Pure Appl. Chem., Vol. 81, No. 7, pp. 1313–1321, 2009.
doi:10.1351/PAC-CON-08-08-18

NMR characterization and dynamics of vanadium(V) complexes with tripod (hydroquinonate/phenolate) iminodiacetate ligands in aqueous solution*

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Abstract: Reaction of NH_4VO_3 with (phenolate/hydroquinonate) iminodiacetate tripod ligands in aqueous solution in the pH range 7–8 results in the isolation of three new dioxido vanadium(V) complexes, one dinuclear $(NH_4)_4\{(V^VO)_2$[μ-bicah(6-)-N,O,O,O]}·$8H_2O$, (H_6bicah, 2,5-bis[*N*,*N*′-bis(carboxymethyl)aminomethyl]-hydroquinone), and two mononuclear $(NH_4)_2\{(V^VO)_2$[Hcah(3-)-N,O,O,O]·$2H_2O$, (H_4cah, 2-[*N*,*N*′-bis(carboxymethyl)aminomethyl]-hydroquinone) and $(NH_4)_2\{(V^VO)$[Hcacp(3-)-N,O,O,O]} $4H_2O$, (H_4cacp, 2-[*N*,*N*′-bis(carboxymethyl)aminomethyl]-4-carboxyphenol). The ^{51}V, ^1H, and ^{13}C NMR spectra in D_2O show the coordination environment of vanadium in the above complexes to be octahedral, with four out of six positions to be occupied by the two carboxylate oxygen, one hydroquinonate oxygen, and one amine nitrogen atoms of the tripod ligand. The two acetate arms are in *cis* position to each other. Variable-temperature ^1H and ^{13}C NMR measurements show that the complexes are kinetically labile. An intramolecular exchange that proceeds through the opening of the phenolate/hydroquinonate chelate ring has been revealed by 2D{^1H} NMR EXSY (exchange spectroscopy).

Keywords: vanadium; phenolate; hydroquinonate; iminodiacetate; NMR; exchange; tyrosine; transferrin.

INTRODUCTION

Vanadium has been found to be an important biological element participating in several enzymatic reactions and exhibiting insulinomimetic properties [1]. The mechanisms with regard to how vanadium(III), (IV), and (V) compounds act in biological systems remain elusive, in part because of the rich aqueous chemistry of vanadium under physiological conditions as well as the multiple targets of vanadium in the cell [2]. Hydrolytic and redox stability and lability of the complexes have been suggested to be two important properties with respect to the biotransformations that occur under physiological conditions. Information on the lability of the vanadium complexes with various donor atoms is essential in order to determine the pathways and the targets of vanadium in the biological systems as well as

*Paper based on a presentation at the 6th International Symposium on Chemistry and Biological Chemistry of Vanadium, 17–19 July 2008, Lisbon, Portugal. Other presentations are published in this issue, pp. 1187–1330.

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to synthesize more stable and less labile biologically active compounds under physiological conditions [3].

Tyrosine and tyrosine derivatives play a distinctive role in physiological interactions involving vanadium in oxidation states +3, +4, and +5. For example, in transferrin, an efficient transport protein for simple vanadate species, two tyrosines in the C- and the N-terminal lobe are involved in vanadium coordination [4,5]. Protein phosphatases and kinases are inhibited or stimulated by vanadate, and it has been proposed that this activity of vanadates is related to the vanadium coordination to tyrosine (or serine or theonine) in the active site of the enzymes [6–9]. It has also been suggested that the vanadate insuline mimetic effect may be due to vanadylation of the tyrosine residues at the intracellular site of the insulin membrane receptor [8,9].

The investigation of the interaction of vanadium with tyrosine/phenolate-type ligands is the key for understanding the interaction of vanadium with the tyrosine residue in these biological systems. However, the interaction of vanadium with tyrosine (HOTyr) in aqueous solutions is weak [10–13]. The vanadate–HOTyr formation constants in water/acetone are small, 1.8 M^{-1} for the $HVO_3(OTyr)^-$ and 1.1 M^{-1} for the $VO_2(OTyr)_2^-$ [12a]. Tyrosine dipeptides such as Tyr-Gly and Gly-Tyr are sufficiently more effective ligands for vanadate-exhibiting complex formation constants between 30 and 150 M^{-1} [12b]. Multinuclear NMR studies showed that the dipeptides containing tyrosine coordinate mainly in a tridentate fashion through the carboxylate, the amino, and the deprotonate amide-N groups [11,12b]. The phenolic oxygen of tyrosine is not directly ligated to the metal ion. The tridentate coordination mode of Gly-Tyr has been observed in the solid-state structure of the vanadyl complex [VO(*o*-phen)(Gly-Tyr)], in which the tyrosine phenol oxygen does not participate in coordination [13]. Formation rates have been determined for only a few vanadium-containing complexes. The reaction of vanadate with phenolic groups in aqueous solution at 25 °C has been reported to be completed in milliseconds [14].

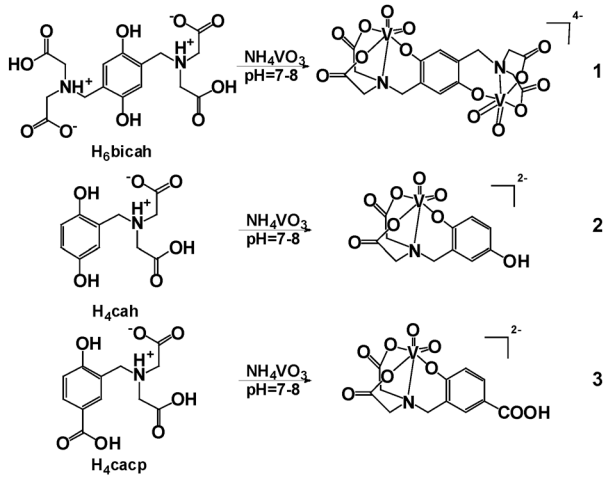
In order to stabilize the coordination of phenolate oxygen to the metal, we have synthesized new tripod phenolate/hydroquinonate ligands substituted with iminodiacetic group at *o*-position [15–18]. The iminodiacetate arms have been employed to mimic the protein environment in enzyme active sites around tyrosine. In addition, ligation of the metal ion to the negative charged carboxylate groups, results in charged complexes which are water-soluble, permitting the exploration of vanadium-phenolate chemistry in aqueous solution, better mimicking the biological systems. The hydroquinonate complexes present additional interest because of the redox nature of the hydroquinone moiety, which has been found to give rise to proton-induced metal-hydroquinone electron transfer [17,19].

Herein, we report the synthesis of the solid-state and NMR aqueous solution characterization and the investigation of the dynamic behavior of vanadium(V) complexes with tripod phenolate/hydroquinate ligands. These complexes are hydrolytically stable in the pH range 7–8.5 but are labile, exhibiting a fast intramolecular exchange through the opening of the phenolate/hydroquinonate chelate ring.

RESULT AND DISCUSSION

Syntheses and solid-state characterization of compounds 1–3

The syntheses of the vanadium(V)/hydroquinonate/phenolate complexes are summarized in Scheme 1. At pH below 7, the complexes are reduced, giving green and at pH below 6 dark blue solutions originated from vanadium(IV)/semiquinonate [17,18] and from vanadium(IV/V) oxygen-bridged complexes [16]. Above pH 8.5, the complexes partially hydrolyze (less than 5 % at pH 8.5) to form vanadate, vanadate oligomers, and free ligand. It appears that isolation of **1–3** may be best carried out in the pH range 7–8.5, free of any complicating redox reactions. Indeed, mixing NH_4VO_3 with each one of the ligands at pH 7.0–7.5 resulted in **1–3** in 42–69 % yield. Complexes **1** and **3** are stable in aqueous or D_2O solutions in the pH range 7–8.5 for several weeks, and their isolated crystalline materials were used in the present solution studies. However, aqueous solutions of complex **2** are not stable even at pH 8.5 driv-



Scheme 1 Synthetic routes leading to the isolation of compounds **1–3**.

ing to partial reduction of vanadium(V) to vanadium(IV) by the hydroquinonate ligand, as was evident by ^{1}H NMR spectroscopy.

The spectroscopic properties of **1** (IR, UV–vis, and NMR spectroscopies) are exactly the same with those of the complex $Na_4\{(V^VO_2)_2[\mu\text{-bicah}(\text{-}6\text{-})\text{-}N,O,O,O]\}\cdot 11H_2O$ that has been previously reported by us [18], revealing that the anions of both the Na^+ and NH_4^+ salts are identical in solid state and in solution. Figure 1 shows the structure and the labeling of the dinuclear anion, which has been obtained from the X-ray crystal structure of $Na_4\{(V^VO_2)_2[\mu\text{-bicah}(\text{-}6\text{-})\text{-}N,O,O,O]\}\cdot 11H_2O$. The hydroquinonate ligand bridges together two equivalent vanadium(V) ions. Each vanadium atom is found in a distorted octahedral geometry coordinated to the one hydroquinonate oxygen, two carboxylate oxygen, and one amine nitrogen atoms of the iminodiacetate group and two oxido groups. The two acetate groups in each vanadium center are in *cis* position to each other. The two *cis* oxido groups of the first vanadium atom are arranged in *trans* position toward the two oxido groups of the second vanadium atom in the molecule. The most important features of this structure are the very short vanadium hydroquinonate oxygen bond distances [V–O(5), 1.864(3) Å]. The longer V–O(3) bond length [2.209(3) Å] compared with the V–O(1) [2.019(3) Å] is due to the strong *trans* influence of the oxido group in position *trans* to O(3).

The infrared spectra of **1–3** show two bands, one symmetric and one antisymmetric at 889, 868 for **1**, 945, 907 for **2**, and 916, 880 cm^{-1} for **3** attributed to the V=O bonds of VO_2^+. The carboxylate stretching vibrations appear as two peaks, one antisymmetric and one symmetric at ~1632 and ~1396 cm^{-1}, respectively, in all complexes, indicating coordination of vanadium atom from the carboxylate oxygen atoms of the iminodiacetate group. A 10–20 cm^{-1} shift of the $C\text{–}O_{phenolate/hydroquinonate}$ stretching vibration to higher energy in the complexes compared to the free ligands also shows coordination of the vanadium(V) ions with the phenolate/hydroquinonate oxygen atoms.

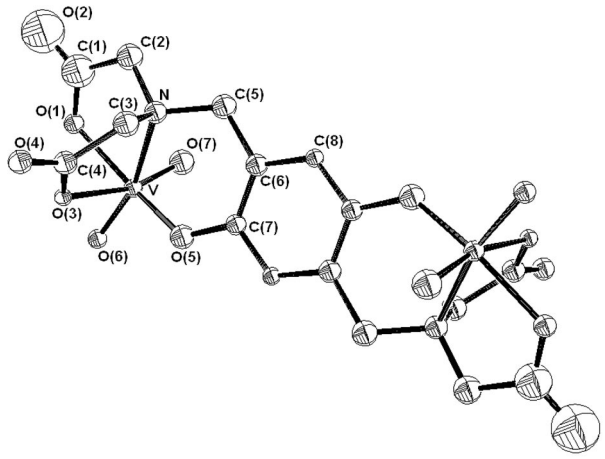


Fig. 1 ORTEP representation (50 % thermal ellipsoids) of the crystal structure of $\{(V^{V}O_2)_2$[μ-bicah(-6-)-N,O,O,O]$\}^{4-}$. Space group *P*-1, unit cell $a = 9.664(6)$, $b = 12.009(4)$, $c = 14.629(4)$ Å, $\alpha = 97.69(2)$, $\beta = 101.01(4)$, $\gamma = 99.78(4)°$.

NMR characterization in aqueous solution

Each of the ^{51}V NMR spectra of the aqueous solutions of **1–3** (50 mM) show one peak at –493, –495, and –501 ppm, respectively. These chemical shifts are close to the expected for octahedral vanadium(V) dioxido aminocarboxylates complexes [20,21]. Apparently, the coordination environment of vanadium atom in complexes **1–3** in solution is the same with that found in the crystal structure (Fig. 1).

The ^{13}C and ^{1}H spectra of **1–3** at room temperature and pD from 7 to 8.5 gave broad peaks which became sharper at 0 °C (Figs. 2 and 3), indicating a dynamic process in this temperature range.

The aliphatic region of the ^{1}H NMR spectrum of **1** at 0 °C gave five peaks assigned to the protons of the acetate groups. The relatively large number of peaks shows that the environment around the vanadium atom is asymmetric with the two acetate arms in *cis* position to each other (only three peaks are expected for a complex having the acetate arms in *trans* position), in agreement with the crystal structure of complex (Fig. 1). The fact that two peaks were observed for the carboxylate carbons in ^{13}C NMR spectrum at 0 °C (Fig. 3A) also supports the *cis* position of the acetate groups. In a similar fashion, the ^{1}H NMR spectrum of **3** at 0 °C (Fig. 2B) shows the asymmetric environment of the protons that belong to the *cis* acetate groups. The aromatic region of the ^{1}H NMR spectrum of **1** at 0 °C gave one peak, indicating that only the dinuclear species is present in solution.

Another important change that is observed in the ^{13}C NMR of **1** is that the C_2 and C_5 peaks are broader at lower temperature and the C_3 is split into two peaks, indicating the presence of two exchanging isomers in solution. The ^{1}H and ^{13}C spectra show that the environment around the vanadium atom is the same in both isomers. Thus, the only possibility is the two isomers to have the structures depicted in Fig. 3B. One isomer has the structure found in solid state by X-ray crystallography with the V=O bonds of the two vanadium atoms to be in *trans* position (*trans*,*trans* isomer) and the other, the *cis*,*trans* structure, which is produced from the *trans*,*trans* isomer by the mirror *trans* location of the C(3)–C(4)–O(3)–O(4) acetate group with the in *trans* position oxido group, O(7), performed at one vanadium center.

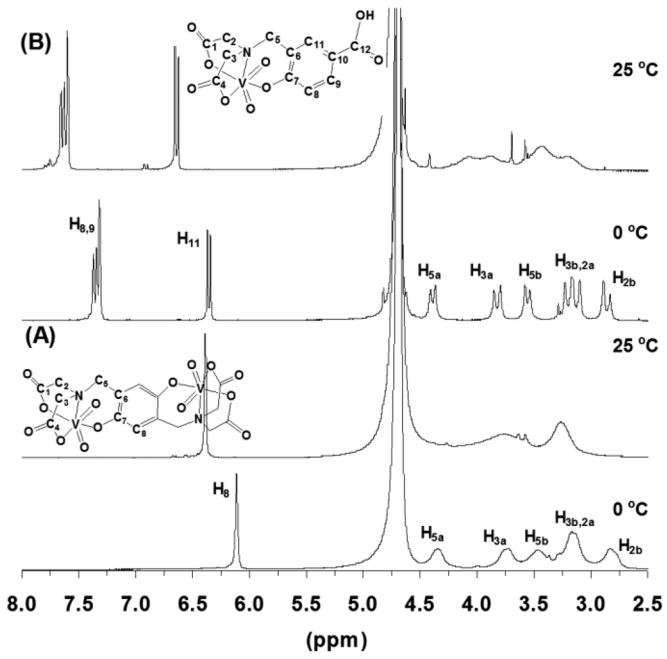


Fig. 2 ^{1}H NMR spectra of (A) **1** (50 mM) and (B) **3** (50 mM) and assignments, at 25 and 0 °C, pD = 7.0. The labels a and b show the geminal protons.

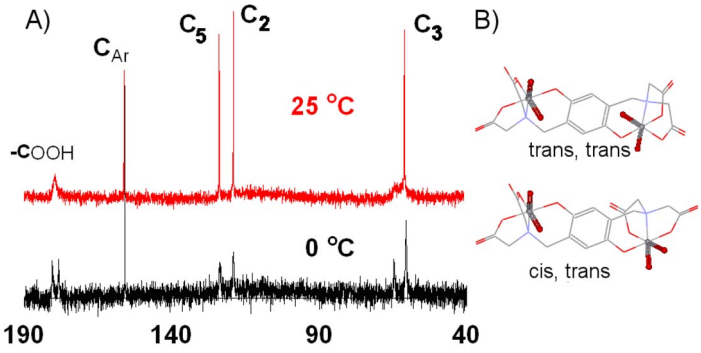


Fig. 3 (A) ^{13}C NMR spectra of **1** (100 mM) and assignments (numbering based on Fig. 1), at 25 and 0 °C, pD = 8.0. The aromatic carbon atoms are named with the symbol C_{Ar}. (B) Drawings of the two isomers of **1** present in aqueous solution showing in boldface the positions of the four V=O bonds.

The mechanism of the dynamic process in the aqueous solution of the complexes was investigated by 2D{^{1}H} NMR EXSY. The aliphatic region of the 2D EXSY spectrum of **3** at pD 6.85 and mixing time 0.10 s is shown in Fig. 4. The spectrum shows cross-peaks only between H_{2a}-H_{3a}, H_{2b}-H_{3b}, and H_{5a}-H_{5b}. The absence of cross-peaks between the geminal protons of each acetate group supports that the carboxylate oxygen atoms remain attached to the vanadium(V) ion during the exchange.

There are two possible mechanisms: (1) The first one occurs by twisting of the donor atoms around the C_3 axis that passes from the vanadium atom and from the center of the plane defined from the two oxido and the phenolate oxygen atoms, with no break of any bond. (2) The second mechanism goes through the break of the V–$O_{phenolate/hydroquinonate}$ bond, reorientation of the acetate groups, and reattachment of the phenolate/hydroquinonate oxygen to the vanadium(V) ion. The rate of a twist mech-

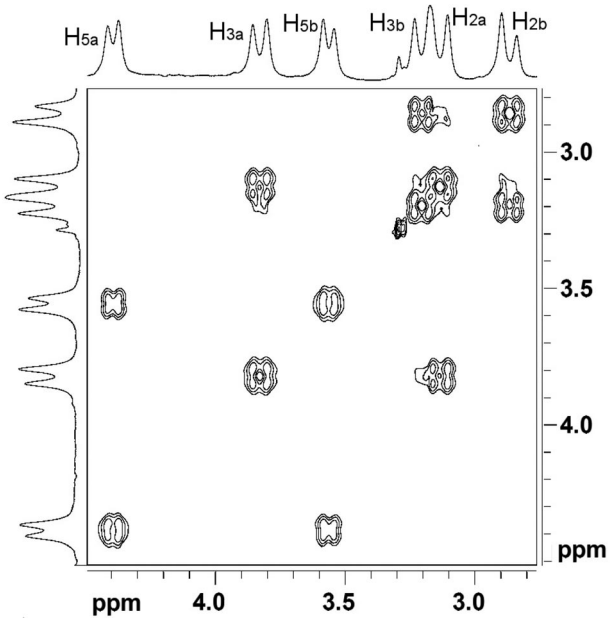


Fig. 4 Part of the 2D{^{1}H} EXSY spectrum of **3** at pH 6.85 and mixing time 0.10 s. The spectrum was acquired using 128 increments (with 16 scans each) covering 1.7 ppm in both dimensions and was run with temperature control at 0 °C (numbering based on Fig. 1).

anism is expected to be independent of the different types of iminodiacetate tripod ligands. Other vanadium(V) complexes with tripod iminodiacetate ligands containing a pyridine nitrogen [22], or an alkoxy oxygen [23] instead of phenolate oxygen atom are not fluxional at room temperature. Thus, the twist mechanism is excluded. The fact that the phenolate oxygen introduces the lability in these complexes supports the latter mechanism.

BIOLOGICAL RELEVANCE AND CONCLUSIONS

The interaction of pharmaceuticals with serum proteins is an important aspect in drug metabolism. Serum proteins transferrin (Tf) and albumin (HAS) form stable complexes with vanadate and vanadyl and probably act as mediators for vanadium delivery to the cells [24]. Recently, it has been reported that the fate of the vanadium complexes exhibiting antidiabetic properties is the complete dissociation or the formation of ternary complexes with Tf and HSA [24a,25]. Apparently, serum proteins are capable of strongly affecting the distribution, biotransformation, and ultimately the mechanism of action of vanadium pharmaceuticals. There is a need to develop a better understanding of the coordination chemistry of these proteins (open/close geometry, coordination number, dynamics, and architecture of ion sites, etc.). Our model study shows that the vanadium bonds with the two tyrosines in Tf are probably the most labile. It is possible, the unwrapping of one or two tyrosine ligating groups from the metal ion to be the primary step for the release of the metal from the protein or the formation of a free site of attack for an incoming ligand. Although VO_2^+ or VO^{2+} are bound very strongly to Tf, the uptake and release processes and competitive displacements of metal ions may be kinetically controlled [26]. It might be possible to fine-tune ligands for vanadium ions to achieve kinetic control over transferring uptake. In this study, we have shown that tripod ligands form stable complexes with vanadate at physiological pH and are ideal for controlling the lability of the complex by different donor atoms. Thus, further in

vitro/in vivo studies of these molecules might provide insight into the chemical form of the vanadium species that leads to its biological potency and in particular its antidiabetic activity.

In conclusion, we have prepared one dinuclear and two mononuclear vanadium(V) complexes by reacting aqueous solutions of NH_4VO_3 with tripod iminodiacetate phenolate/hydroquinonate ligands at pH 7–8. The new complexes are hydrolytically stable in the pH range 7–8.5, as this was evidenced by ^{51}V NMR spectroscopy. Variable-temperature ^1H and 2D{^1H} NMR EXSY show an intramolecular exchange reaction between the two acetate groups and the two geminal aminomethylene protons. This exchange proceeds through a break of the vanadium(V) phenolate/hydroquinonate oxygen bond and opening of the phenolate chelate ring, reorientation of the acetate and the oxido groups, and reattachment of the phenolate oxygen to the vanadium atom. The higher lability of the $V–O_{phenolate}$ bond compared to the $V–O_{carboxylate}$ is surprising considering that the $V–O_{phenolate}$ bond is much shorter than $V–O_{carboxylate}$, exhibiting a partial double character based on the crystallographic data.

More kinetic and theoretical studies are under way in order to better understand the high lability of the $V–O_{phenolate}$ bond.

EXPERIMENTAL SECTION

Physical measurements

Fourier transform-infrared (FT-IR) transmission spectra of the compounds, pressed in KBr pellets, were acquired on a Shimadzu IRprestige-21 spectrophotometer model. Microanalyses for C, H, and N were performed by a Euro-Vector EA3000 CHN elemental analyzer. NMR spectra were recorded on a 300 MHz Avance Brucker spectrophotometer operating at 300, 75.5, and 78.9 MHz for ^1H, ^{13}C, and ^{51}V nuclei, respectively. The ^1H, ^{13}C, and ^{51}V NMR spectra at 0 and 25 °C were recorded using a sweep width of 6173, 4500, and 75 188 Hz, respectively, and a 30° pulse. The standard NOESY pulse sequence (90°-t_1-90°-t_m-90°) was applied in the 2D {^1H} EXSY-NOESY measurements, and these spectra were acquired using 128 increments (with 16 scans each) covering 1.7 ppm in both dimensions and 0.10–0.20 s mixing times (t_m). The 2D {^1H} EXSY-NOESY experiments were performed at 0 °C.

Ligand preparation

The ligands referred to in this study, 2,5-bis[*N*,*N*′-bis(carboxymethyl)aminomethyl]-hydroquinone (H_6bicah), 2-[*N*,*N*′-bis(carboxymethyl)aminomethyl]-hydroquinone (H_4cah), and 2-[*N*,*N*′-bis(carboxymethyl)aminomethyl]-4-carboxyphenol (H_4cacp), were synthesized based on the Mannich-type reaction reported in the literature [16,18].

Synthesis of $[NH_4]_4\{(V^VO)_2[\mu$-bicah(6-)-N,O,O,O]$\}\cdot 8H_2O$, 1

H_6bicah (0.50 g, 1.2 mmol) was dissolved in water (15 ml) by dropwise addition of NaOH (5 M), under argon (pH ~6.0). To the resulting pale red–orange solution, 5 ml of a warm aqueous solution of NH_4VO_3 (0.28 g, 2.4 mmol) was added. Upon addition of NH_4VO_3, the color of the solution turned to yellow–brown (pH ~6.5). The pH was adjusted at 8.0 by the dropwise addition of NaOH (5 M) under argon, and the color of the solution changed to deep red–brown. The reaction mixture was filtered, and ethyl alcohol was added to the filtration (pH 8.2, ethyl alcohol:water; 2:1) and stored at 4 °C for a day, affording deep red–brown crystals. Yield: 0.64 g (69 %, based on H_6bicah). Elemental analysis calc'd. (%) for $C_{16}H_{46}O_{22}N_6V_2$ (776.45): C 24.75, H 5.97, N 10.82; found: C 24.72, H 6.02, N 10.78.

Synthesis of $[NH_4]_2\{(V^VO)_2[Hcah(3\text{-})\text{-}N,O,O,O]\cdot 2H_2O$, 2

H_4cah (0.50 g, 2.0 mmol) was dissolved in water (15 ml) by dropwise addition of NaOH (5 M), under argon (pH ~5.5). To the above brown solution, NH_4VO_3 (0.23 g, 2.0 mmol) dissolved in water (5 ml) was added, resulting in a dark brown solution (pH ~6.0). The pH of the solution was adjusted at 8.0 by the dropwise addition of NaOH (5 M) under argon, and the color of the solution changed to deep red–brown. The reaction mixture was filtered, and ethyl alcohol was added to the filtration (pH 8.0, ethyl alcohol:water; 2:1) and stored at 4 °C for a day, affording deep red–brown microcrystalline solid of **2**. Yield: 0.46 g (56 %, based on H_4cah). Elemental analysis calc'd. (%) for $C_{11}H_{22}O_{10}N_3V$ (407.25): C 32.44, H 5.44, N 10.32; found: C 32.36, H 5.49, 10.38.

Synthesis of $[NH_4]_2\{(V^VO)[Hcacp(3\text{-})\text{-}N,O,O,O]\}\cdot 4H_2O$, 3

H_4cacp (0.50 g, 1.8 mmol) was dissolved in water (20 ml) by dropwise addition of NaOH (5 M), under argon (pH ~5.5). To the resulting pale yellow solution, 5 ml of a warm aqueous solution of NH_4VO_3 (0.21 g, 1.8 mmol) was added. Upon addition of NH_4VO_3, the color of the solution turned to bright yellow (pH ~5.0). The pH was adjusted at 7.5 by the dropwise addition of NaOH (5 M) under argon, and the color of the solution changed to yellow–brown. The reaction mixture was filtered, and ethyl alcohol was added to the filtration (pH 7.6, ethyl alcohol:water; 2:1) and stored at 4 °C for a day, affording orange–brown microcrystalline solid of **3**. Yield: 0.36 g (42 %, based on H_4cacp). Elemental analysis calc'd. (%) for $C_{12}H_{26}O_{13}N_3V$ (471.29): C 30.58, H 5.56, N 8.92; found: C 30.41, H 5.62, 8.86.

ACKNOWLEDGMENTS

The authors acknowledge the Research Promotion Foundation of Cyprus for the financial support of this work with the proposal TEXNO/0506/19.

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