Reaction Chemistry of BMOV, Bis(maltolato)oxovanadium(IV)—A Potent Insulin Mimetic Agent

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Abstract: The reaction chemistry of the potent insulin-mimetic agent bis(maltolato)oxovanadium(IV) (abbreviated **BMOV** or $VO(ma)_2$) is reported. $VO(ma)_2$ ($\log K_1 = 8.80(2)$, $\log K_2 = 7.51(2)$, $\log \beta_2 = 16.31(3)$) has a rich coordination chemistry, forming a number of V(IV) and V(V) derivatives. In aqueous solution it is slowly oxidized by molecular oxygen to $[VO_2(ma)_2]^-$ ($\log K_1 = 7.5(1)$, $\log K_2 = 6.2(1)$, $\log \beta_2 = 13.7(1)$); in alcohols a variety of V(V) analogs $VO(OR)(ma)_2$ ($R = CH_3$, C_2H_5, i-C_3H_7) are formed by aerial oxidation. All these vanadate complexes can be interconverted by reaction with the appropriate alcohol or water. In addition, the six-coordinate V(IV) pyridine adduct $VO(ma)_2py$ can be formed and this undergoes oxidation to V(V) complexes much more slowly, demonstrating that a vacant coordinate site is required for the coordination of O_2 to $VO(ma)_2$ before inner-sphere oxidation can take place. ^{51}V NMR and electrochemistry have been studied as a function of pH; a complete study of the aqueous chemistry of $VO(ma)_2$ and $[VO_2(ma)_2]^-$ has been undertaken because the oral activity of $VO(ma)_2$ as an insulin-mimetic may be related to the chemical properties of the two compounds in water. Oral gavage studies in STZ-diabetic rats have been performed which showed that the intact complex is required for activity and that the presence of a biologically compatible reducing agent, ascorbic acid, neither interferes with nor augments the insulin-mimetic effect of $VO(ma)_2$. The X-ray structures of $VO(ma)_2$ and the *cis*-VO_2 compound $K[VO_2(ma)_2]\cdot H_2O$ have been determined; crystals of $VO(ma)_2$ [BMOV] are monoclinic, $P2_1/n$, $a = 7.366(1)$, $b = 12.759(2)$, $c = 13.190(1)$ Å, $\beta = 97.31(1)°$, $Z = 4$, and those of $K[VO_2(ma)_2]\cdot H_2O$ are monoclinic, $P2_1/n$, $a = 7.1841(9)$, $b = 12.196(1)$, $c = 17.147(1)$ Å, $\beta = 96.64(1)°$, $Z = 4$. The structure of $VO(ma)_2$ was solved by direct methods and that of $K[VO_2(ma)_2]\cdot H_2O$ by the Patterson method. The structures were refined by full-matrix least-squares procedures to $R = 0.076$ and 0.033 ($R_w = 0.075$ and 0.034) for 1078 and 3232 reflections with $I \geq 3\sigma(I)$, respectively. $VO(ma)_2$ forms a square pyramid with the O_4 set from the two maltolato ligands in the base and the vanadyl V=O apical. $[VO_2(ma)_2]^-$ is roughly octahedral with a *cis*-$[VO_2]^+$ unit being completed by two ma^- ligands. The macroscopic structure is a chain with six-coordinate K^+ ions linking adjacent $[VO_2(ma)_2]^-$ units through coordination to the chelating ligand O atoms and water molecules.

Introduction

Over the past decade, numerous laboratories have reported on the insulin-mimetic properties of vanadate and vanadyl both *in vitro* and *in vivo*.[2-5] Since insulin is not active *per orum*, this has catalyzed great interest in the possible therapeutic value of vanadium as an orally active agent against diabetes mellitus. Among vanadium's most significant relevant *in vitro* effects in isolated tissues are increased glucose uptake and stimulation of glycogen synthesis in rat diaphragm, liver, and fat cells[6] and enhanced glucose transport and oxidation in rat adipocytes and skeletal muscle[7-9] as well as inhibition of lipolysis[10] and activation of lipogenesis in rat adipocytes.[11] Because type II diabetes (non-insulin-dependent diabetes mellitus—NIDDM—which affects millions of people worldwide) is characterized at least initially by hyperinsulinemia and insulin resistance, *not* insulin deficiency, it is highly significant that vanadium stimulates glucose metabolism without increasing the circulating concentration of insulin.

Systematic studies of the inhibitory effects of vanadium compounds on the Na^+-K^+ ATPase were initiated by Cantley and co-workers[12,13] in the late 1970s using sodium orthovanadate (actually $[H_2VO_4]^-/[HVO_4]^{2-}$ at ~pH 7). Vanadate acts as a transition state analogue of phosphate, i.e., it is a phosphate mimic; it also inhibits many other enzyme systems with

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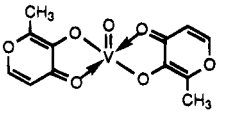
phosphoprotein intermediates.[14-22] Vanadyl has been shown to have a weaker effect but this may be entirely due to the presence or formation of low concentration of vanadate. In 1985, the *in vivo* insulin-mimetic effects of vanadate were first reported in the streptozotocin (STZ) diabetic rat.[23] There has been significant research activity on the insulin-like effects of vanadate; however, complications arise with the use of vanadate *in vivo*. Vanadate is poorly absorbed from the gastrointestinal tract into the blood and the necessary dosage is close to the toxic level. Subsequent work by McNeill and co-workers as well as other labs has shown that vanadyl sulfate was less toxic than vanadate but that it too is poorly absorbed.[2-5] It became evident that manipulation of the chemical form of the vanadium administered is necessary to allow for a less toxic, more easily absorbed agent which could be administered in a lower dose.

We first reported on the insulin-mimetic properties of bis-(maltolato)oxovanadium(IV) (commonly known by its acronym **BMOV** but abbreviated here as $VO(ma)_2$) in 1992[24] and have subsequently shown that it is effective and nontoxic over a six month period of administration in STZ-diabetic rats[25-27] and two to three times more potent than vanadyl sulfate.[28] The ligand maltol was chosen for its lack of toxicity (it is an approved food additive in both Canada and the U.S.A.) and for its ability, in separate (*in vivo*) studies, to mobilize other metal ions, such as aluminum,[29-31] gallium,[32] and iron.[33] By enhancing gastrointestinal absorption (through a passive diffusion process for a low-molecular weight water soluble, but neutrally charged and lipophilic complex), we desired to reduce toxicity by decreasing the amount of administered vanadium. Since the development of $VO(ma)_2$, its insulin-mimetic properties have been shown to be highly desirable—it displays considerable improvement in cardiac dysfunction in STZ-diabetic rats,[26] significant activity in the prevention of long-term diabetes induced pathology,[27] and attenuation of hyperinsulinemia and hypertension in genetically hypertensive (SHR) rats.[34]

There have been previous and concurrent attempts to modify the biological uptake of vanadium by changing the chemical form in which it is supplied from either vanadate or vanadyl. Work on peroxovanadate compositions as insulin mimics has involved coadministration *in vitro* of solution mixtures of vanadate and peroxide[2,35-37] and more recently of discrete mono- and diperoxovanadate chelate complexes.[38,39] The latter have been found to be very active *in vitro*,[39] but no *in vivo* data have been reported as yet (certainly none by oral administration). A variety of vanadyl complexes have been proposed[40-42] for the oral treatment of diabetes, although poor stability and low stability in water are two frustratingly simple problems which inhibit their utility.

It is apparent that $VO(ma)_2$ displays potentially useful properties; however, its reactivity and aqueous chemistry have



$VO(ma)_2$

never been completely explored, despite sporadic mentions in the literature. The direct electrochemical preparation of $VO(ma)_2$ was reported in 1978 although the compound was incompletely characterized;[43] its electron paramagnetic resonance spectrum has been reported twice,[44,45] and alkoxo-oxovanadium(V) derivatives of the maltolato anion (ma^-) ($VO(OR)ma_2$) have seen scattered mention since the 1960s.[46]

$VO(ma)_2$ is orally-active most likely due to the concomitant properties of neutral charge and water solubility and is therefore readily administrable in drinking water at mM concentrations. The preparation and testing of additional analogs with these properties, combined with further chemical studies of $VO(ma)_2$, should allow us to improve the efficacy of oral vanadium treatment. In order to better understand the action of $VO(ma)_2$ *in vivo*, the reactivity and the aqueous chemistry of this compound and some V(V) analogs, $[VO_2(ma)_2]^-$ and $VO(OR)(ma)_2$, have been undertaken and are presented here. It is expected that the insulin-mimetic action of $VO(ma)_2$ *in vivo* should be dependent on both its redox characteristics and its coordination chemistry; to this end, we have studied exhaustively

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the aqueous chemistry of $VO(ma)_2$ in an attempt to gain information which can be used to understand, and improve on, its function and reactivity in biological environments. $VO(ma)_2$ is highly active and nontoxic orally; therefore representing a potential breakthrough in the treatment of diabetes mellitus.

Experimental Section

Materials. Chemicals and solvents used were reagent grade (Fisher, Aldrich) and used without further purification unless otherwise noted. Water was deionized (Barnstead D8902 and D8904 cartridges) and distilled (Corning MP-1 Megapure Still) before use. $VOSO_4 \cdot 3H_2O$ was obtained from Aldrich, NH_4VO_3 from Sigma, and maltol (3-hydroxy-2-methyl-4-pyrone, Hma) from Sigma or Pfizer. The yields reported refer to isolated yields.

Instrumentation. Infrared (IR) spectra were recorded as KBr disks in the range 4000−400 cm^{-1} on a Perkin Elmer PE 783 spectrophotometer and were referenced to polystyrene film. Mass spectra (+ ion detection unless otherwise specified) were obtained with a Kratos MS 50 (electron-impact ionization, EI), a Kratos Concept II H32Q (Cs^+ liquid secondary ion mass spectrometry, LSIMS), or an AEI MS-9 (fast atom bombardment, FAB) instrument. UV−vis spectra were recorded on a Shimadzu UV-2100 spectrometer. Melting points were measured uncorrected with a Mel-Temp apparatus; however, unless otherwise noted, the vanadium complexes were nonvolatile charring and decomposing above 120 °C. Room temperature (293 K) magnetic susceptibilities were measured on a Johnson Matthey magnetic susceptibility balance, using $Hg[Co(NCS)_4]$ as the susceptibility standard; diamagnetic corrections were estimated by using Pascal's constants. Analyses for C, H, N were performed by Mr. Peter Borda in the UBC Chemistry Department.

NMR Spectroscopy. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200E, WM-400, or Varian XL-300 instruments. Chemical shifts are referenced to DSS for the proton spectra and an external reference of TMS in $CDCl_3$ for the carbon spectra. ^{51}V NMR spectra were recorded on a Varian XL-300 (100 kHz spectral width, 12 μs pulse angle, 0.02 s acquisition time) or a Bruker WM-400 (40 kHz spectral width, 60 μs pulse angle, 0.05 s acquisition time) spectrometer operating at 78.86 or 105.15 MHz, respectively, and are referenced to neat $VOCl_3$. Concentration studies were carried out in aqueous 1 M HEPES buffer solution using ^{51}V NMR spectroscopy. The vanadium spectra were treated with a polynomial baseline flattening routine (Bruker software) before integrals were obtained.

Electrochemistry. Cyclic voltammetric data were obtained using a Princeton Applied Research (PAR) Model 264 polarographic analyzer/stripping voltammeter and a PAR Model RE0089 X-Y recorder; measurements were carried out under an argon atmosphere at room temperature with solution concentrations of 10^{-3} M in complex $(VO)(ma)_2$ and $[VO_2(ma)_2]^-$ in water; $VO(OR)(ma)_2$ in CH_3CN with or without ROH, R = CH_3, C_2H_5, i-C_3H_7). The supporting electrolyte was 0.2 or 0.5 M tetraethyl ammonium perchlorate (TEAP) for nonaqueous solutions or 0.15 M sodium chloride for aqueous solutions. Voltammograms were recorded using a platinum working electrode, a platinum wire counter electrode, and an Ag/AgCl reference electrode checked periodically relative to a 10^{-3} M CH_3CN solution of ferrocene containing 0.1 M TEAP for which the ferrocenium/ferrocene reduction potential was 0.20 V and ΔE_p = 72 mV at a scan rate of 100 mV s^{-1}.

Potentiometric Equilibrium Measurements. Potentiometric measurements of maltol in the absence, and presence, of vanadyl ion were performed with a Fisher Acumet 950 pH equipped with an Orion Ross glass and calomel reference electrodes. The electrode was calibrated before each titration and, often afterwards, by titrating a known amount of aqueous HCl with a known concentration of NaOH. A plot of mV (measured) vs pH (calculated) gave a working slope and intercept so that the pH could be read as $-\log [H^+]$ directly. A Metrohm automatic burette (Dosimat 665) was used for the NaOH additions, and the burette and pH meter were interfaced to a PC such that each titration was automated. The temperature of the solutions in covered, water jacketed beakers was kept constant at 25.0 ± 0.1 °C by a Julabo circulating bath. The ionic strength was fixed at 0.15 M NaCl. Argon, which had been passed through 10% NaOH, was bubbled through the solutions to exclude CO_2.

The ligand was checked for purity by ^1H NMR and elemental analysis before titration. The vanadyl solution was prepared by dilution of its atomic absorption standard. Sodium hydroxide and sodium chloride were added to neutralize the excess acid present and to bring the ionic strength to 0.15 M Na^+. The vanadyl solution was then titrated with standardized NaOH from pH 2 to 2.5 to obtain the amount of excess acid present by Gran's method.[47] NaOH solutions (0.1 M) were prepared from dilution of 50% NaOH with freshly boiled distilled, deionized water, and standardized potentiometrically against potassium hydrogen phthalate.

The ratio of ligand to metal used was 1:10 < L:M < 10:1. Concentrations were in the range 1−10 mM. A total of six titrations were performed for maltol alone, and ten titrations defined the V(IV)−maltol equilibria. Maltol was titrated over the range 3 < pH < 9, while the vanadyl−maltol solutions were titrated from pH 2 to 4. Vanadium(IV) hydrolysis occurs above pH 4 when ligand to metal ratios are less than 2, and this hydrolysis is slow and ill defined. Also, in the higher pH regime, the vanadyl maltolate complexes and the vanadyl hydrolysis products were susceptible to oxidation. Complexation was rapid (1−3 min per point to give a stable pH reading) between pH 2 and 4; however, above pH 4, equilibrium was slow owing to hydrolysis/oxidation (*vide supra*).

The protonation constant for maltol and the vanadyl−maltol stability constants were determined by using the program BEST.[48] This program sets up simultaneous mass-balance equations for all the components present at each addition of base and calculates the pH at each data point according to the current set of stability constants and total concentrations of each component. The best fit of the data consisted simply of the two metal-ligand species $VO(ma)^+$ and $VO(ma)_2$. The hydrolysis species $VO(OH)^+$ and $[(VO)_2(OH)_2]^{2+}$ were included in the calculation,[49] but these did not form to any appreciable extent under the conditions employed. A plot of $\bar{n}$ ($\bar{n}$ = mol of bound ligand per mol of metal ion) vs $\log[ma^-]$ showed all the data coinciding to a single curve which plateaued at $\bar{n}$ = 2 indicative of a system in which only binary metal-ligand species prevail (see Figure 5). Typically 100 data points were collected in the buffer region of metal-ligand complexation.

Spectrophotometry. Since the 1:1 vanadyl maltolate complex was partially formed even at pH 2, variable pH spectrophotometry was employed to obtain an accurate value for the 1:1 stability constant. This was necessary since any error in the total acid concentration would be absorbed in this constant. Calculation of K_1 by variable pH spectrophotometry requires accurate knowledge of the total vanadium and maltol concentrations as well as accurate pH measurement but is independent of any excess acid present (from the vanadyl standard solution). From potentiometric measurements employing an excess of vanadyl ion, a range of K_1 values was obtained with low precision (±0.2 log units); however, this value was used to obtain the conditions in which the only species present were vanadyl, maltol, and $VO(ma)^+$. Using these conditions (L:M < 0.2, pH 2−3), the effect of pH on absorbance range 315−335 nm was studied. Neither vanadyl nor maltol absorb in this range, hence the change in absorbance was because of $VO(ma)^+$. The equilibrium constant was written in terms of $VO(ma)^+$ (eq 1).

$$K_1 = [VO(ma)^+][H^+]/K_a(C_{VO^{2+}} - [VO(ma)^+])(C_{Hma} - [VO(ma)^+]) \quad (1)$$

Here, K_a refers to the K_a of maltol and $C_{VO}{}^{2+}$ and C_{Hma} to the total vanadium and maltol concentrations, respectively. Since $[VO(ma)^+]$ = Abs/ϵ in the absorbance range studied, ϵ and K_1 could be varied iteratively as a function of pH until consistent results were reached. This was done at five wavelengths utilizing 11 pH points at 3 different L:M ratios to give consistent results.

Preparation of Complexes. Bis(maltolato)oxovanadium(IV), BMOV, $VO(ma)_2$. $VOSO_4 \cdot 3H_2O$ (50 g, 230 mmol) dissolved in 50 mL of hot water was added slowly to a solution of maltol (59 g, 468 mmol) dissolved in 250 mL of hot water. In order to bring the pH of the solution to ~8.5, KOH (26 g, 481 mmol) in 20 mL of water was slowly added (dropwise over 2 h). The resulting mixture was refluxed overnight, and, upon cooling to room temperature, a birefringent purple/green solid was collected by vacuum filtration. The solid was washed with 3 portions (100 mL) of cold water and dried overnight *in vacuo*.

The yield was 64 g, 88% based on V; the compound decomposes above 240 °C: IR (cm^{-1}, KBr disk) 1610, 1550, 1485 ($\nu_{C=O}$ and $\nu_{C=C}$); 995 ($\nu_{V=O}$); EIMS m/z = 317 (M^+, $[C_{12}H_{10}O_7V]^+$); UV−vis (H_2O) λ_{max} = 441 (ϵ = 90 M^{-1} cm^{-1}), 625 (15), 860 (30). The solid state magnetic moment was 1.72 μ_B. EPR (RT, $CHCl_3$): eight-line pattern, g_o = 1.963 ± 0.001, A_o = 103.7 ± 0.1 × 10^{-4} cm^{-1}. Solubility in water = 8.5 mM (under Ar). Anal. Calcd (found) for $C_{12}H_{10}O_7V$: C, 45.45 (45.47); H, 3.18 (3.16).

Bis(maltolato)oxo(pyridine)vanadium(IV), VO(py)(ma)$_2$·0.25H$_2$O. $VO(ma)_2$ (0.28 g, 0.88 mmol) was dissolved in neat pyridine (2 g, 25 mmol) left to stand for 2 days. Addition of 20 mL of diethyl ether followed by vigorous shaking of the solution led to precipitation of a brown solid, which was isolated by filtration, washed with 20 mL diethyl ether, and dried *in vacuo* to yield a brown powder (0.21 g, 61% based on V): IR (cm^{-1}, KBr disk) 1580 ($\nu_{C=O}$), 975 ($\nu_{V=O}$); FABMS: m/z = 398 ($[M + 1]^+$), 317 ($[M - py]^+$). The solid state magnetic moment was 1.75 μ_B. Anal. Calcd (found) for $C_{17}H_{15.5}NO_{7.25}V$: C, 50.95 (50.98); H, 3.83 (3.90); N, 3.47 (3.50).

***cis*-Bis(maltolato)methoxyoxovanadium(V), *cis*-VO(OCH$_3$)(ma)$_2$.** $VO(ma)_2$ (5 g, 16 mmol) was dissolved in 50 mL of methanol and stirred in air for 24 h. The solution was cooled overnight at −35 °C, and the bright red crystalline product was collected by filtration. The yield was 3.8 g, 70% based on V; the compound decomposes above 160 °C. This reaction is greatly accelerated by adding an excess (3−6 equiv) of H_2O_2 (reaction times of 15−30 min): IR (cm^{-1}, KBr disk) 1620, 1550, 1480 ($\nu_{C=O}$ and $\nu_{C=C}$); 975 (s, $\nu_{V=O}$); FABMS m/z = 348 (M^+, $[C_{13}H_{13}O_8V]^+$); ^1H NMR (CD_3OD) 2.45 (s, 6H), 3.34 (s, 3H), 6.45 (d, 2H, ^3J = 5.5 Hz), 8.18 (d, 2H, ^3J = 5.5 Hz). A low temperature ^1H NMR experiment clearly showed the two unique maltol ligand environments (*vide infra*). $E_{1/2}$ (V vs Ag/AgCl) = 0.11 rev, −0.45 irrev; −0.20 rev (excess MeOH); ^{51}V NMR −413 ($CHCl_3$), −421 (MeOH, excess Hma), −423 (toluene); UV−vis (MeOH, excess Hma) λ_{max} = 448 (ϵ = 3700 M^{-1} cm^{-1}). Anal. Calcd (found) for $C_{13}H_{13}O_8V$: C, 44.83 (44.88); H, 3.76 (3.74). The compound is diamagnetic.

cis-$VO(OCH_3)(ma)_2$ was also prepared from $VO(py)(ma)_2$. Brown $VO(py)(ma)_2$ (0.16 g, 0.4 mmol) was dissolved in 30 mL of methanol, the clear red solution was stirred in air for 2 days, and the volume was subsequently reduced to 5 mL by rotary evaporation. Following the addition of 25 mL of diethyl ether, the solution was stored at 5 °C for a week. The bright red precipitate was isolated, washed with diethyl ether, and dried *in vacuo* to yield 0.048 g, 34% based on V.

***cis*-Ethoxybis(maltolato)oxovanadium(V), *cis*-VO(OC$_2$H$_5$)(ma)$_2$.** $VO(ma)_2$ (5 g, 16 mmol) was dissolved in 50 mL of ethanol and stirred in air for 3 days. The solution was cooled overnight at −35 °C, and the bright red crystalline product was collected by filtration. The yield was 4.9 g, 86% based on V; the compound melts at 140 °C. This reaction is greatly accelerated using an excess (3−6 equiv) of H_2O_2 (reaction times of 15−30 min): IR (cm^{-1}, KBr disk) 1620, 1580, 1520, 1480 ($\nu_{C=O}$ and $\nu_{C=C}$); 970 (s, $\nu_{V=O}$); FABMS m/z = 361 (M^+, $[C_{14}H_{15}O_8V]^+$), 345; ^1H NMR ($CDCl_3$) 1.48 (t, 3H, ^3J = 7.5 Hz), 2.45 (s, 6H), 5.8 (q, 2H, ^3J = 7.5 Hz), 6.47 (br, 2H), 7.8 (br, 2H); $E_{1/2}$ (V vs Ag/AgCl) = 0.12 rev, −0.46 irrev; −0.29 rev (excess EtOH); ^{51}V NMR (EtOH) −430 (excess Hma); UV−vis (EtOH, excess Hma) λ_{max} = 445 (ϵ = 3690 M^{-1} cm^{-1}). Anal. Calcd (found) for $C_{14}H_{15}O_8V$: C, 46.42 (46.47); H, 4.17 (4.20). The compound is diamagnetic.

***cis*-Bis(maltolato)oxoisopropoxovanadium(V), *cis*-VO(O*i*-C$_3$H$_7$)(ma)$_2$).** $VO(ma)_2$ (5 g, 16 mmol) was dissolved in 50 mL of isopropyl alcohol and stirred in air for 8 days. The solution was cooled overnight at −35 °C, and the bright red crystalline product was collected by filtration. The yield was 5.4 g, 91% based on V; the compound decomposes above 160 °C. This reaction is greatly accelerated using an excess (3−6 equiv) of H_2O_2 (reaction times of 15−30 min): IR (cm^{-1}, Kbr disk) 1585 (s, $\nu_{C=O}$); 965 (s, $\nu_{V=O}$); EIMS m/z = 375 ($[M - H]^+$); ^1H NMR ($CDCl_3$) 148 (d, 6H, ^3J = 6 Hz), 2.48 (s, 6H), 6.40 (septet, 1H, ^3J = 6 Hz), 6.48 (br, 2H), 7.78 (br, 2H); $E_{1/2}$ (V vs Ag/AgCl) = 0.12 rev, −0.48 irrev; ^{51}V NMR (isopropyl alcohol) −445 (excess Hma); UV−vis (isopropyl alcohol, excess Hma) λ_{max} = 440 (ϵ = 3680 M^{-1} cm^{-1}). Anal. Calcd (found) for $C_{15}H_{17}O_8V$: C, 47.89 (48.10); H, 4.55 (4.60). The compound is diamagnetic.

Ammonium *cis*-Bis(maltolato)dioxovanadate(V), [NH$_4$] *cis*-[VO$_2$(ma)$_2$]·H$_2$O. To a solution of NH_4VO_3 (5 g, 42.7 mmol) in 15 mL of water was added maltol (10.8 g, 85.6 mmol), and the resulting solution was allowed to stir overnight in air. A yellow solid was collected by filtration and dried *in vacuo*. Heating the reaction results in decomposition. The yield was 11 g, 70% based on V. IR (cm^{-1}, KBr disk) 1585 (s, $\nu_{C=O}$); 910, 875 (s, $\nu_{V=O}$); LSIMS m/z = 369 ($[M + NH_4]^+$); ^1H NMR (D_2O) 2.28 (s, 6H), 6.45 (d, 2H, ^3J = 5 Hz), 8.00 (d, 2H, ^3J = 5 Hz); ^{51}V NMR (H_2O) −496; UV−vis (H_2O, excess Hma) λ_{max} = 410 (ϵ = 420 M^{-1} cm^{-1}). Anal. Calcd (found) for $C_{12}H_{16}NO_9V$: C, 39.04 (39.13); H, 4.37 (4.36), N, 3.79 (3.72). The compound is diamagnetic.

Potassium *cis*-Bis(maltolato)dioxovanadate(V), K *cis*-[VO$_2$(ma)$_2$]·H$_2$O. To a solution of a $VO(OR)(ma)_2$ complex (R = CH_3, C_2H_5) (50 mmol) in 15 mL of the appropriate alcohol (ROH) was added KOH (7 g, 125 mmol) in a minimum amount of water. The solution was allowed to stir for 30 min. A yellow solid was collected by filtration and dried *in vacuo* (heating the reaction results in decomposition). The yield was 6 g, 30% based on V; the compound decomposes above 120 °C. IR (cm^{-1}, KBr disk): 1585 (s, $\nu_{C=O}$); 905, 890 (s, $\nu_{V=O}$). LSIMS: m/z = 376 (M^+, $(K[VO_2(ma)_2])^+$). Anal. Calcd (found) for $C_{12}H_{12}KO_9V$: C, 36.93 (36.96); H, 3.10 (3.00). The other characterization was similar to that for the ammonium salt.

μ-Oxobis[bis(maltolato)oxovanadium(V)], V$_2$O$_3$(ma)$_4$. Treatment of $[VO_2(ma)_2]^-$ or any of the vanadate esters $VO(OR)(ma)_2$ (R = CH_3, C_2H_5, *i*-C_3H_7) in wet alcohols with a small amount of water at pH 4 led to the precipitation of the purple product in moderate yield (~20−40%): IR (cm^{-1}, KBr disk) 1590 (s, $\nu_{C=O}$): 965, 760, 710, 620 (s, $\nu_{O=V-O-V=O}$); LSIMS m/z = 604, 317 ($[VO(ma)_2]^+$). Anal. Calcd (found) for $C_{24}H_{20}O_{15}V_2$: C, 44.33 (44.18); H, 3.10 (3.06). ^1H or ^{51}V NMR or UV−vis were not obtained as the compound is unstable with respect to vanadate and/or $[VO_2(ma)_2]^-$ in water. It is diamagnetic.

X-ray Crystallographic Analyses of VO(ma)$_2$ and K[VO$_2$(ma)$_2$]·H$_2$O. Crystallographic data appear in the supporting information. The final unit-cell parameters were obtained by least-squares on the setting angles for 25 reflections with 2θ = 18.2−24.4° for $VO(ma)_2$ and 43.4−49.0° for $K[VO_2(ma)_2]\cdot H_2O$. The intensities of three standard reflections, measured every 200 reflections throughout the data collections, showed only small random fluctuations in each case. The data were processed[47-50] and corrected for Lorentz and polarization effects and absorption (empirical, based on azimuthal scans for three reflections).

The structure of $VO(ma)_2$ was solved by direct methods and that of $K[VO_2(ma)_2]\cdot H_2O$ was solved by conventional heavy atom methods, the coordinates of the V and K atoms being determined from the Patterson function and those of the remaining non-hydrogen atoms from subsequent difference Fourier syntheses. The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms associated with the water molecule in $K[VO_2(ma)_2]\cdot H_2O$ were placed in difference map positions but were not refined. The remaining hydrogen atoms were fixed in calculated positions with C−H = 0.98 Å and $B_H = 1.2\ B_{bonded\ atom}$. Difference maps suggested 1:1 orientational disorder of both methyl groups in $K[VO_2(ma)_2]\cdot H_2O$—this was incorporated into the model. A secondary extinction correction was applied for $K[VO_2(ma)_2]\cdot H_2O$, the final value of the extinction coefficient being 4.8(5) × 10^{-7}. Neutral atom scattering factors and anomalous dispersion corrections were taken from the *International Tables for X-ray Crystallography*.[51]

There was a rather large residual peak (1.6 e $Å^{-3}$) in the final difference map of $VO(ma)_2$, located 2.1 Å from the vanadium atom, but only 1.8 Å from a methyl carbon atom of a neighboring molecule. This peak and the relatively high agreement factors are consistent with the presence of a minor twin component in the crystal used for data collection. The residual peak is probably a "ghost" of the vanadium atom arising from the minor twin component. It was very difficult obtaining crystals of $VO(ma)_2$ suitable for X-ray studies. Although

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Table 1. Selected Bond Distances (Å) and Angles (deg) in $VO(ma)_2$ with Estimated Standard Deviations

Bond Distances (Å)

atom	atom	distance	atom	atom	distance
V(1)	O(2)	1.971(8)	V(1)	O(3)	1.998(8)
V(1)	O(5)	1.958(8)	V(1)	O(6)	2.024(8)
V(1)	O(7)	1.596(7)	O(2)	C(3)	1.36(1)
O(3)	C(4)	1.29(1)	O(5)	C(9)	1.36(1)
O(6)	C(10)	1.27(1)	C(3)	C(4)	1.39(2)
C(9)	C(10)	1.42(2)			

Bond Angles (deg)

atom	atom	atom	angle	atom	atom	atom	angle
O(2)	V(1)	O(3)	82.5(4)	O(2)	V(1)	O(5)	140.6(3)
O(2)	V(1)	O(6)	87.6(4)	O(2)	V(1)	O(7)	108.7(4)
O(3)	V(1)	O(5)	86.3(4)	O(3)	V(1)	O(6)	146.8(3)
O(3)	V(1)	O(7)	107.0(5)	O(5)	V(1)	O(6)	81.5(3)
O(5)	V(1)	O(7)	110.6(4)	O(6)	V(1)	O(7)	106.1(5)
V(1)	O(3)	C(4)	112.9(8)	V(1)	O(2)	C(3)	108.1(7)
V(1)	O(5)	C(9)	111.9(7)	V(1)	O(6)	C(10)	112.3(8)
O(2)	C(3)	C(4)	120(1)	O(5)	C(9)	C(10)	115(1)
O(3)	C(4)	C(3)	114(1)	O(6)	C(10)	C(9)	117(1)

Table 2. Selected Bond Distances (Å) and Angles (deg) in $K[VO_2(ma)_2]\cdot H_2O$ with Estimated Standard Deviations[a]

Bond Distances (Å)

atom	atom	distance	atom	atom	distance
V(1)	O(2)	1.963(1)	V(1)	O(3)	2.276(2)
V(1)	O(5)	1.999(1)	V(1)	O(6)	2.189(2)
V(1)	O(7)	1.633(2)	V(1)	O(8)	1.643(2)
O(3)	C(4)	1.258(2)	O(5)	C(9)	1.329(3)
O(6)	C(10)	1.256(3)	O(2)	C(3)	1.330(2)
C(3)	C(4)	1.440(3)	C(9)	C(10)	1.437(3)
K(1)	O(2)′	2.706(1)	K(1)	O(5)	2.814(2)
K(1)	O(7)′	2.867(2)	K(1)	O(7)″	2.872(2)
K(1)	O(8)	2.899(2)	K(1)	O(8)″	2.740(2)
K(1)	O(9)	3.042(3)			

Bond Angles (deg)

atom	atom	atom	angle	atom	atom	atom	angle
O(2)	V(1)	O(3)	76.69(5)	V(1)	O(2)	K(1)*	102.77(6)
O(2)	V(1)	O(5)	155.62(6)	V(1)	O(2)	C(3)	117.9(1)
O(2)	V(1)	O(6)	85.14(6)	V(1)	O(3)	C(4)	109.7(1)
O(2)	V(1)	O(7)	93.89(7)	V(1)	O(5)	K(1)	102.06(6)
O(2)	V(1)	O(8)	102.00(7)	V(1)	O(5)	C(9)	116.8(1)
O(3)	V(1)	O(5)	83.00(6)	V(1)	O(6)	C(10)	112.5(1)
O(3)	V(1)	O(6)	75.74(6)	O(5)	V(1)	O(6)	76.82(6)
O(3)	V(1)	O(7)	164.94(7)	O(5)	V(1)	O(7)	102.88(7)
O(3)	V(1)	O(8)	89.88(7)	O(5)	V(1)	O(8)	91.19(7)
O(6)	V(1)	O(7)	91.95(7)	V(1)	O(8)	K(1)	109.37(7)
O(6)	V(1)	O(8)	162.17(7)	V(1)	O(8)	K(1)″	102.28(7)
O(7)	V(1)	O(8)	103.70(8)	V(1)	O(7)	K(1)″	97.39(7)
V(1)	O(7)	K(1)*	106.39(7)	O(2)	C(3)	C(4)	117.2(2)
O(3)	C(4)	C(3)	118.1(2)	O(5)	C(9)	C(10)	116.3(2)

[a] Symmetry operations: (′) $x-1, y, z$; (″) $-x, 1-y, 1-z$; (*) $x+1, y, z$.

Table 3. Hydrogen Bond Data for $K[VO_2(ma)_2]\cdot H_2O$[a]

interaction	D−H (Å)	H···A (Å)	D···A (Å)	D−H···A (deg)
O(9)−H(1)···O(8)	1.08	1.81	2.783(3)	148
O(9)−H(2)···O(5)[1]	1.05	1.89	2.922(3)	165
C(11)−H(11)···O(9)[2]	0.98	2.29	3.112(3)	141

[a] Superscripts refer to symmetry operations: (1) $-x, 1-y, 1-z$; (2) $1/2+x, 1/2-y, z-1/2$.

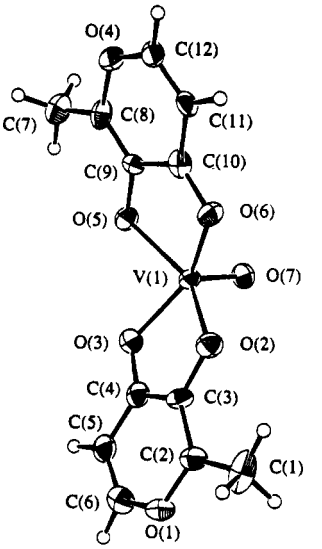


Figure 1. ORTEP view of $VO(ma)_2$. Ellipsoids are shown at the 33% probability level.

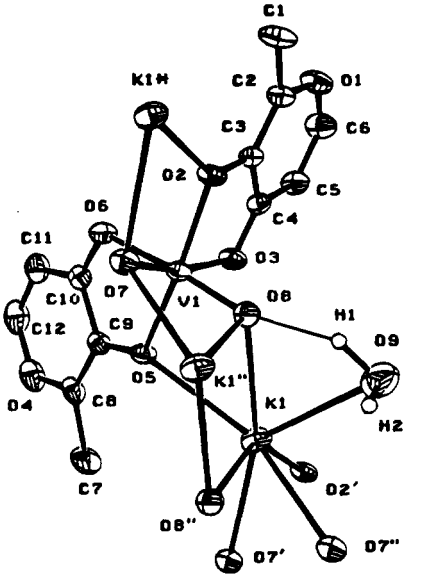


Figure 2. ORTEP view of $K[VO_2(ma)_2]\cdot H_2O$. Ellipsoids are shown at the 33% probability level.

the crystals appeared to be good, they invariably displayed very broad or split diffraction maxima suggesting twinning. The crystal used for data collection was carefully cleaved, under a polarizing microscope, along a twin boundary and showed sharper diffraction peaks than any other crystal examined (average ω peak width at half-height = 0.37° compared with values of 0.60−1.4° for the other specimens). The resulting structure, although not particularly accurate, is sufficient to establish the *trans* structure of $VO(ma)_2$ (Figure 1).

Selected bond lengths and angles for each complex and details of the hydrogen-bonding in $K[VO_2(ma)_2]\cdot H_2O$ appear in Tables 1−3, respectively. ORTEP representations of $VO(ma)_2$ and $K[VO_2(ma)_2]\cdot H_2O$ appear in Figures 1 and 2, respectively. Complete tables of crystallographic data, bond lengths and angles, final atomic coordinates and equivalent isotropic thermal parameters, hydrogen atom coordinates, anisotropic thermal parameters, bond lengths and angles involving hydrogen, torsion angles, intermolecular contacts, and least-squares planes are included as supporting information.

Gavage of STZ-Diabetic Rats—Effect of Intact $VO(ma)_2$. Forty-eight male Wistar rats weighing between 190 and 220 g were obtained from the Animal Care Unit at U.B.C. Animals were housed two rats per cage, were on a 12 h light/dark schedule, and were allowed *ad libitum* access to food (Purina Lab Chow) and fluid. Diabetes was induced by a single intravenous tail vein injection of STZ 60 mg kg^{-1} in 0.9% NaCl. Intravenous injections were done under light halothane anaesthesia. The diabetic state was confirmed 3 days following the STZ injection by a blood glucometer test using an Ames glucometer. Blood glucose levels greater than 13 mM were taken as diabetic. All treatment protocols were initiated 7 days following the STZ injection.

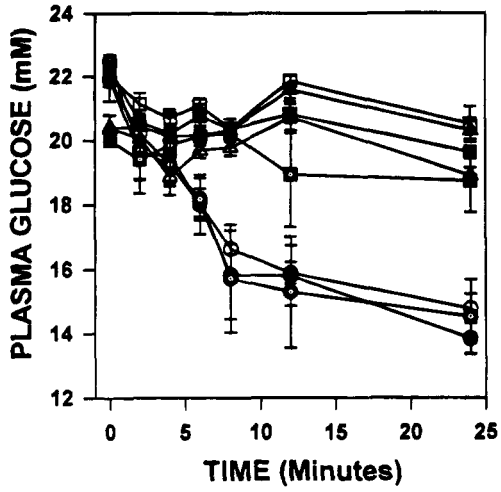


Figure 3. Plasma glucose values over time following the oral gavage administration of a single dose. A 10-fold excess of Hma was administered either preceeding or following treatment with vanadium-(IV) as vanadyl sulfate (VS) or $VO(ma)_2$. The doses of the compounds administered were $VO(ma)_2$ 0.4 mmol kg^{-1}, VS 0.4 mmol kg^{-1}, Hma 4 mmol kg^{-1}, or 3% gum arabic. The eight experimental groups were $VO(ma)_2$ (●, $n = 6$), Hma preceeding $VO(ma)_2$ (O, $n = 6$), $VO(ma)_2$ preceeding Hma (⊙), $n = 6$), VS (■, $n = 6$), Hma preceeding VS (□, $n = 6$), VS preceeding Hma (⊡, $n = 6$), Hma (▲, $n = 6$), and 3% gum arabic (△, $n = 6$). * Significantly different $p < 0.05$.

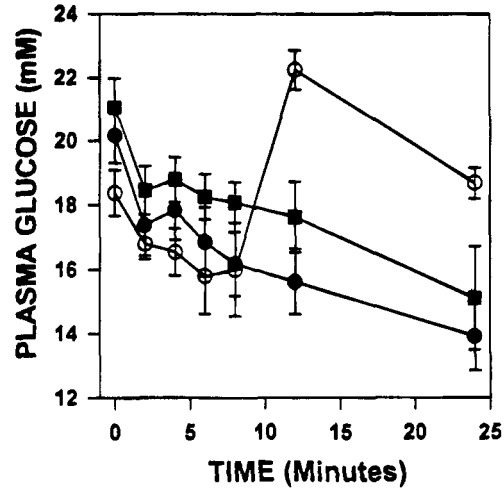


Figure 4. Acute study of plasma glucose response to oral gavage administration of $VO(ma)_2$ 0.4 mmol kg^{-1} alone and in the presence of 10% ascorbic acid ($VO(ma)_2$, ●, $n = 16$; 10% ascorbic acid, O, $n = 6$; $VO(ma)_2$ plus 10% ascorbic acid, ■, $n = 18$).

Blood for analysis of plasma glucose levels was done by nicking the tip of the tail and expressing blood into heparinized capillary tubes. The blood was centrifuged at 10 000 × g for 15 min, and the plasma was collected and immediately analyzed for plasma glucose determination using a Boehringer Mannheim kit (glucose oxidase method).

Animals were randomly divided into eight treatment groups as shown in Figure 3. The compounds administered were vanadyl sulfate (VS) 0.4 mmol kg^{-1}, $VO(ma)_2$ 0.4 mmol kg^{-1}, maltol (Hma) 4 mmol kg^{-1} (10 equiv), and 3% Gum Arabic. VS was administered as a solution dissolved in water, and $VO(ma)_2$ was administered as a suspension in 3% Gum Arabic. Each administration was given as a single gavage dose. The eight treatment groups were VS, $VO(ma)_2$, Hma, Gum Arabic, and VS or $VO(ma)_2$ plus Hma (either preceeding or following vanadium administration). Blood was collected immediately before administration and at 2, 4, 6, 8, 12, and 24 h following administration. Values are presented as means ± standard error of the means. Analysis of variance (ANOVA) was done followed by Newman–Keuls with a probability less than 0.05 taken as significant.

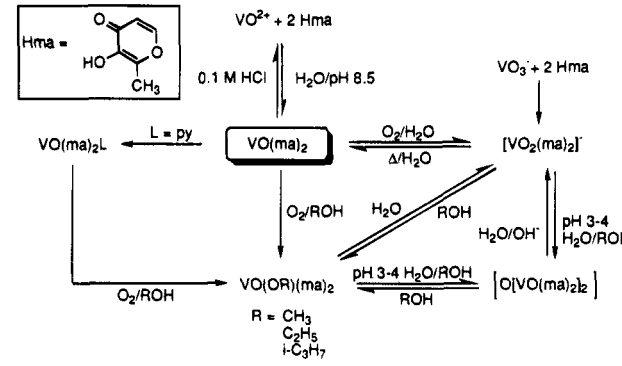
Gavage of STZ-Diabetic Rats—Effect of Ascorbate-Preserved Solution. Fifty-eight male diabetic Wistar rats were randomly divided into five treatment groups: 5% (w/w) ascorbic acid ($n = 6$), 10% ascorbic acid ($n = 6$), $VO(ma)_2$ plus 5% ascorbic acid ($n = 18$), $VO(ma)_2$ plus 10% ascorbic acid ($n = 12$), and $VO(ma)_2$ ($n = 16$). Diabetes induction, treatment protocol, solution preparation, and plasma glucose analysis were done as described above. The dose of $VO(ma)_2$ was 0.4 mmol kg^{-1}. Blood was collected immediately before administration and at 2, 4, 6, 8, 12, and 24 h following administration. Data for the 10% ascorbic acid, $VO(ma)_2$, and $VO(ma)_2$ plus 10% ascorbic acid groups are shown in Figure 4.

Results and Discussion

$VO(ma)_2$. $VO(ma)_2$ can be prepared in large amounts in >90% yield in water by combining maltol (3-hydroxy-2-methyl-4-pyrone) and vanadyl sulfate (2:1), raising the pH of the solution to 8.5, refluxing overnight, and collecting the deep purple-green (birefringent) compound which precipitates upon cooling. The routine characterization of $VO(ma)_2$ was as expected (elemental analysis and IR and mass spectra).

$VO(ma)_2$ is paramagnetic in the solid state (1 upe), and in nonpolar solvents with the expected eight-line EPR spectrum ($CHCl_3$, $g_o = 1.963 \pm 0.001$, $A_o = 103.7 \pm 0.1 \times 10^{-4}$ cm^{-1}),

Scheme 1



but this is complicated in most other solvents, including water, by the presence of solvates and ligand orientational isomers.[52] In the presence of excess Hma, $VO(ma)_2$ is slowly and cleanly oxidized by molecular oxygen[53] in aerobic water ($t_{1/2} \sim 24$ h) to the diamagnetic bis(maltolato)dioxovanadate(V) monoanion $[VO_2(ma)_2]^-$ (^{51}V NMR $\delta = -496$) or in aerobic alcohols to $VO(OR)(ma)_2$ R = CH_3, C_2H_5, i-C_3H_7, all of which have been separately synthesized and characterized (see below and Scheme 1). The oxidation of $VO(ma)_2$ in either water or alcohols can be slowed dramatically in the presence of good donor ligands by the formation of six coordinate adducts such as $VO(ma)_2py$, and it could be indefinitely suppressed with 5–10 equiv of ascorbic acid. The oxidation could be speeded up dramatically by iodosobenzene or hydrogen peroxide; however, no peroxovanadate species were ever detected under the experimental conditions (~3–6 equiv H_2O_2) despite a very careful search, peroxovanadate complexes being both ubiquitous[54] and of interest as insulin mimics in their own right.[39]

The window of stability to hydrolysis of $VO(ma)_2$ was deduced from the UV/vis spectrum; in the region $3 < pH < 8$, the spectrum (and therefore the ligand environment around the VO^{2+} center) remained relatively constant and was consistent with an O_4 or an O_5 ligand donor set.[55] Above pH >9, changes in the spectrum suggested hydrolysis and/or oxidation of

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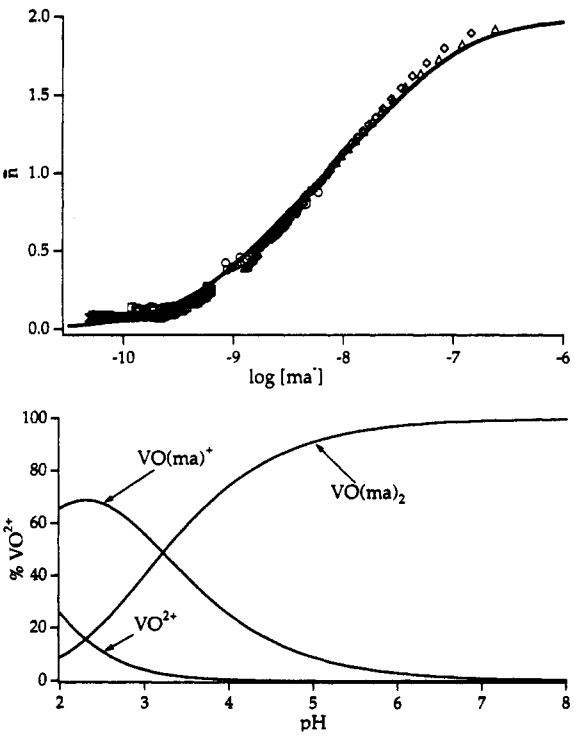

Figure 5. Titration curve as a plot of $\bar{n}$ vs the logarithm of the free ligand concentration for L:M ratios ranging from 0.17 to 10 (top) and speciation diagram (bottom) for the VO^{2+}/Hma system.

vanadyl.[56] In acidic or basic solutions, different environments were observed, corresponding to aqua and hydrolyzed/oxidized species. The spectrum of $VO(ma)_2$ was consistent with those previously discussed in detail for vanadyl:ligand 1:2 complexes.[57,58]

$$H^+ + ma^- \rightleftharpoons Hma \quad \log K_a = 8.46(2) \qquad (2)$$

$$VO^{2+} + ma^- \rightleftharpoons VO(ma)^+ \quad \log K_1 = 8.80(2) \qquad (3)$$

$$VO(ma)^+ + ma^- \rightleftharpoons VO(ma)_2 \quad \log K_2 = 7.51(2) \qquad (4)$$

$$VO^{2+} + 2ma^- \rightleftharpoons VO(ma)_2 \quad \log \beta_2 = 16.31(3) \qquad (5)$$

The solution equilibria in the vanadyl−maltol system were studied in the pH range 2−4 to avoid any problems with hydrolysis or oxidation. This pH range was adequate for determining the 1:1 and 2:1 formation constants since maltol is a strong chelator. The stability constants determined are shown in eqs 2−5 (the number in parentheses refers to 3σ in the last digit). Figure 5 shows a plot of $\bar{n}$ vs the logarithm of the free ligand concentration for L:M ratios ranging from 0.17 to 10. The coincidence of all the data to one curve is indicative of the high quality of the data collected and shows that there are only binary metal-ligand species present (namely ML and ML_2) and no protonated or hydroxo complexes in the pH range studied.[59] Although $K_1 > K_2$, at a 2:1 ratio, the 1:1 species dominates only at low pH, and the dominant species at physiological pH under reducing conditions should be BMOV, as shown by a speciation diagram extrapolated to pH 8 (Figure 5). The speciation diagram is consistent with the variable pH optical spectra.

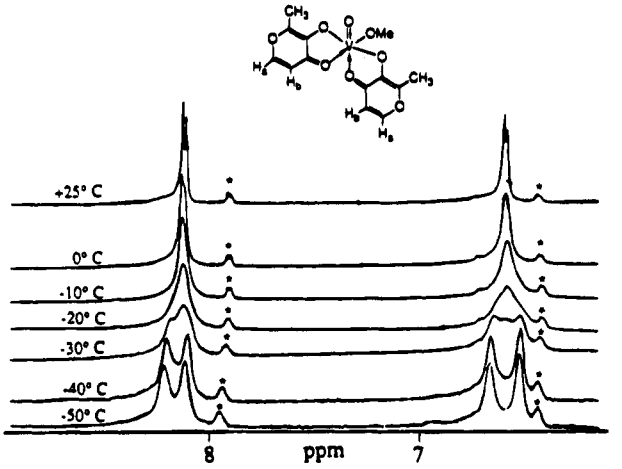

Figure 6. Variable temperature ^1H NMR spectra of the ring hydrogens in $VO(OCH_3)(ma)_2$ (CD_3OD, * = Hma).

Structure of $VO(ma)_2$. Crystals of $VO(ma)_2$ suitable for X-ray diffraction eluded us for several years, most samples having a ligand orientation disorder (*cis/trans* about the base of the square pyramid); a similar orientational disorder was seen in the structure of $Al(ma)_3$ several years ago.[60] The *cis* and *trans* isomers are in equilibrium in solution, and it is likely that after years of trying, we simply crystallized the *trans* isomer first. (Detailed solution EPR studies of $VO(ma)_2$ in a variety of solvents will be published elsewhere.[52])

The structure of $VO(ma)_2$, although not particularly accurate, is sufficient to establish the *trans* structure of $VO(ma)_2$ in the solid state (Figure 1). It is a fairly straightforward square pyramidal structure with the two maltolato ligands in a *trans* arrangement around the base of the square pyramid and the V=O unit axial. The V=O distance of 1.597(7) is consistent with vanadyl distances in related complexes; the maltolato intraligand distances, although an order of magnitude less accurate, are consistent with those we have seen in related structures.[60,61] Interestingly, although the corresponding interatomic distances in each ligand are not significantly different, the V−O(hydroxo) and V−O(keto) distances V(1)−O(5) (1.959(8) Å) and V(1)−O(6) (2.024(8) Å) are significantly different from one another and are much better resolved than their analogs in the other ma^- ligand (V(1)−O(2) (1.971(8) Å) and V(1)−O(3) (1.998(8) Å)).

Reaction Chemistry. The reaction chemistry of $VO(ma)_2$ as elucidated in this study is found in Scheme 1. The oxidation of $VO(ma)_2$ in H_2O and methanol has been separately studied, and its kinetics are the subject of a separate submission.[53]

As noted above, $VO(ma)_2$ is slowly oxidized[53] in aerobic water ($t_{1/2} \sim 24$ h) to $[VO_2(ma)_2]^-$, or in aerobic alcohols to $VO(OR)(ma)_2$ R = CH_3, C_2H_5, i-C_3H_7. These species are respectively analogous to vanadate carboxylate and vanadate esters (a correlation previously noted by Floriani and coworkers).[62] As well, by judicious choice of conditions the acid anhydride analog $V_2O_3(ma)_4$ can be prepared, although its solution stability was extremely limited to very concentrated solutions. The characterization of $V_2O_3(ma)_4$ was complete (consistent analysis, μ-O IR stretches); however, it is much less robust than any other species reported in Scheme 1.

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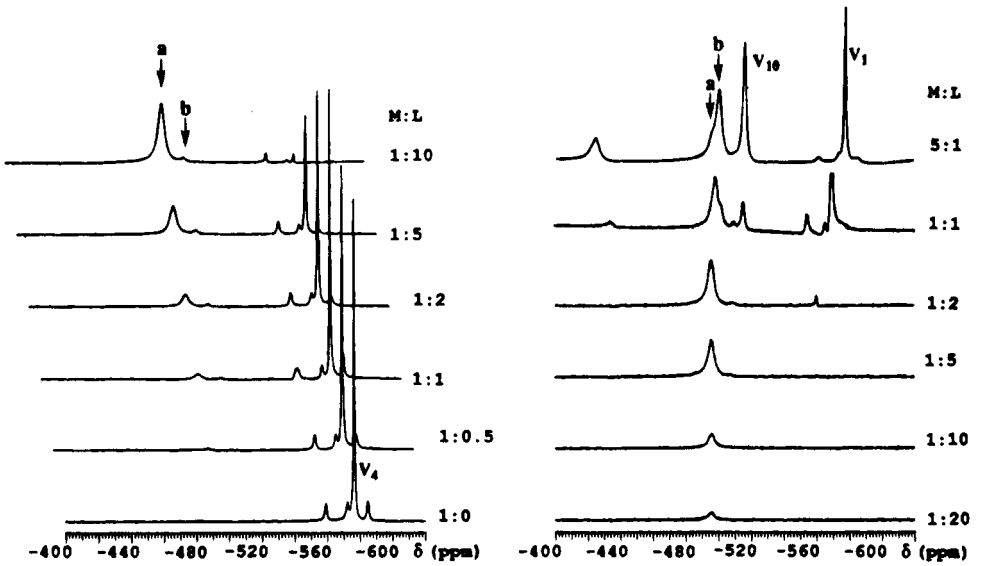

Figure 7. Variable ratio ^{51}V NMR spectra of the vanadate/maltol system. Hma (0−100 mM) added to 10 mM vanadate pH 7 (left) and vanadate (0−50 mM) added to 10 mM Hma pH 5.5 (right); 0.15 M NaCl, 25 °C, under Ar in both cases.

^{51}V NMR was used to monitor the formation of the appropriate vanadate ester complexes in the appropriate alcohol. The ^{51}V NMR chemical shifts were invariant in the presence of excess maltol; in wet alcohol slow conversion to $[VO_2(ma)_2]^-$ and vanadate was observed. The characteristic ^{51}V NMR chemical shifts of each ester could also be used to monitor transesterification reactions by changing the alcohol (e.g., $VO(OCH_3)(ma)_2$ in C_2H_5OH quantitatively gave $VO(OC_2H_5)(ma)_2$ in the presence of excess Hma). Excess Hma and alcohol were both required to prevent hydrolysis to $[VO_2(ma)_2]^-$ and its monomaltolato analog $VO_2(ma)(H_2O)_2$ (*vide infra*) as well as to suppress the formation of trace amounts of $VO(OR)_3$. $[VO_2(ma)_2]^-$ and $VO(OR)(ma)_2$ could be quantitatively interconverted by dissolution in alcohol or water, respectively; again excess Hma kept these interconversions simple otherwise small amounts of $VO_2(ma)(H_2O)_2$ were detected (^{51}V NMR δ = −509, varied with pH according to the deprotonation of bound H_2O). Dissolution of $[VO_2(ma)_2]^-$ or $VO(OR)(ma)_2$ in boiling water gave ~75% recovery of $VO(ma)_2$ presumably from oxidation of maltol or alcohol. Electrochemical results showed all the maltolato−V(V) complexes to be reasonable reducing agents (*vide infra*).

A variable temperature ^1H NMR study of $VO(OCH_3)(ma)_2$ in CD_3OD (Figure 6) clearly shows the one environment for the maltolato ligand at room temperature (one doublet for each of the ring hydrogens H_a at 8.18 and H_b at 6.45 ppm) and the two separate environments at −50 °C for H_a as the 8.18 peak is split into what is presumably two overlapping doublets, as does the 6.45 ppm peak for H_b. This would sugest a *cis*-$VO(OCH_3)$ structure with the two maltolato ligands also *cis* as shown in Figure 6, and we have recently found this to be true in the solid state by an X-ray determination.[53]

A few of these observations were reported in a study by Stewart and Porte nearly 25 years ago as part of an EPR investigation of VOL_2 complexes.[44] They postulated the existence of a sixth coordinate ligand *trans* to the V=O in complexes of VO^{2+} with maltol and other ligands; they also postulated the reversible oxidation of $VO(ma)_2$ in water or alcohols to "*trans*-VO(OH) or -VO(OR)" species of V(V). We have now unambiguously shown these to be the *cis*-$[VO_2(ma)_2]^-$ and *cis*-$VO(OR)(ma)_2$, respectively. The oxidant in their study was presumed to be dissolved oxygen, a correct assumption on their part.[53] Initial oxygen substitution might occur in the *trans* position to V=O, since that coordination site is open in the square pyramidal $VO(ma)_2$, followed by apical to basal rearrangement to form a *cis* product. Stewart and Porte also noted that no evidence was found for dimer formation.[44]

Despite careful searching, no evidence was found for peroxovanadate species upon oxidation of $VO(ma)_2$ in water or alcohol or from the reaction of $VO(OR)(ma)_2$ with peroxide. Ascorbate (100%) or heating in boiling water (75% recovery on average of three determinations) reduces all of these back to $VO(ma)_2$.

Structure of $K[VO_2(ma)_2]\cdot H_2O$. Potassium bis(maltolato)-dioxovanadium(V) monohydrate crystallizes as the potassium salt with one water molecule of crystallization. The solid state structure of this compound may be viewed as a three dimensional coordination polymer, with the potassium cation serving as a bridging unit between three anions. The ORTEP drawing in Figure 2 shows the vanadium(V) atom complexed by an O_6 donor set in a pseudo octahedral environment. Although there is no crystallography imposed twofold axis, the anion exhibits little deviation from C_2 symmetry. The two oxo-oxygen atoms are found *cis* to one another, making an angle of 103.7° The V=O bonds are essentially equivalent, averaging 1.638 Å and are indicative of vanadium−oxygen double bonds. The expected symmetric $\nu_{V=O}$ and asymmetric $\nu_{V=O}$ bands (890 and 910 cm^{-1}, respectively) also support the assignment of extensive π-interactions between the vanadium and oxo groups. The configuration of the VO_2^+ moiety seen here is in accord to those seen in a number of closely related complexes.[63]

The structural *trans* effect is observed, wherein the four complexing bonds to the maltolato oxygen atoms separate into two distinctive pairs according to their disposition with respect to the oxo groups. V−O bonds that are *cis* to both oxo groups average 1.98 Å; those that are *trans* to one oxo group and *cis* to the other are 0.23 Å longer. The neutral ketone oxygen atoms of the maltolato ligands were found *trans* to the oxo groups consistent with the stronger field hydroxy oxygens having a strong orbital overlap with the vanadyl V; recently a similar observation was noted for $[VO_2(8\text{-hydroxyquinolinato})_2]^-$.[62] In each of the maltolato ligands, all non-hydrogen atoms are essentially planar and form a dihedral angle of 76° to one

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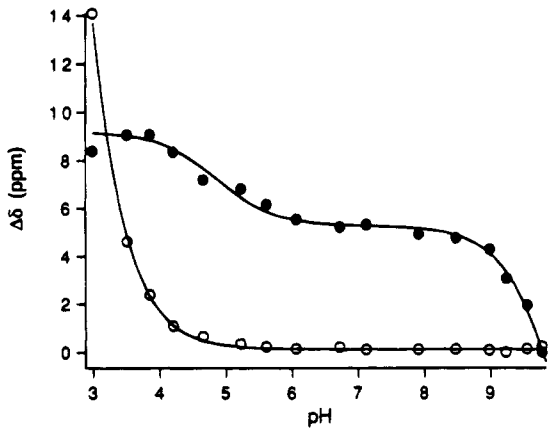

Figure 8. Change in ^{51}V NMR chemical shifts as a function of pH for $[VO_2(ma)_2]^-$ (○) and $[VO_2(ma)(H_2O)_2]$ (●). Solid lines calculated based on equilibria discussed in the text.

another. In the solid state $[VO_2(ma)_2]^-$ is chiral with both enantiomers present in the unit cell and related by the C_2 axis.

^{51}V NMR of the V(V)/Maltol System. The reaction of vanadate with increasing concentrations of maltol was studied in order to examine the nature and stoichiometry of the V(V) species formed in solution. To a 10 mM solution of vanadate at pH 7 was added increasing equivalents of maltol, and the ^{51}V NMR spectra were monitored. (With no maltol added, the only observable species are the expected vanadate oligomers,[21] V_1 ($\delta = -559$ ppm), V_2 ($\delta = -572$ ppm), V_4 ($\delta = -576$ ppm), and V_5 ($\delta = -584$ ppm)). For L:M ratios of 0.5:1 to 10:1 (Figure 7) (left)), the gradual appearance of peaks due to increasing complexation, nominally assigned as peaks **a** (~98%, $\delta = -496$ ppm) and **b** (~2%, $\delta = -509$ ppm) were observed with higher ligand concentrations. There were no changes in the chemical shifts of the vanadate oligomers, and no other resonances were detected. As the ligand concentration was increased, and the maltolato complexes were formed in increasing amounts, a concomitant reduction in the intensity of the peak assigned to V_4 (and to a lesser extent V_5) was observed. Similarly, the concentration of maltol was fixed (10 mM) while the concentration of vanadate varied, and the spectra were recorded (Figure 7, right). From the concentration studies, the peaks **a** and **b** were assigned to $[VO_2(ma)_2]^-$ and $[VO_2(ma)(OH)(H_2O)]^-$, respectively.

A variable pH study (20 mM maltol:10 mM vanadate) showed that both peaks **a** and **b** were pH dependent. The change in chemical shift with pH for each species is shown in Figure 8. The solid lines are calculated based on the following equilibria:

$$\underset{\delta = -505 \text{ ppm}}{[VO_2(ma)(H_2O)_2]} \rightleftharpoons \underset{\delta = -509 \text{ ppm}}{[VO_2(ma)(OH)(H_2O)]^-} + H^+ \quad pK_1 = 4.85(5) \quad (6)$$

$$\underset{\delta = -509 \text{ ppm}}{[VO_2(ma)(OH)(H_2O)]^-} \rightleftharpoons \underset{\delta = -524 \text{ ppm}}{[VO_2(ma)(OH)_2]^{2-}} + H^+ \quad pK_2 = 10.05(5) \quad (7)$$

$$\underset{\delta = -410 \text{ ppm}}{[VO(OH)(ma)_2]} \rightleftharpoons \underset{\delta = -496 \text{ ppm}}{[VO_2(ma)_2]^-} + H^+ \quad pK = 2.3(1) \quad (8)$$

From the concentration studies, the following equilibrium constants were determined (where "V_1", "Vma", and "V(ma)$_2$" are generic descriptors for the mixed protonation states of vanadate and the mono- and bismaltolato V(V) complexes, respectively):

$$\text{"}V_1\text{"} + ma^- \rightleftharpoons \text{"Vma"} \quad K_{01} = [\text{"Vma"}]/[\text{"}V_1\text{"}][ma^-] = (3.9 \pm 0.4) \times 10^2\ M^{-1} \quad (9)$$

$$\text{"Vma"} + ma^- \rightleftharpoons \text{"V(ma)}_2\text{"} \quad K_{12} = [\text{"V(ma)}_2\text{"}]/[\text{"Vma"}][ma^-] = (1.3 \pm 0.1) \times 10^4\ M^{-1} \quad (10)$$

A plot of ["Vma"] vs ["V_1"][ma$^-$] was linear with slope K_{01}, while a plot of ["V(ma)$_2$"] vs ["Vma"][ma$^-$] was linear with slope K_{12}. At pH 7 (the pH at which the equilibrium study was carried out), "V(ma)$_2$" is $[VO_2(ma)_2]^-$, while "Vma" exists as $[VO_2(ma)(OH)(H_2O)]^-$. At this pH, the monovanadate, "V_1" exists as a 10:1 mixture of $[H_2VO_4]^-$:$[HVO_4]^{2-}$.[64] Taking this ratio into account, along with the pK_a of $[VO_2(ma)(H_2O)_2]$ (eq 6), the stepwise stability constants for the reaction of pervanadyl, VO_2^+, with maltol can be calculated (eqs 11−13).

$$VO_2^+ + ma^- \rightleftharpoons [VO_2(ma)(H_2O)_2] \quad \log K_1 = 7.5(1) \quad (11)$$

$$[VO_2(ma)(H_2O)_2] + ma^- \rightleftharpoons [VO_2(ma)_2]^- \quad \log K_2 = 6.2(1) \quad (12)$$

$$VO_2^+ + 2ma^- \rightleftharpoons [VO_2(ma)_2]^- \quad \log \beta_2 = 13.7(1) \quad (13)$$

The calculated stepwise formation constants with VO_2^+ are over one order of magnitude less than the corresponding values with VO^{2+}. This is in accord with the trend seen in the formation constants of oxalic and malonic acids with V(V) and V(IV)[64] and should be expected because of the higher positive charge on the vanadium(IV) species.

It should be noted that although a value for the protonation of one of the oxo groups in $[VO_2(ma)_2]^-$ is given (eq 8), the vanadium(V) species is spontaneously reduced in an acidic medium, such that at pH 3 only about 3% of the V(V) signal was present, the remainder being reduced to V(IV) (verified by EPR). Therefore, the species at −410 ppm, tentatively assigned to $[VO(OH)(ma)_2]$, is never physically present at a large concentration. Similarly, although $[VO_2(ma)(H_2O)_2]$ has a higher formation constant than the bis-ligand $[VO_2(ma)_2]^-$, its formation is only favored (mathematically) in acidic conditions; however, since the V(V)−maltol system is spontaneously reduced below pH 4, $[VO_2(ma)(H_2O)_2]$ and its deprotonated analogues only exist as very minor species between pH 4 and 10.

The major V(V)−maltol species present between pH 4 and 8 is $[VO_2(ma)_2]^-$ ($\delta = -496$ ppm), with reduction to V(IV) occurring below pH 4 and V(V) hydrolysis above pH 8. This can be seen in Figure 9. The aqueous chemistry of the intact complex $[VO_2(ma)_2]^-$ (as the NH_4^+ salt) was studied by variable pH ^{51}V NMR, Figure 9 (right) and the bis- and monomaltolato complexes labeled **a** and **b**, respectively. In a similar experiment, the variable pH ^{51}V NMR spectra of a solution of VO(ma)$_2$ were also recorded (Figure 9 (left)). In basic solution a V_1 peak was observed at $\delta = -537$. As the pH was lowered, peaks **a** and **b** appeared at $\delta = -496$ and -510 ppm, respectively. As the acidity of the solution is increased, V_1

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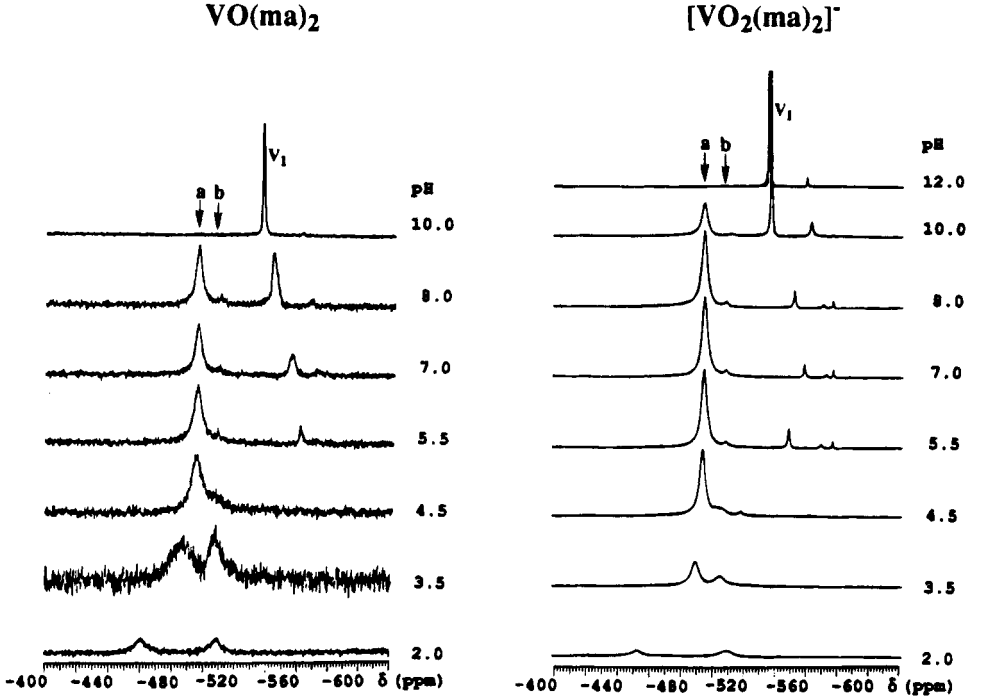

Figure 9. Variable pH ^{51}V NMR spectra of a solution of $VO(ma)_2$ (left) and of genuine $[VO_2(ma)_2]^-$ (right); both 10 mM, 0.15 M NaCl, 25 °C.

shifted to −560 ppm and disappeared below pH 5.5. No spectra could be observed below pH 2. These results prove that the same vanadium(V) complexes form in a solution of $VO(ma)_2$, even under relatively acidic conditions. The mechanism for the formation of these vanadate complexes is by the oxidation of $VO(ma)_2$ with O_2 to form $[VO_2(ma)_2]^-$ [53] and subsequently vanadate oligomers. Comparison of the ^{51}V NMR spectra obtained in the variable pH studies of $VO(ma)_2$ and $NH_4[VO_2(ma)_2]$ (Figure 9) reveals that the spectra are nearly coincident at identical pH values (the discrepancies owing to the slow redox kinetics).

Variable pH Electrochemistry of $VO(ma)_2$ and $[VO_2(ma)_2]^-$. Of the common oxidation states of vanadium, only V(III), V(IV), and V(V) are of any significance when considering physiological systems, V(II) being far too reducing to exist under normal conditions. In acid, the predominant species for these oxidation states are V^{3+}, VO^{2+}, and *cis*-VO_2^+. As the pH is raised, hydrolysis occurs, and a number of monomeric and oligomeric vanadium species are formed.[21,49,64,65] In the vanadium−maltolate system, V(V/IV) is most likely to be the only important redox couple. Previous electrochemical studies, performed in H_2O, have shown that the potential for this couple in five-coordinate vanadyl species generally lies between +0.3 and 1 V vs Ag/AgCl (for example +0.42 V observed for an *N,N*-oxovanadium(IV) Schiff base complex)[66] and is dependent upon the pH, ligands bound to the vanadyl center, and other ligands in solution.[66]

The variable pH cyclic voltammetry of $VO(ma)_2$ and $[VO_2(ma)_2]^-$ is shown in Figure 10 (left and right, respectively). For $VO(ma)_2$ $5 < pH < 8$, an irreversible wave was observed; $\Delta E \gg 72$ mV, $i_c/i_a > 1$ (Table 4). As the acidity of the solution is increased, the wave becomes increasingly quasi-reversible ($i_c/i_a \sim 1$). The wave obtained at pH 2.5 most closely resembled reversibility as defined by the ferrocenium/ferrocene redox couple ($\Delta E \sim 72$ mV, $i_c/i_a = 1$) and corresponded to a solution containing a mixture of $VO(ma)_2$, $VO(ma)^+$, VO^{2+}. In the extremes of acid and base, the waves obtained appeared similar to those of vanadyl(IV) and vanadate(V), respectively. The $E_{1/2}$ value of 0.55 V vs Ag/AgCl at pH 2.5 is not an unexpected value for the V(V/IV) redox couple. The marked dependence of (quasi-) reversibility with pH can be explained by the steady conversion of $VO(ma)_2$ to $[VO_2(ma)_2]^-$ and the diprotic $[VO_2(ma)(H_2O)_2]$. The reduction of the dioxovanadium(V) species

$$VO(ma)_2 \rightleftharpoons [VO(ma)_2]^+ + e^- \quad (14)$$

$$[VO(ma)_2]^+ + H_2O \rightarrow [VO_2(ma)_2]^- + 2H^+ \quad (15)$$

is not reversible (*vide infra*), and the variable pH ^{51}V NMR showed that the stability of the V(V)−maltolato system with respect to spontaneous reduction is pH dependent and that reduction increases with decreasing pH (*vide supra*). The reversibility of eq 14 is dependent on the rate of reaction of eq 15, and this reaction is clearly pH dependent. A study on the oxidation of $VO(ma)_2$ by O_2 in water showed[53] that the rate of conversion to $[VO_2(ma)_2]^-$ increases with pH and this would explain the decreasing quasi-reversibility with increasing pH. Although a L:M ratio of 2:1 would give a mixture of species in solution, in the pH range where irreversibility is dominant (4−8), the 2:1 complex should dominate (*vide supra*), and it appears that the fast (in this pH range) reaction eq 15 is the cause of irreversibility. The redox couple corresponding to V(IV/III) frequently has potentials ranging from 0.2 to −1.0 V; in this study no waves were observed in the region −1.4 to 0 V, or above 0.75 V, indicating that there is only one redox couple of importance involved.

The variable pH electrochemistry of $NH_4[VO_2(ma)_2]$ gave irreversible waves for $pH > 4$ (Figure 10). As the pH is lowered, the waves became increasingly reversible. At pH 2.5, $E_{1/2} = 0.45$ V, $\Delta E = 67$ mV, and $i_c/i_a = \sim 1$. This corresponds to the V^V/V^{IV} redox couple and, quite reasonably, appears very similar to that for $VO(ma)_2$. EPR confirmed that as acidity is increased in a solution of $[VO_2(ma)_2]^-$ increasing amounts of $VO(ma)_2$ are formed; the first EPR signal occurs at $pH < 4$, at which point electrochemical reversibility was also manifested.

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(66) Bonadies, J. A.; Butler, W. M.; Pecoraro, V. L.; Carrano, C. J. *Inorg. Chem.* **1987**, *26*, 1218.

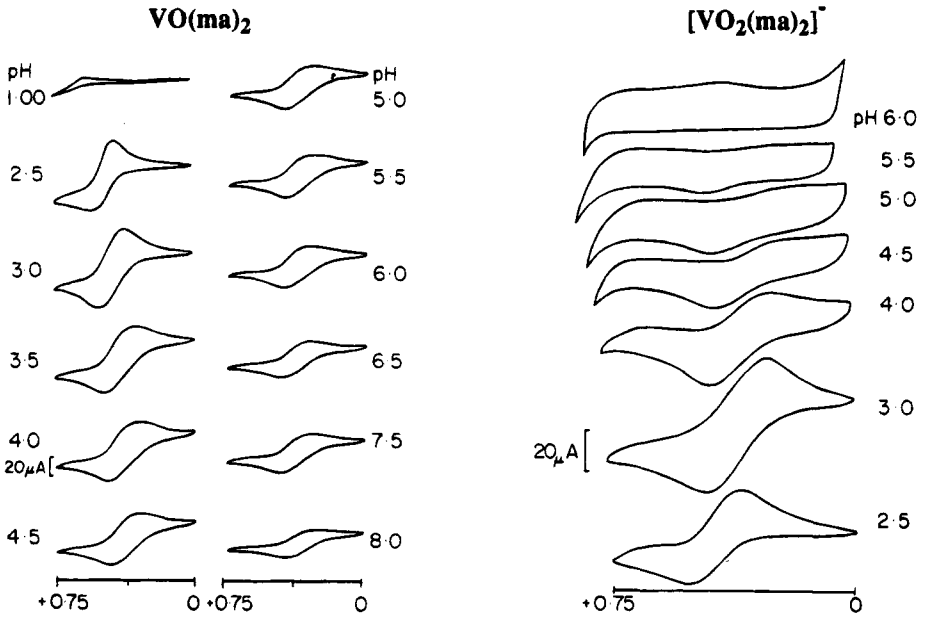

Figure 10. Variable pH cyclic voltammetry of $VO(ma)_2$ (left) and $[VO_2(ma)_2]^-$ (right); 0.15 M NaCl, 25 °C, under Ar, scan rate 100 mV s^{-1}, vs Ag/AgCl.

Table 4. Redox Potentials (V vs Ag/AgCl; ±0.01 V) of $VO(ma)_2$ at Variable pH (25 °C, 0.15 M NaCl, under Ar)

pH	$E_{1/2}$ (V)	ΔE (mV)[a]	i_c/i_a
2.5	0.55	71	1.00
3.0	0.51	68	1.03
3.5	0.48	65	1.03
4.0	0.47	64	1.01
≥5.0	≤0.45	≤55	≫1

[a] ΔE = 72 mV, i_c/i_a = 1.00 for ferrocinium/ferrocene.

Hence, it appears that $VO(ma)_2$ and $[VO_2(ma)_2]^-$ exhibit reversible electrochemical behavior in aqueous solution at pH 2.5 to 3; differences between $E_{1/2}$ values of $VO(ma)_2$ and $[VO_2(ma)_2]^-$ determined here presumably are due to the differing amounts of $VO(ma)_2$ present in either solution, the "concentration" of $VO(ma)_2$ as well as the kinetics of reduction of $[VO_2(ma)_2]^-$, which are both pH and concentration dependent.

The cyclic voltammetry of the *cis*-$VO(OR)(ma)_2$ species shed considerable light on the stability of those complexes in the presence and absence of an excess of the appropriate alcohol (Figure 11). For R = Me or Et in the presence of excess methanol or ethanol, a nicely reversible one electron reduction took place at −0.36 or −0.29 V vs Ag/AgCl, respectively. In the absence of excess alcohol, the two alkoxy species $VO(OR)(ma)_2$ R = Me or Et showed the same two redox processes, an irreversible reduction at −0.46 V and a reversible process at −0.10 V. The excess alcohol was required to maintain the integrity of the $VO(OR)(ma)_2$ complex under reducing conditions. In its absence, common irreversible and reversible processes took place leading to decomposition—no $VO(OR)(ma)_2$ was recovered from these solutions. For the R = i-C_3H_7 complex the same two processes were seen in the absence of excess isopropyl alcohol, but the one electron reduction in the absence of excess isopropyl alcohol was irreversible, presumably the kinetics of reduction are too slow for the process to be reversible. The kinetics of aerial oxidation of $VO(ma)_2$ to $VO(OR)(ma)_2$ in isopropyl alcohol are also much slower. ^{51}V NMR spectra of the $VO(OR)(ma)_2$ complexes in CH_3CN showed clearly that the complexes were stable in the presence of excess ROH but were unstable without excess ROH, forming small amounts of unidentified species at δ −460 and −470.

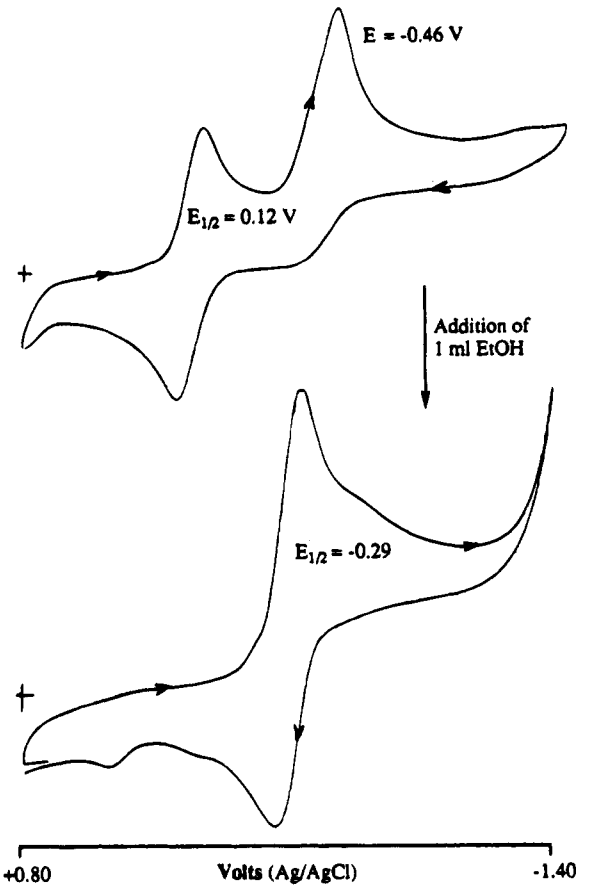

Figure 11. Cyclic voltammetry of $VO(OC_2H_5)(ma)_2$ in CH_3CN with and without excess ethanol added (0.2 M TEAP, 25 °C, 100 mV s^{-1}, 50 μA full scale for each voltammogram).

Diabetic Rat Studies. In order to assess the possibility of hydrolysis and the necessity for the complex to be administered intact a simple gavage screen was undertaken. At the doses used, there was no reduction in plasma glucose levels at any time with any vanadyl sulfate, maltol, or 3% gum arabic treatments. Plasma glucose levels were significantly reduced by all $VO(ma)_2$ treatments within 6−8 h following administration (Figure 3). While treatment with $VO(ma)_2$ was effective

in reducing plasma glucose levels acutely over a 24 h period, vanadyl sulfate did not have any effect on glucose levels, even in the presence of an excess of Hma (Figure 3). This suggests that the coadministration of Hma does not facilitate glucose uptake in response to vanadium. The reduction in glucose observed with $VO(ma)_2$ was not different, whether there was an excess of Hma present or not, suggesting that Hma must be complexed to the vanadium prior to administration and that the complex must be provided intact for the insulin-mimetic activity to be expressed *in vivo*. These results indicate that the difference in the insulin-like effects between $VO(ma)_2$ and vanadyl sulfate may be a result of an increase in the gastrointestinal absorption of vanadium due to the complexation of vanadyl with the maltolate anion.

Since ascorbic acid is a biologically compatible reducing agent, it was of interest to check whether its presence in aqueous suspensions of $VO(ma)_2$ would potentiate the insulin mimetic effect of $VO(ma)_2$ by preventing its oxidation to $[VO_2(ma)_2]^-$. *In vitro* reactivity studies showed clearly that all the V(V) complexes $[VO_2(ma)_2]^-$ and $VO(OR)(ma)_2$ could be cleanly reduced in aerobic water to $VO(ma)_2$ (both glutathione and cysteine worked as well but were not as clean). As is clearly shown in Figure 4, 10% ascorbic acid administered with $VO(ma)_2$ did not enhance the effects of $VO(ma)_2$ on glucose-lowering suggesting that the intact V(IV) $VO(ma)_2$ complex is present in the suspensions administered to the animals to that an adequate insulin-mimetic effect was expressed.

In comparing the oral efficacy of the V(IV) and V(V) maltol complexes, oral gavage administration of $VO(ma)_2$ and $NH_4[VO_2(ma)_2]$ demonstrated a decline in plasma glucose levels of 53% and 33% to 12.19 ± 2.25 and 14.88 ± 3.12 mM, respectively, in STZ-diabetic rats by 24 h following acute administration of 0.55 mmol kg^{-1}. However, the onset of action of $NH_4[VO_2(ma)_2]$ appeared to be slower than $VO(ma)_2$ as indicated by 12 h plasma glucose levels of 13.34 ± 1.85 mM for $VO(ma)_2$ and 20.13 ± 1.3 mM for $NH_4[VO_2(ma)_2]$. In addition, acute administration of $NH_4[VO_2(ma)_2]$ was associated with gastrointestinal problems (primarily diarrhea) and transient (≤4 h duration) lethargy and cyanosis which were not observed in the $VO(ma)_2$-treated animals. These data suggest that $VO(ma)_2$ is the preferred drug form.

Concluding Remarks. The extensive reaction chemistry of $VO(ma)_2$ pertinent to its insulin-mimetic action has been worked out. From simple animal experiments conducted in conjunction with the chemical studies, it is clear that the intact complex must be administered for its biological activity to be expressed.

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Supporting Information Available: Tables of crystallographic data, bond lengths and angles, final atomic coordinates and equivalent isotropic thermal parameters, hydrogen atom coordinates, anisotropic thermal parameters, bond lengths and angles involving hydrogen, torsion angles, intermolecular contacts, and least-squares planes (29 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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