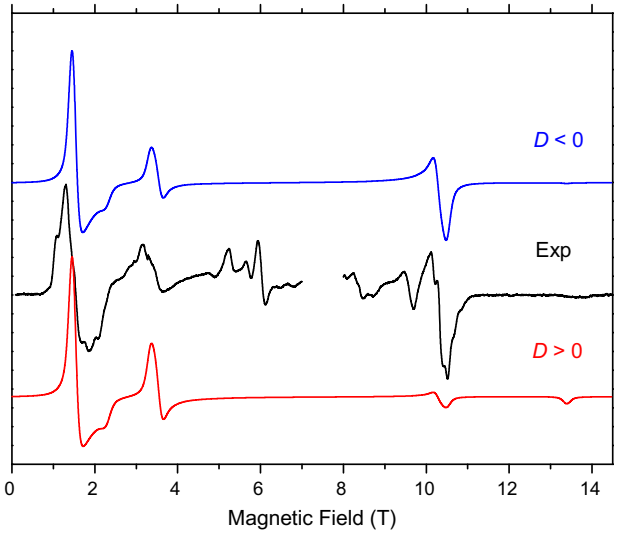


Fig. 5. HFEPR spectra of polycrystalline $[V(dipic)(H_2O)_2F]\cdot 1.5H_2O$, recorded at 10 K and 208 GHz (black middle trace) accompanied by its simulations (color traces) using the following spin Hamiltonian parameters: $S = 1$, $|D| = 5.56\ cm^{-1}$, $|E| = 0.056\ cm^{-1}$, $g_{x,y} = 1.92$; $g_z = 2.00$. Blue (upper) trace: negative zfs; red (lower) trace: positive zfs. The former reproduce the experimental intensities of some turning points somewhat better. The $g \sim 1.95$ spectral region containing V(IV) resonances was left out of the experimental spectrum.

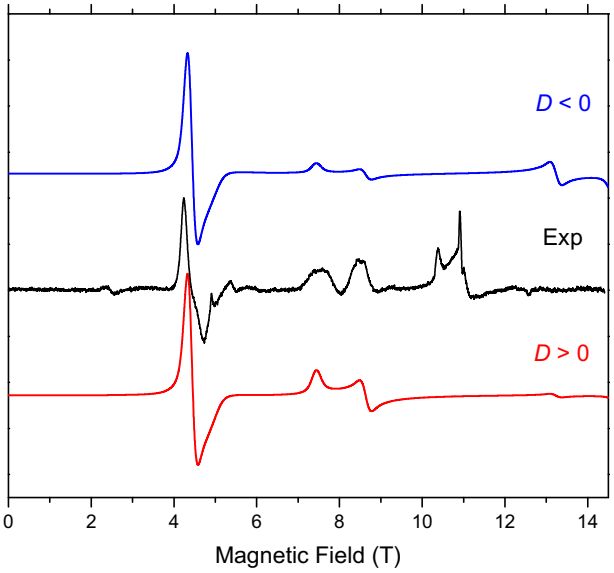


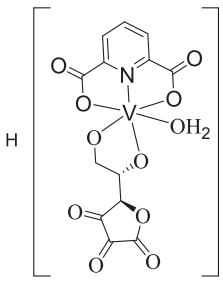
Fig. 6. HFEPR spectrum of an aqueous solution of 500 mM *L*-ascorbic acid and 100 mM of $NH_4[VO_2(dipic)]$ at 10 K and 302.4 GHz (black or middle trace) accompanied by its simulations (color traces) using the following spin Hamiltonian parameters: $S = 1$, $|D| = 5.05\ cm^{-1}$, $|E| = 0.373\ cm^{-1}$, $g_{x,y} = 1.9$; $g_z = 2.1$. Blue or upper trace: negative zfs; red or lower trace: positive zfs. The latter reproduces the experimental intensities of some turning points better. The group of resonances from 10.4 to 11.1 T originates from V(IV). A weak resonance at ca. 2.5 T and the complex shape of the "half-field" $\Delta Ms = \pm 2$ transition point to a presence of "minority" species in addition to the dominant one.

The synthesis and structural characterization of a new derivative of the V(V)-dipic series, $[VO_2(dipic\text{-}Br)]^-$, allow for a detailed comparison to known systems [61–63,65,66,74]. Many parameters were similar if not identical to the previous complex ions reported (Table 2). However, one interesting difference is that one of the V=O bonds on $[VO_2(dipic\text{-}Br)]^-$ anion is free and the other is involved in the H-bonding network. This translates to a 0.0089 Å difference in the bond length of the two V=O bonds which is a significant change for a double bond. This also allows for some twisting of the VO_2 unit in comparison to the O–V–O/N plane. Importantly, this difference can explain the asymmetry that is observed in the system and thus can undoubtedly explain why the Br-substituted derivative has a long V–N bond which is only exceeded by the dipic-NO_2 ligand [77].

The reactions of vanadium compounds with biological reductants are important to the mode of action of vanadium compounds as insulin-like agents [3,9,11,21,23,24,27]. Given that *L*-ascorbic acid is a naturally occurring biological reductant [55,56], its reaction with vanadium compounds is important, more so when V(V)-dipicolinate complexes are used as insulin-like agents. As such, we believe that this redox process is linked to the mode of action with vanadium compounds that have insulin-like properties. Several studies of vanadium compounds reacting with *L*-ascorbic acid, reduced glutathione and *L*-cysteine have been reported, and in most cases several species are believed to be formed in aqueous solution [23,39,40,57–59,78–80]. However, such studies have generally focused on the biological effects [23,39,40,81,82], characterization of the nature of these complexes [58,78–80,82–84], or kinetic studies determining the rates and mechanisms of reactions [57,59,85], while limited spectroscopic characterization of the proposed species is available and none using HFEPR spectroscopy characterizing V(III) species. In this work we focus on application of X-band EPR and HFEPR spectroscopy to characterize the reaction of V(V)-dipic-X

(where X = H, Cl, Br, OH, and NH_2) complexes with *L*-ascorbic acid. Specifically, we provide two types of evidence for the reduction of vanadium, a formation of V(IV)-species as well as V(III) species.

The spectroscopic data have proven that in solutions of 100 mM V-dipic-X (where X = H, Cl, Br, OH, and NH_2) complexes in the presence of 500 mM *L*-ascorbic acid, at least one V(IV)-dipic species, presumably the 1:2 complex, as well as a second species, presumably as a VO^{2+} is formed *in situ*. A previous study [64] on the complexes made from dipic and dipic-OH systems suggested that the 1:1 species and the VO^{2+} species might have overlapping signals or convert rapidly at the timescale of the experiment. Similarly for the five $[VO_2(dipic\text{-}X)]^-$ (where X = H, Cl, Br, OH, and NH_2) derivatives studied here, we also observed only two V(IV) species in the X-band EPR spectra. Based on the ambient temperature EPR spectra of the V(IV)O-dipic system containing 3.7 mM $VOSO_4$ and 15.0 mM dipicolinic acid [64] at pH 1.83, 3.66, 4.19, 4.58, 5.25, and 7.35, we concluded that the following vanadium(IV)-containing species with $dipic^{2-}$, $dipic\text{-}Br^{2-}$, $dipic\text{-}Cl^{2-}$, $dipic\text{-}NH_2{}^{2-}$, and $dipic\text{-}OH^{2-}$ ligands were formed at pH 3.66, 4.19, 4.19, 5.25, and 7.35, respectively, on standing at room temperature (see Fig. 3). However, upon standing, solutions containing 100 mM $[VO_2dipic\text{-}X]^-$ (where X = H, Br, Cl, NH_2, and OH) with 500 mM *L*-ascorbic acid under acid conditions for 2–4 weeks, V(III) species were observed. The nature of these species was investigated using two model V(III) compounds: $[V(dipic)(Hdipic)(H_2O)]\cdot 3H_2O$ and $[V(dipic)(H_2O)_2F]\cdot 1.5H_2O$ in the solid state as reference systems. We chose both a 1:2 and a 1:1 dipic complex for comparison in order to determine the parameters for each coordination geometry. The resulting spin Hamiltonian parameters do not differ between the two complexes, but are strongly indicative of a (distorted) octahedral coordination sphere of vanadium, as seen by comparing these two complexes with other known examples of this type of V(III) compounds known from the literature. In particular, the spin Hamiltonian parameters in $[V(dipic)(Hdipic)(H_2O)]\cdot 3H_2O$ and $[V(dipic)(H_2O)_2F]\cdot 1.5H_2O$ are very close to those of the complex $Na[V(trdta)]\cdot 3H_2O$ (where trda = trimethylenediamine-N,N,N′,N′-tetraacetate), when studied as a solid [76]. The $Na[V(trdta)]\cdot 3H_2O$ complex in aqueous solution shows additional triplet states, as will be discussed below. Equally significantly, the spin Hamiltonian parameters of both solid complexes studied in this work are very similar to a series of quasi-octahedral complexes of V(III) with mixed N and O coordination investigated previously [86,87]. It is thus established that $[V(dipic)(Hdipic)(H_2O)]\cdot 3H_2O$ and $[V(dipic)(H_2O)_2F]\cdot 1.5H_2O$ can both serve as models for the $V^{III}(dipic)$ species in solution. Indeed, the spectra and spin Hamiltonian parameters we obtained from the *in situ* mixture of $NH_4[VO_2(dipic)]$ with *L*-ascorbic acid are very similar to those obtained from both solids, leaving no doubt that reduction of V(V) with excess *L*-ascorbic acid over extended period of time leads to the formation of a V(III) species. Based on this result, we propose the following structure for the V(III) species with a dipicolinate ligand. Under acidic conditions at pH 1.83, H_2A is expected to be the predominate species of *L*-ascorbic acid [55,56], but on standing under ambient conditions, dehydroascorbic acid, the oxidized product is formed. It is possible that dehydroascorbic acid will coordinate as a bidentate ligand in the complex as shown below.



In view of the previous results obtained by some of us on three different V(III) complexes with polycarboxylate ligands including edta, nta, and trda [76] it is somewhat surprising that we only see one clear "minority species" in the HFEPR spectra in addition to the majority one. In the quoted study, the complexes displayed a wide variety of spin Hamiltonian parameters attributed to different species formed in solution due to many modes of coordination. The dipic ligand, it appears, is more uniform in this respect than the polycarboxylate ligands studied before.

The work carried out in here on the series of substituted V(V)-dipic complexes was utilized to probe the nature of the reduced V-species being formed in the presence of *L*-ascorbic acid. The results show that the entire series of compound are reduced by *L*-ascorbic acid; at low concentrations of the acid, V(IV) species are formed, and at higher concentrations V(III) forms. These results demonstrate that it is possible to form V(III) complexes under mild conditions, given sufficient reaction time. As we showed previously with the V(V)-mercaptoethanol system, the nature of the redox reaction is likely to be very sensitive to factors such as concentration, pH and redox potentials of the species involved in the reaction [79].

5. Conclusion

The reaction between V-dipic complexes and *L*-ascorbic acid was investigated with the objective of providing spectroscopic characterization of the species that form. We observed both the formation of V(IV) complexes and V(III) complexes depending on the conditions. We have successfully acquired HFEPR spectra for V(III)-dipic complexes formed from the reaction of corresponding V(V)dipic complexes with *L*-ascorbic acid and propose that the solution species is distorted octahedral in geometry. In addition, the dipicolinic acid derivative with a Br group was prepared. When complexed to vanadium, this ligand was found to support a geometry similar to a ligand with a much more electron withdrawing substituent [77]. Based on the H-bonding packing diagram, we concluded that this unusual geometry may be a result of the H-bonding network and packing scheme.

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Appendix A. Supplementary material

CCDC 966675 contains the supplementary crystallographic data for $NH_4[VO_2(dipic\text{-}Br)]$. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ica.2013.12.001.

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