Speciation in Vanadium Bioinorganic Systems. 2. An NMR, ESR, and Potentiometric Study of the Aqueous H^+−Vanadate−Maltol System

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A systematic study of the physiologically interesting vanadium−maltol (V−MaH) system has been performed in 0.150 M Na(Cl) at 25 °C, using NMR, ESR, and potentiometric techniques. Complexation occurs within a wide pH range, from around 1 up to 10.5. However, a pH-, concentration-, and time-dependent spontaneous reduction of vanadium(V) to vanadium(IV) occurs. From ESR spectra the conditions for this reduction are evaluated and discussed. From potentiometric (glass electrode) and quantitative ^{51}V NMR measurements, the full speciation in the $H^+-H_2VO_4^-$−MaH system was determined in the pH range 5−10.5. Data were evaluated with the computer program LAKE, which is able to treat combined emf and NMR data. The pK_a value for MaH was determined to be 8.437 ± 0.005. In the ternary system, three complexes are formed: VMa_2^-, VMa^-, and VMa^{2-}, having $\log \beta_{0,1,2} = 7.02 \pm 0.03$, $\log \beta_{0,1,1} = 2.66 \pm 0.05$, and $\log \beta_{-1,1,1} = -7.37 \pm 0.21$. The errors given are 3σ. The VMa_2^- complex appears as the main species in a pH range from 4.5 to 8.5, whereas both mononuclear monoligand species are minor. Equilibrium conditions are illustrated in distribution diagrams, and the structures of the complexes formed are proposed.

Introduction

Vanadium is a trace metal with exceptional properties. Both its cationic and anionic forms can interact with biomolecules, and also its coordination chemistry plays a predominant role in these interactions. Among several biological functions of vanadium, many important therapeutic effects have been described, including hormonal, cardiovascular, and anticarcinogenic activities (reviewed in refs 1 and 2a)).

Because of the physiological relevance of vanadium, a better understanding of its complexation behavior with organic ligands is of vital interest. The interactions of this metal with proteins and its role in enzymatic reactions have been studied extensively in order to explain the potent inhibitory and activating effects of vanadate (reviewed in ref 2b)).

Since 1980 the insulin mimetic properties of vanadium compounds have been important subjects of investigation.[3] Most of the work that has been done in this field is summarized in ref 4. However, the real mechanism by which vanadate acts as an insulin mimic still remains unclear. In the development of oral substitutes for insulin, maltol (3-hydroxy-2-methyl-4-pyrone) is one of the most promising ligands.[5,6] In the following, maltol will often be abbreviated MaH. Its structure is shown in Figure 1. The vanadium−maltol complexation process, mostly focused on the V(IV) interactions, has recently been studied by Glover et al.[7,22]

In the present work a complete systematic equilibrium study of the V(V)−MaH system at 25 °C has been performed to unambiguously establish the stoichiometry and formation constants of the complexes formed. A 0.150 M Na(Cl) medium was chosen, as it resembles physiological conditions. Potentiometric and ^{51}V NMR spectroscopy measurements have been performed and combined electromotive force (emf) and quantitative NMR equilibrium data have been evaluated with the LAKE computer program.[8] V(IV) ESR spectra were used as a qualitative tool to detect spontaneous reduction of vanadium(V) in the solutions and to facilitate the exclusion of nonequilibrium data. As a result, the complete speciation in the system has been determined.

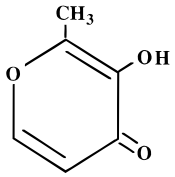

Figure 1. Structure of maltol (3-hydroxy-2-methyl-4-pyrone).

Experimental Section

Chemicals and Analyses. Maltol ($C_6H_6O_3$; Janssen Chimica 99%) was used without further purification. Vanadate stock solutions were prepared by dissolving sodium metavanadate (E. Merck p.a.) in hot water. The solutions were then cooled to room temperature, filtered through a porous glass G4 filter, and standardized by evaporation to the solid ($NaVO_3$). Sodium chloride (E. Merck p.a.) was dried at 180 °C and used without further purification. Diluted solutions of hydrochloric acid (E. Merck p.a.) were standardized against tris(hydroxymethyl)aminomethane (TRISMA-base). Diluted sodium hydroxide was prepared from a saturated NaOH solution (50% NaOH and 50% H_2O) and standardized against the hydrochloric acids. In all preparations of solutions boiled distilled water was used. After boiling, the water was cooled and stored in the absence of air. Alkaline solutions were prepared and stored under argon to protect them from atmospheric CO_2(g). As vanadate−maltol solutions were found to be sensitive to light to some extent, the solutions were shielded from light during preparation and were stored in darkness.

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Notation. The equilibria studied are written with the components H^+, $H_2VO_4^-$, and MaH. Thus, the complexes are formed according to

$$pH^+ + qH_2VO_4^- + rMaH \rightleftharpoons (H^+)_p(H_2VO_4^-)_q(MaH)_r^{p-q}$$

Formation constants are denoted $\beta_{p,q,r}$, and complexes are often given the notation (p,q,r) or $V_xMa_y^{-z}$. The total concentration of maltol ([MaH] + [Ma^-]) is denoted [Ma] and that of vanadium is denoted [V].

Potentiometric Measurements. Emf measurements in the binary H^+−MaH and ternary H^+−$H_2VO_4^-$−MaH systems were carried out with an automated potentiometric titrator, as a series of titrations in 0.150 M Na(Cl) medium at 25 °C. The glass electrodes used were of the general-purpose type, Ingold 201-NS. The free hydrogen ion concentration was determined by measuring the emf of the cell:

$$-Ag,AgCl/0.150\ M\ Na(Cl)//eq\ solution/glass\ electrode+$$

The measured emf (in millivolts) may be written as $E = E_0 + 59.157 \log [H^+] + E_j$, where E_j /mV $= -331[H^+] + 42.5K_w[H^+]$ for the experimental setup used. E_j is the liquid junction potential at the 0.150 M Na(Cl)//equilibrium solution interface. K_w (1.746×10^{-14}) is the ionic product of water in 0.150 M Na(Cl) and at 25 °C.[9] The constant E_0 was determined separately in a solution with known [H^+], before and after each titration.

Owing to fast spontaneous reduction of V(V) and polycondensation of maltol in parts of the pH range, the conventional titration technique had to be complemented. Therefore, instead of titrating a solution over a period of several days, individual samples were prepared directly at different pH values, total concentrations, and concentration ratios. pH was then measured separately with an Ingold U420-6-S7/100 combination electrode, which had been calibrated against buffer solutions of known [H^+] in 0.150 Na(Cl). These samples were also used for NMR measurements and reduction was checked with ESR. All solutions were protected from atmospheric carbon dioxide by an argon gas stream.

NMR Spectroscopy. ^{51}V NMR spectra were recorded at 131.5 MHz (11.7 T) using a Bruker AMX-500 MHz spectrometer. The probe temperature was 25 ± 1 °C. The chemical shifts are reported relative to the external reference standard $VOCl_3$. The field frequency stabilization was locked to deuterium by placing the 8 mm sample tubes into 10 mm tubes containing D_2O. Typically, spectral widths of 200 ppm (26.9 kHz) were used, and data for the FID were accumulated in 4K blocks. A 90° pulse angle was employed and, owing to short relaxation times, no relaxation delay was used.

ESR Spectroscopy. X-band ESR spectra, recorded as the first derivative of absorption, were collected on a Bruker ESP 300E instrument at 9.8 GHz. Samples (aqueous) were contained in 115 μL capillary tubes, and spectra were scanned from 2900 to 4200 G. Microwave power was 5 mW.

Computer Calculations. The emf and quantitative ^{51}V NMR data were evaluated with the least squares program LAKE.[8] LAKE is able to calculate formation constants with standard deviations from, for instance, emf data obtained in titrations/individual solutions, integral NMR data or combined emf−NMR data. Formation constants for systematically chosen complexes $(H^+)_p(H_2VO_4^-)_q(MaH)_r^{p-q}$ are varied so that the error squares sum, $U = \sum(W_i\ \Delta A_i)^2$, is minimized. The complex or set of complexes having the lowest U value forms the model which best explains the experimental data. A_i can be the total concentrations of components, free species concentrations, NMR peak integrals, chemical shifts, or combinations of these. W_i is a weighting factor that must be set to give the different types of data their proper weights. Here we have used a weighting factor that gives NMR peak integrals a predominant contribution to the sum of residuals. In addition, a quality weight is used giving even low vanadium concentrations a considerable contribution to the error squares sum. Calculation and plotting of distribution diagrams were performed with the program SOLGASWATER.[10]

Potentiometric Data. The acidity constant for maltol was determined from three titrations (112 experimental points). The pH range was 2.0 < pH < 9.0, and the total concentration range covered was 5 < [Ma]/mM < 20.

In the vanadate−maltol system, polycondensation of maltol in alkaline solutions and fast reduction of V(V) in acid solutions led to highly restrictive titration conditions. Therefore only two titrations (69 experimental points) were recorded. The pH range was 7.4 < pH < 9.9 , and the concentration ranges were 5 < [V]/mM < 20 and 10 < [Ma]/mM < 20.

NMR Data. In the V−MaH system, 48 spectra were recorded in the ranges 2.9 < pH < 9.9, 1.25 < [V]/mM < 20, and 1.6 < [Ma]/mM < 40. The pH of each solution was measured directly after the NMR measurements with the carefully calibrated combination electrode mentioned earlier. Spectra were then quantitatively evaluated using the Bruker software computer program UXNMR/P to obtain precise integral values.

ESR Data. Fifty-two spectra were recorded in the ternary system in order to check and evaluate vanadium reduction in the solutions. The results were used to determine the experimental conditions suitable for NMR and potentiometric measurements. To verify that no reduction had occurred in the samples that were to be used for quantitative NMR evaluation, all solutions were checked by ESR directly before or after the NMR measurements.

Table 1. Species and Formation Constants for Vanadium(V) [0.150 M Na(Cl), 25 °C] Used in LAKE Calculations on the V−MaH System[a]

p,q,r	formula	notation	log β	pK_a
−1,1,0	HVO_4^{2-}	V_1	−8.17	
0,1,0	$H_2VO_4^-$		0	8.17
2,1,0	VO_2^+		7.00	
−2,2,0	$V_2O_7^{4-}$	V_2	−16.19	
−1,2,0	$HV_2O_7^{3-}$		−5.85	10.34
0,2,0	$H_2V_2O_7^{2-}$		2.65	8.50
−2,4,0	$V_4O_{13}^{6-}$	l-V_4	−9.98	
−1,4,0	$HV_4O_{13}^{5-}$		0.63	9.35
0,4,0	$V_4O_{12}^{4-}$	V_4	9.24	
0,5,0	$V_5O_{15}^{5-}$	V_5	11.17	
4,10,0	$V_{10}O_{28}^{6-}$		50.28	
5,10,0	$HV_{10}O_{28}^{5-}$	V_{10}	56.90	6.62
6,10,0	$H_2V_{10}O_{28}^{4-}$		61.07	4.17
7,10,0	$H_3V_{10}O_{28}^{3-}$		62.93	1.86

[a] The (p,q,r) notation is explained in the Experimental Section.

Results and Discussion

To establish the speciation in the ternary H^+−$H_2VO_4^-$−MaH system, the binary subsystems H^+−$H_2VO_4^-$ and H^+−MaH should first be precisely known. The equilibrium conditions and NMR characteristics of the vanadate system in 0.150 M Na(Cl) have recently been studied[11] (as part of a larger study of the Na^+ dependence on the vanadate equilibria). This is the only complete study on the vanadate speciation in the physiologically relevant 0.150 M Na(Cl) medium. The speciation is essentially the same as in the earlier studied 0.600 M Na(Cl) medium.[12] In the lower medium, however, highly negatively charged species, e.g., the tetramer, are unfavored, whereas the lower charged mononuclear species are stabilized. This shows the importance of using proper vanadate formation constants which are valid for the medium studied. The equilibrium constants are presented in Table 1.

The acidity constant for maltol in 0.150 M Na(Cl) had to be determined in the present work. The pK_a value was shown to be 8.437 ± 0.005 (Table 2). The error given is 3σ. During the work on the H^+−MaH system, a color change in alkaline maltol solutions was noticed. Due to polycondensation reac-

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Table 2. Composition, Notation, Formation Constants (β), and Acidity Constants (pK_a) for the H^+-MaH and $H^+-H_2VO_4^-$−MaH systems [0.150 M Na(Cl), 25 °C]

p,q,r	notation	log β ($\pm 3\sigma$)	pK_a
0,0,1	MaH	0	8.437
−1,0,1	Ma^-	−8.437 (5)	
0,1,2	VMa_2^-	7.02 (3)	
0,1,1	VMa^-	2.66 (5)	10.0
−1,1,1	VMa^{2-}	−7.37 (21)	

tions, the solutions change from colorless to pale yellow in approximately 20 h for a 20 mM solution. This fact was a limiting factor in the handling of alkaline maltol solutions during the measurements.

Before consideration of the results for the ternary $H^+-H_2VO_4^-$−MaH system, the problem with spontaneous reduction of vanadate will be discussed. The study of the system is focused mainly on three different pH ranges: "acid" solutions, pH between 3 and 4; "neutral" solutions, pH of approximately 6.5; and "alkaline" solutions, pH 8.5−10. For simplicity, solutions will be denoted only as acid, neutral, and alkaline in the following discussion.

It is known from earlier work[7] that reduction of vanadium occurs in acid V−MaH solutions. In this study reduction was observed in a wide pH range and was sometimes accompanied by color changes. Reduction appears after different time intervals which depend on pH (Figure 2), concentrations, and ratios of vanadium and maltol. Reduction occurs over time scales which range from immediately after mixing to 2 weeks, and was carefully checked using ESR as a qualitative and semiquantitative tool. In Figure 2a, a spectrum of an acid vanadyl−maltol ($VO^{2+}-MaH$) solution is shown. The major feature of this spectrum is coincident with the feature of a pure VO^{2+} spectrum. There are, however, some small peaks present which probably arise from a V(IV)−maltol complex. Figure 2b shows a spectrum of a spontaneously reduced V(V)−MaH solution. The main feature in this spectrum originates from the V−MaH complexation. VO^{2+} is seen only as a shoulder, showing that most V(IV) present is bound to maltol and is not present as free VO^{2+}. The reason for this is that the total concentration of V(IV) is much lower in solution 2b than in 2a giving a higher [Ma]/[V(IV)] ratio. Figure 2b−d reveals the dependence of reduction on pH and, moreover, that the main feature is the same no matter which pH value. In an acid [V]/[Ma] = 20/20 mM solution, approximately 10% of vanadium(V) is reduced after 2 days. The same solution at neutral pH remains mostly unreduced even after 2 weeks. On the alkaline side, reduction occurs in shorter time (2.5% after 4 days). The [V]/[Ma] ratio is an additional parameter that affects the reduction rate, which is higher at a ratio of 1/2. A schematic representation of the nonreductive conditions for neutral to alkaline solutions is shown in Figure 3. It is clearly seen that both pH and the [Ma]/[V] ratio affect the number of days a solution remains unreduced. In addition, reduction is enhanced by UV light and therefore all solutions were stored in darkness.

The observations above indicate that a careful quantitative vanadate−maltol study can be performed at neutral pH. Solutions at more alkaline pH may also be used if time is carefully taken into account. The present study is based on titrations at neutral to alkaline pH and on ^{51}V NMR measurements at different pH. Solutions were checked with ESR before measurement of the quantitative NMR spectra to be sure that no reduction had occurred. The pH of each solution used for equilibrium analysis was measured directly before or after the ESR and NMR measurements. This is important because pH changes when reduction occurs. In acid solutions pH was seen to increase on reduction, whereas in neutral and alkaline samples pH decreased.

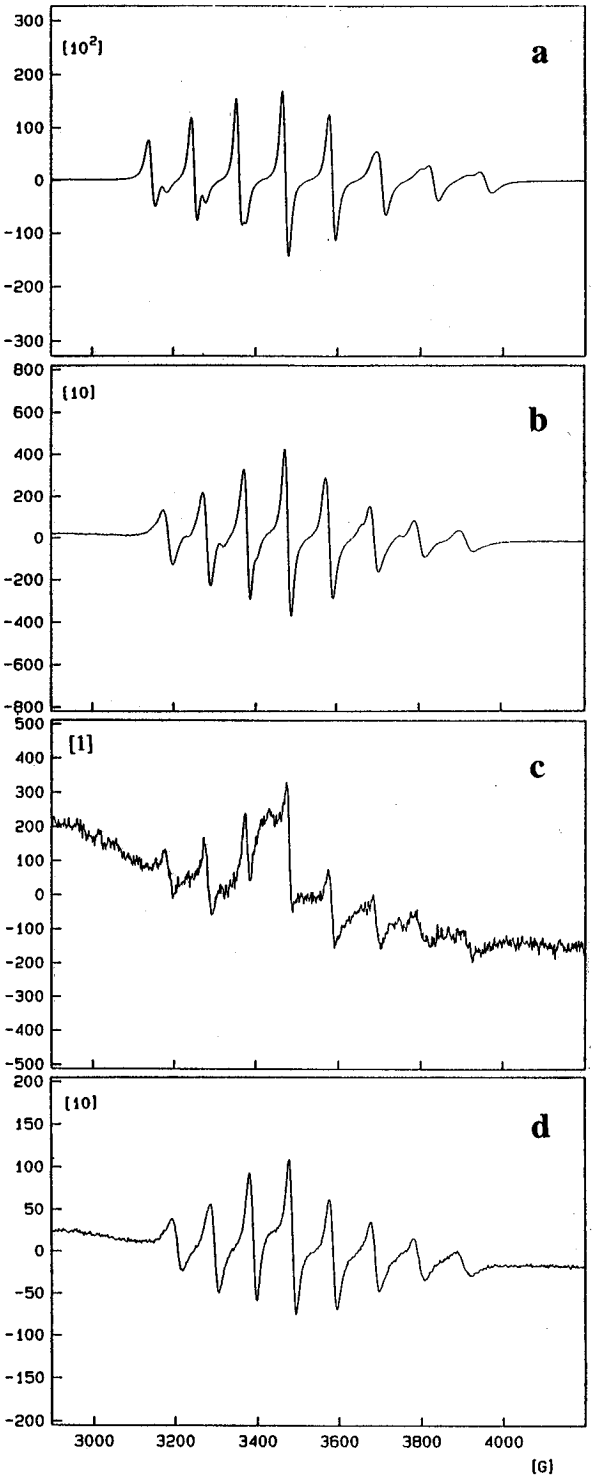

Figure 2. V(IV) ESR spectra of (a) a V(IV)−maltol solution, and (b−d) spontaneously reduced vanadium(V)−maltol solutions. Effects of pH on reduction rate. Note the different magnification scales in the upper left corner of each spectrum. (a)VO^{2+}−maltol acid solution ([V]/[Ma] = 10/20 mM, pH = 0.6). (b) Vanadate−maltol acid solution ([V]/[Ma] = 20/20 mM, pH = 3.7, age = 2 days). (c) Vanadate−maltol neutral solution ([V]/[Ma] = 20/20 mM, pH = 6.1, age = 2 weeks). (d) Vanadate−maltol alkaline solution ([V]/[Ma] = 20/20 mM, pH = 9.5, age = 4 days).

^{51}V NMR spectra show two resonances originating from vanadium−maltol complexes (Figure 4). Both exist in a wide pH range. The main peak has a shift of −496 ppm. The smaller peak has a shift of −509 ppm. However, from pH 8.5 and

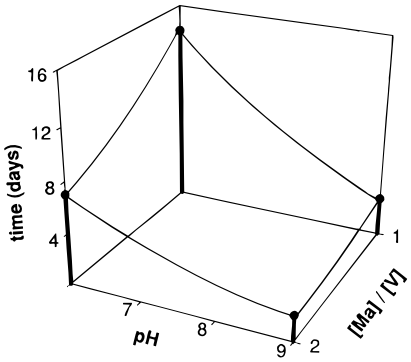

Figure 3. Schematic representation of the nonreductive working conditions. Samples were kept in the inner volume to avoid reduction of V(V).

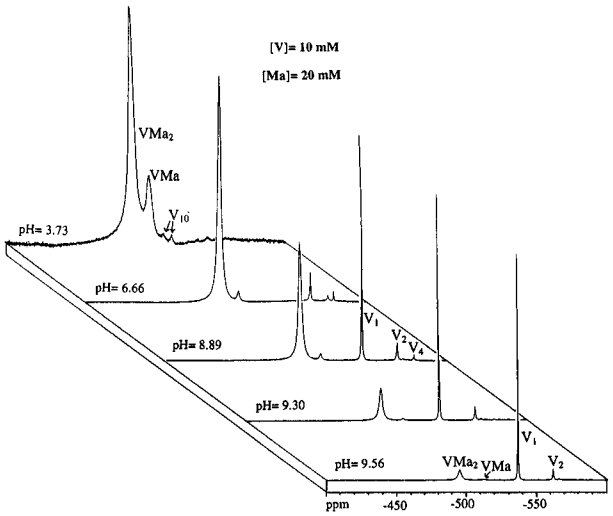

Figure 4. ^{51}V NMR spectra of aqueous solutions of vanadate and maltol ([V]/[Ma] = 10/20 mM) at different pH values.

higher, the −509 peak is shifting upfield, indicating deprotonation of this complex. Also, at pH < 5 a downfield shifting of this resonance occurs and at the same pH the −496 resonance shifts downfield dramatically. Moreover, from the NMR spectra it is seen that in fresh acid solutions the relative amounts of the two resonances are changing. Immediately after mixing, the intensity of the −509 resonance exceeds that at −496. With time the −496 resonance increases at the expense of that at −509 and dominates after about 24 h. As it has not been possible to determine the speciation in the unstable acid solutions, the reason for the shift changes is unclear. It may be caused by protonation of the complexes and/or interaction between species.

Not only pH but also the ratio between [V] and [Ma] affects the extent of complexation as seen in Figure 5. Complexation is clearly favored by an excess of MaH at neutral pH. At a 0.5/1 ratio at [V] = 10 mM (the same ratio as in Figure 4), integration of the NMR resonances shows that 93% of the vanadium is bound to maltol. An increase in the ratio causes a decrease in complexation, as expected. At a 1/1 ratio at [V] = 10 mM, 47% of vanadium is bound to maltol. At a 6/1 ratio only 8.5% of vanadium is involved in complexation. This behavior strongly points to the formation of a predominating vanadium:maltol 1:2 complex. That this complex has a VMa_2^- composition will be shown later. Note that the percentage values discussed above are valid only for the total concentrations given.

To determine the speciation of the vanadium complexes formed, data were collected in a wide range with respect to

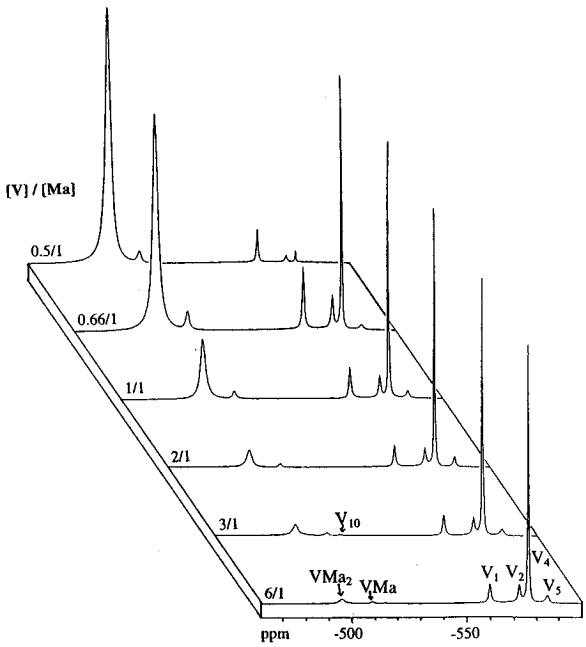

Figure 5. ^{51}V NMR spectra of aqueous neutral solutions of 10 mM vanadate at different [V]/[Ma] ratios.

pH, total concentrations, and concentration ratios. It was possible to determine the speciation from pH around 5 to 10. Since equilibria have to be achieved before reduction occurs, the speciation at pH < 5 could not be determined. To find the complex or set of complexes that best fitted the experimental data, different models were tested. By use of the computer program LAKE,[8] formation constants with corresponding errors were calculated for different species. Several LAKE calculations were made to test different models. Without doubt, a (0,1,2) complex fully explains the −496 resonance. The small −509 resonance was shown to originate from a V:MaH 1:1 stoichiometry. (0,1,1) and (0,2,2) complexes were both tested, but the monomer resulted in a lower *U* value and a much better fit to the experimental data. As residuals still remained on data points at high pH, a deprotonated 1:1 species was included in the model. This lowered the *U* value even more and no systematic residuals remained. The existence of the deprotonated species is also to be expected, considering the shift change of the NMR resonance at −509 ppm. Thus, three V−MaH complexes, having the compositions (0,1,2), (0,1,1) and (−1,1,1), fully explain the potentiometric and quantitatively evaluated ^{51}V NMR data. The formation constants are reported in Table 2. The 1:2 complex is strong, having a log $\beta_{0,1,2} = 7.02 \pm 0.03$. The values of log $\beta_{0,1,1} = 2.66 \pm 0.05$ and log $\beta_{-1,1,1} = -7.37 \pm 0.21$ give a pK_a of 10.0. As this deprotonation is accompanied by a ^{51}V NMR shift change, it indicates that the loss of the proton takes place close to the vanadium atom.

The distribution of vanadium as a function of pH has been calculated and plotted for [V] = 10 mM and [Ma] = 20 mM as well as for [V] = 20 mM and [Ma] = 20 mM. See Figure 6:I. For clarity, no vanadium-containing species with $F_V < 5\%$ have been shown, except for the (0,1,1) complex, VMa^-. The (0,1,2) complex, VMa_2^-, has its maximum concentration at pH between 4.5 and 8.5 at the ratio of 1/2 (Figure 6:Ia), where it binds about 90% of the total vanadium. This strong complexation ability of vanadium to maltol at neutral and slightly acidic pH makes it physiologically very important. At the 1/1 ratio (Figure 6:Ib) the VMa_2^- complex binds only around 45% of total vanadium. The amount of V bound in the 1:1 complexes is always low. For both V/MaH ratios only 1−3% is bound. The corresponding maltol distribution is shown in Figure 6:II. Almost all

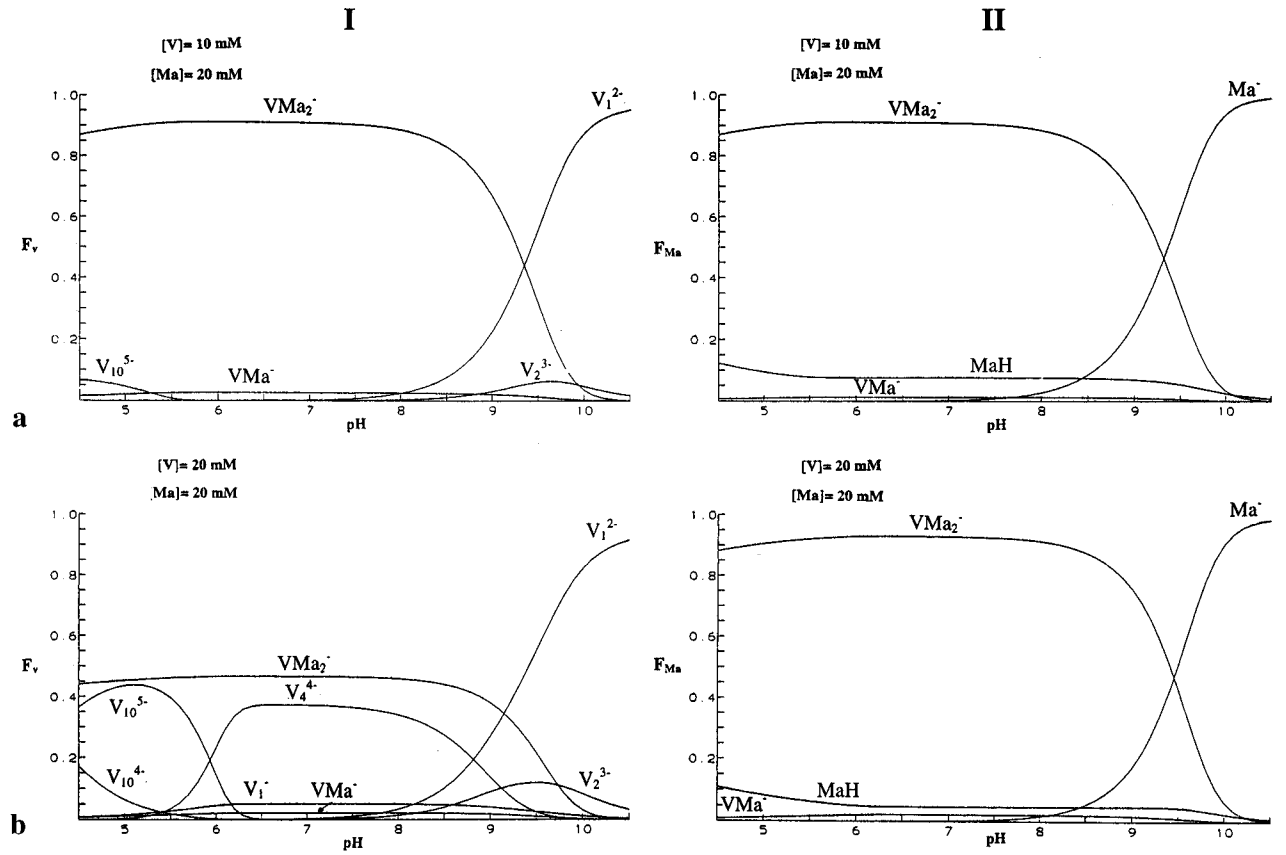

Figure 6. Diagrams showing the distribution of (I) vanadium, F_V, vs pH and (II) maltol, F_{Ma}, vs pH. (a) [V]/[MaH] ratio = 0.5 and (b) [V]/[MaH] ratio = 1. F_X for a component X is defined as the ratio between [X] in a given species and total [X] in the solution. For clarity no vanadium-containing species with <5% of total [V], except the (0,1,1) complex, are shown in (I).

maltol, for both conditions around 93%, is bound to vanadium in the complexes. Maintaining a constant pH of 6.5 (an average of the measured neutral solutions), [V] = 10 mM, and changing the [Ma] shows that full complexation is reached at [Ma] = 23 mM (Figure 7a). At [V] = 10 mM and pH = 6.5, a 1:2 ratio is optimal for complexation studies, giving around 93% of the V bound and only 7% free MaH. However, if the concentrations are lowered by a factor of 100 ([V] = 0.1 mM), the calculated amount of vanadium bound in different complexes changes dramatically. At a 1/2 ratio only 18% is bound in the VMa_2^- complex, but 6% in the VMa^- species (Figure 7b). At even lower vanadium concentrations (0.01 mM) and a twofold excess of maltol, equal amounts of vanadium will be bound in each of the VMa_2^- and VMa^- species. However, at this very low concentrations the total amount of vanadium bound is only 2%. This clearly shows the importance of taking total concentrations and not only ratios into account in the transferring of results from an equilibrium analysis to physiological conditions.

The hypothesis of a hexacoordinated cis structure for vanadium in the VMa_2^- complex (Figure 8) is based on previous studies of complexes containing an MO_2 group, with M a metal in d^0 electronic configuration.[13] This structure has also been described in several complexes with bidentate organic ligands.[14−17] For the VMa species a hexacoordinated structure is proposed, but five-coordination, by exclusion of the H_2O ligand, is also plausible. The deprotonation site on the VMa^- species close to the vanadium atom is confirmed by the ^{51}V NMR shift change at alkaline pH. The ^{51}V NMR resonances are symmetrical, and no isomeric species have been identified.

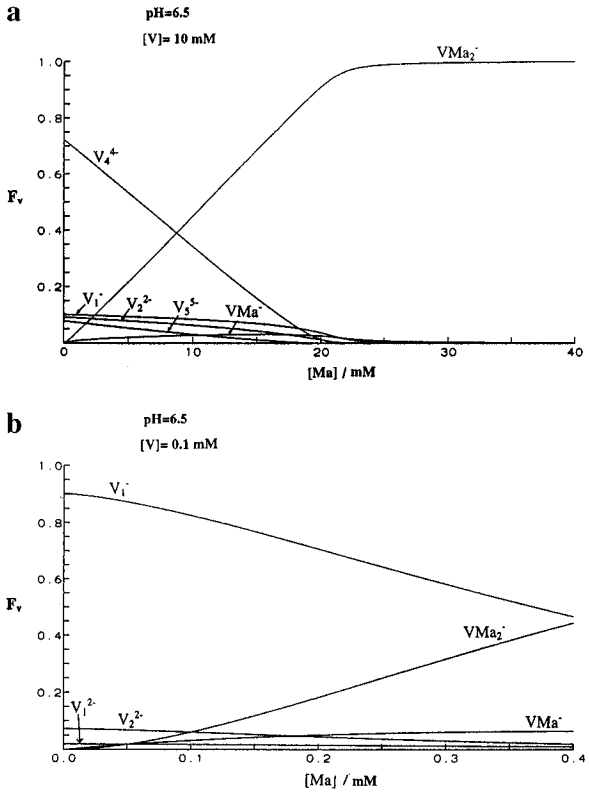

Figure 7. Diagrams showing the distribution of vanadium, F_V, vs the total concentration of maltol at pH = 6.5. (a) [V] = 10 mM and (b) [V] = 0.1 mM. F_V is defined in Figure 6.

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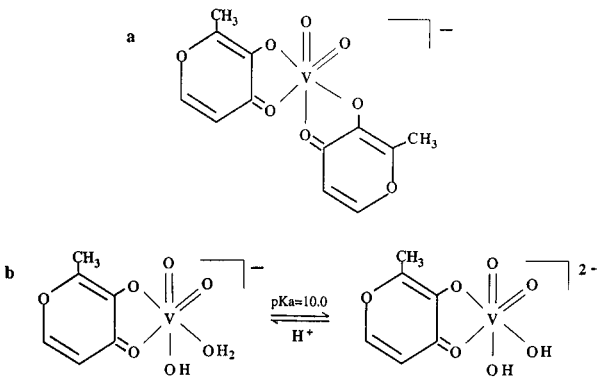

Figure 8. Proposed schematic structure of the V−MaH complexes. (a) The VMa_2^- species, (0,1,2) in (*p*,*q*,*r*) notation. (b) The VMa^- and VMa^{2-} species, (0,1,1) and (−1,1,1) in (*p*,*q*,*r*) notation.

Conclusions and Future Plans

The present study has revealed how redox reactions can interfere in V(V)−organic ligand systems, and therefore make a complete equilibrium analysis very difficult. Every precaution must be taken to ascertain that, in the solutions used to evaluate quantitative equilibrium data, vanadate is not reduced. As reduction is not always accompanied by color changes, V(IV) ESR data are important to exclude/confirm reduction. Combined emf−NMR−ESR studies are therefore certainly to be recommended. Reduction of V(V) in acid solutions has often occurred in the systems we have studied so far. In addition to the present maltol system, reduction has also been found in the oxalate,[18] citrate,[19] histidine,[20] and glycyltyrosine[21] systems. Since both V(V) and V(IV) complexes with maltol have been shown to be biologically active, the redox chemistry is of vital interest. We therefore plan to perform a complete redox equilibrium analysis of the H^+−V(V)−MaH−e^- system. This study may also elucidate the speciation in acid V(V)−MaH solutions, where the spontaneous reduction of V(V) has been most troublesome.

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