

# Aqueous acid–base chemistry involving dioxovanadium(V) complexes of 2,6-pyridinedimethanol, and the X-ray structures of $\text{Na}[\text{VO}_2\{2,6-(\text{OCH}_2)_2\text{NC}_5\text{H}_3\}] \cdot 4\text{H}_2\text{O}$ and $[1-H-2,6-(\text{HOCH}_2)_2\text{NC}_5\text{H}_3]^+ \text{Cl}^-$

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## Abstract

Reaction of  $\text{NH}_4\text{VO}_3$  with 2,6-pyridinedimethanol in water at 85 °C followed by the room temperature addition of HCl (aq) yields  $[\text{HVO}_2(\text{pydim})]_x$  (pydim = 2,6-pyridinedimethanolato dianion), as a sparingly soluble off-white solid. This acid may be deprotonated by titration with NaOH (aq), yielding  $\text{Na}[\text{VO}_2(\text{pydim})] \cdot 4\text{H}_2\text{O}$ , which has been structurally characterized by single-crystal X-ray diffraction. Treating  $\text{Na}[\text{VO}_2(\text{pydim})] \cdot 4\text{H}_2\text{O}$  with HCl (aq) regenerates  $[\text{HVO}_2(\text{pydim})]_x$ , but reaction with additional NaOH (aq) displaces the pyridinedimethanolato ligand from the vanadium center. Similarly, treating  $[\text{HVO}_2(\text{pydim})]_x$  with excess HCl (aq) strips the pyridinedimethanolato ligand from the vanadium center and yields the adduct  $[\text{H}_3(\text{pydim})]^+ \text{Cl}^-$  as one component in a mixture of products. This adduct has been structurally characterized by single-crystal X-ray diffraction. The optimum pH range for stable dioxovanadium(V) complexes stabilized by the 2,6-pyridinedimethanolato ligand is at least 1.5–9.4.

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## 1. Introduction

Water-soluble, mononuclear vanadium compounds have been the subject of intense interest in recent years because such compounds might potentially serve as orally administered drugs for lowering glucose levels in the blood of type 2 diabetics [1–16]. Some important new developments in this exciting area of bioinorganic chemistry have been made recently. For example, although inorganic vanadium(V) salts have been known to lower glucose levels since 1899 [17], the first organic

vanadium(V) insulin-mimetic compound was reported as recently as 2000 [18].

Any vanadium complex that is to be used as an orally administered drug for lowering blood glucose levels must be stable in both acidic and neutral environments. This stability is required because the vanadium complex must survive the digestion process where the pH can be as low as 1.0, and must remain intact in the blood where the pH is 7.4. Thus, examination of the stabilities of vanadium complexes as a function of pH is a necessary prerequisite for evaluating the usefulness of such complexes to serve as glucose-lowering drugs [19,20].

Some vanadium-based insulin mimics have been stabilized by the 2,6-pyridinedicarboxylate and 4-hydroxy-2,6-pyridinedicarboxylate ligands [15,18,21,22]. Further-

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more, a number of oxovanadium compounds with other tridentate (O, N, O) ancillary ligands have been reported in the literature recently [23–36]. The aims of this present research are to prepare some oxovanadium(V) complexes stabilized by the similar 2,6-pyridinedimethanolato ligand and to investigate the complex stabilities in aqueous solution as the pH is varied. If these new vanadium complexes are stable from pH  $\sim$  1 to pH  $\sim$  8, then they may be tested as phosphatase inhibitors in order to assess their potential value as glucose-lowering drugs [37].

## 2. Experimental

### 2.1. General considerations

All reactions and manipulations were carried out open to air. Infrared spectra were recorded as KBr pellets on a Nicolet Magna-IR 560 spectrometer, and the data are reported in  $\text{cm}^{-1}$ .  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{51}\text{V}$  NMR spectra were obtained at room temperature on a Varian Mercury 300 MHz FT-NMR spectrometer at the frequencies 300.068, 75.452, and 78.85 MHz, respectively.  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts are reported in parts per million and were referenced externally with respect to a  $\text{D}_2\text{O}$  solution of  $\text{NaOOCCH}_2\text{CH}_2\text{Si}(\text{CH}_3)_3$ ; the protons in the methyl groups are set at  $\delta = 0$  in the  $^1\text{H}$  NMR spectrum and the carbon atoms in the methyl groups are set at  $\delta = 0$  in the  $^{13}\text{C}$  NMR spectrum.  $^{51}\text{V}$  chemical shifts are reported in parts per million and were referenced externally with respect to neat  $\text{VOCl}_3$  ( $\delta = 0$  ppm). Elemental analyses were carried out by Micro Analysis Inc. (Wilmington, DE). pH values were measured using a Fisher Accumet Model 910 pH meter and a saturated KCl electrode. The pH meter was calibrated before use with a 0.05 M potassium hydrogen phthalate buffer solution (pH 4.00) and a  $\text{K}_2\text{HPO}_4/\text{KH}_2\text{PO}_4$  buffer solution (pH 7.00). Unless otherwise noted, reagents were purchased from commercial suppliers and were used without further purification.

#### 2.1.1. Synthesis of $[\text{HVO}_2\{2,6-(\text{OCH}_2)_2\text{NC}_5\text{H}_3\}]_x$ (i.e., $[\text{HVO}_2(\text{pydim})]_x$ where *pydim* = 2,6-pyridinedimethanolato dianion)

A mixture of  $\text{NH}_4\text{VO}_3$  (3.214 g, 27.5 mmol) and 2,6-pyridinedimethanol (3.828 g, 27.5 mmol) in deionized water (60 mL) was stirred at 85 °C for 3 h. The mixture was then cooled to room temperature and filtered. The pH of the yellow homogeneous filtrate (initially 6.6) was lowered to 1.6 by the dropwise addition of conc. HCl (aq) as the mixture was stirred, and an off-white solid precipitated. The solid was isolated by filtration, washed three times with small portions of deionized water, and air-dried. Finally, the off-white solid was vacuum-dried. Yield: 4.796 g (79%). *Anal.* Calc. for  $\text{C}_7\text{H}_8\text{NO}_4\text{V}$ : C, 38.0; H, 3.7; N, 6.3. Found: C, 37.5;

H, 3.6; N, 6.3%. IR data: 3387 (vs), 3104 (m), 3083 (m), 3070 (m), 3043 (m), 2930 (m), 2857 (m), 2835 (m), 1617 (vs), 1574 (m), 1478 (vs), 1452 (vs), 1413 (m), 1387 (m), 1365 (w), 1348 (w), 1300 (m), 1274 (w), 1235 (m), 1174 (m), 1170 (m), 1109 (s), 1083 (vs), 1026 (s), 1009 (w), 952 (vs), 928 (vs), 809 (vs), 770 (m), 730 (m), 696 (vs), 639 (s), 561 (vs), 500 (s), 461 (m).  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ): 4.96 (4H, s), 7.80 (2H, d,  $^3J_{\text{H-H}} = 8$  Hz), 8.37 (1H, t,  $^3J_{\text{H-H}} = 8$  Hz).

#### 2.1.2. Titration of $[\text{HVO}_2(\text{pydim})]_x$ with $\text{OH}^-$ (aq)

An aqueous suspension of  $[\text{HVO}_2(\text{pydim})]_x$  (0.619 g, 2.80 mmol) in deionized water (100 mL) was titrated with an aqueous solution of NaOH (0.262 M). The volume of each aliquot of NaOH (aq) added and the pH after each addition follows: 0 mL NaOH, pH 3.94; 1.00 mL, 4.67; 2.00 mL, 4.94; 3.00 mL, 5.11; 4.00 mL, 5.24; 5.00 mL, 5.33; 6.00 mL, 5.41; 7.00 mL, 5.48; 8.00 mL, 5.54; 9.00 mL, 5.61; 10.00 mL, 5.71; 11.00 mL, 8.80; 12.00 mL, 9.67; 13.00 mL, 10.13; 14.00 mL, 10.44; 16.00 mL, 10.93; 19.00 mL, 11.45; 22.00 mL, 11.92; 25.00 mL, 12.18. The titration data are plotted in Fig. 1.

#### 2.1.3. Preparation of $\text{Na}[\text{VO}_2\{2,6-(\text{OCH}_2)_2\text{NC}_5\text{H}_3\}] \cdot 4\text{H}_2\text{O}$

A gently stirred aqueous suspension (26 mL) of  $[\text{HVO}_2(\text{pydim})]_x$  (1.482 g, 6.70 mmol) was titrated with an aqueous solution of 0.103 M NaOH (65.0 mL, 6.70 mmol). As the basic solution was added, the reaction mixture became pale yellow and more homogeneous. The reaction mixture was kept in an open beaker at room temperature for 16 days. As some of the water evaporated and the solution became more concentrated, colorless needles crystallized. The needles were isolated and air-dried. Yield: 1.291 g. A second crop of crystals was obtained from the yellow aqueous filtrate. Yield: 0.515 g. The total yield is 1.806 g (86%). *Anal.* Calc. for  $\text{C}_7\text{H}_{15}\text{NNaO}_8\text{V}$ : C, 26.7; H, 4.8; N, 4.4. Found: C, 26.9; H, 4.5; N, 4.5%. IR data: 3413 (vs), 2826 (m), 1639 (m), 1609 (s), 1583 (s), 1478 (s), 1443 (s), 1387 (m), 1348 (m), 1274 (w), 1226 (w), 1165 (m), 1096 (s), 1074 (vs), 916 (vs), 907 (vs), 791 (s), 661 (s), 648 (s), 530 (s).  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ): 5.48 (4H, s), 7.44 (2H, d,  $^3J_{\text{H-H}} = 8$  Hz), 8.03 (1H, t,  $^3J_{\text{H-H}} = 8$  Hz).  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ ): 77.8 (2C, t,  $^1J_{\text{C-H}} = 144$  Hz), 120.3 (2C, d,  $^1J_{\text{C-H}} = 173$  Hz), 144.5 (1C, d,  $^1J_{\text{C-H}} = 164$  Hz), 168.0 (2C, s).  $^{51}\text{V}$  NMR ( $\text{D}_2\text{O}$ ):  $-508$  (s).

#### 2.1.4. Hydration determinations

A sample of  $[\text{HVO}_2(\text{pydim})]_x$  (52.1 mg) was stored at 60 °C under a pressure of 2.5 Torr for 12 h. No change in the appearance of the sample was observed, and the mass of the sample was found to be 51.5 mg after the 12 h period.

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