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Formation constants for the ternary complexes of vanadium(III), 8-hidroxyquinoline, and the amino acids histidine, cysteine, aspartic and glutamic acids

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ABSTRACT

Solution equilibria of V(III)-8-hydroxyquinoline (H8HQ) and aspartic acid (H_2Asp), glutamic acid (H_2Glu), cysteine (H_2Cys) and histidine (HHis) ternary systems, have been studied through potentiometric measurements. The formation constants of the resulting mixed ligand complexes at 25 °C were calculated using 3.0 mol·dm^{-3} KCl ionic strength. The species distribution diagrams for the complexes in solution were generated considering the formation of the $[V(8HQ)(H_2Asp)]^{2+}$ and V(8HQ)(Asp) complexes in the vanadium(III)–H8HQ–H_2Asp system. Several species were observed: $[V(8HQ)(HGlu)]^{+}$, V(8HQ)(Glu) and $[V(8HQ)(Glu)(OH)]^{-}$ in the vanadium(III)–H8HQ–H_2Glu system; species; $[V(8HQ)(H_2Cys)]^{2+}$, $[V(8HQ)(HCys)]^{+}$, V(8HQ)(Cys) and $[V(8HQ)(Cys)(OH)]^{-}$ for the vanadium(III)–H8HQ–H_2Cys system, and the complexes $[V(H8HQ)(HHis)]^{4+}$ and $[V(8HQ)(His)]^{+}$ in the vanadium(III)–H8HQ–HHis system.

1. Introduction

A new era in biomedical–diabetic research was initiated with the discovery of insulin in 1922. Daily injections of insulin to insulin-deficient patients lowered their high level of glucose in the blood to normal values, and interrupted an otherwise fatal metabolic disorder. Insulin is the basis of the treatment of virtually all Type I (insulin-dependent) and several Type II (insulin-independent) diabetes. Diabetic patients need to receive insulin via subcutaneous injections as oral administration of insulin is ineffective in mammals [1].

Researchers, particularly in the last three decades, have been searching for insulin-substitutes to assist in the therapy of the disease. During 1975–1980 a renewed interest in vanadium arose in the biochemists and cell biologist communities. This has been attributed mainly to the efficacy of vanadate to inhibit phosphohydrolases at micromolar quantities. An example of such an enzyme is Na^+, K^+-ATPase [2]. The efficacy of vanadate in inhibiting Na^+, K^+-ATPase is historically linked to the finding of the insulino-mimetic actions of vanadium salts.

The synthesis and characterization of V(III)–maltol(ma) complexes as anti-diabetic candidate agents were achieved in 2001 [3]. As with other metal chelates of these and related ligands, reasonable hydrolytic and thermodynamic stabilities were anticipated, and the air stability of $V(ma)_3$ was an unexpected advantage. Treatment with either $V(ma)_3$ or $VO(ma)_2$ resulted in glucose-lowering in STZ-diabetic rats of comparable and significant magnitudes, both when administered by i.p. injections and orally, with no added toxicity, some gastrointestinal distress, and no fatalities [4].

Maltol and ethyl maltol have proven highly suitable as ligands for vanadyl ions, thus as potential insulin enhancing agents for diabetes mellitus. Both bis(maltolato)oxide vanadium(IV) (BMOV), and the ethylmaltol analog, bis(ethylmaltolato)oxide vanadium(IV) (BEOV), have the desired intermediate stability for pro-drug use, and have undergone extensive pre-clinical testing for safety and efficacy. Pharmacokinetic evaluation results in a biodistribution pattern consistent with fairly rapid dissociation and uptake, binding to serum transferring for systemic circulation and transport to tissues, with preferential uptake in bones. BEOV has completed Phase I and has advanced to Phase II clinical trials [5].

Recently, Crans et al. [6] presented the first systematic investigation of the anti-diabetic properties of non-oxide V(IV) complexes. The results suggest that a V(IV)O functionality is necessary for vanadium complexes to exhibit anti-diabetic effects, in agreement with the notion that the biotransformations of V compounds in the organism are more relevant than the nature of the involved species.

Based on the potential role of vanadium(III) complexes in medicine, it is foreseen that after oral administration of these complexes, they may

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encounter other potential vanadium(III) binding molecules in extracellular or intracellular biological fluids. These potential ligands may partially or completely displace the original vanadium(III) carrier molecules from the metal coordination sphere. This suggests that ternary complex formation should be taken into account in a speciation description of these complexes in biological fluids. Such ternary complexes could play a significant role in the absorption and transport of vanadium(III) complexes, and even in their physiological activity [7]. Until now, there are no reports on the speciation of the ternary vanadium(III)–H8HQ (H8HQ = 8-hydroxyquinoline) complexes with aspartic acid (H_2Asp), glutamic acid (H_2Glu), cysteine (H_2Cys) and histidine (HHis) [8,9].

2. Experimental

2.1. Reagents

VCl_3 (Merck p.a), 8-hydroxyquinoline (H8HQ) (Merck p.a.) and all the amino acids (aspartic acid (H_2Asp), glutamic acid (H_2Glu), cysteine (H_2Cys) and histidine (HHis)) (Merck p.a) were used without additional purification. HCl and KOH solutions were prepared using 100.0 mmol·dm^{-3} Titrisol Merck ampoules. The KOH solution was standardized against potassium hydrogen phthalate. The solutions were prepared using triple glass-distilled water, boiled before preparation of the solutions in order to remove any dissolved CO_2. To prevent the hydrolysis of the VCl_3 stock solution containing 200 mmol·dm^{-3} HCl was maintained under a H_2 atmosphere in the presence of a Pt platinized mesh to avoid oxidation of the V(III) solution to V(IV) [10]. Under these conditions the vanadium(III) solution can be maintained. The stability of the vanadium(III) solution was periodically checked by spectrophotometric measurements and it was found to be stable for several weeks. Emf (H) measurements were carried out in aqueous solution at an ionic strength of 3.0 mol·dm^{-3} in KCl. Nitrogen free O_2 and CO_2 were used.

2.2. Methods

The emf (H) measurements were done using a Thermo Orion pH meter (model 520A), a Metrohm EA 876–20 titration vessel, a Lauda Brikmann RM6 thermostatic bath, a Shimadzu UV-1601 PC spectrophotometer, and a quartz cell with 10.0 mm path length. The sealed 100 mL thermostatic double-wall glass titration vessel was fitted with a combined Orion Ross 8102BN pH electrode with a titrant inlet and a magnetic stirrer, in an inert nitrogen atmosphere for the inlet and outlet tubes. The temperature was maintained at (25.0 ± 0.1)°C by constant circulation of water from the thermostatic bath.

The emf (H) measurements were carried out using the REF//S/GE cell, where REF = Ag/AgCl/3.0 *M* KCl, S denotes the equilibrium solution and GE the glass electrode. At 25 °C the emf (mV) of this cell follows Nernst's equation, $E = E^0 + jh + 59.16 \log h$, where h represents the free hydrogen ion concentration, E^0 is the standard potential, and j is a constant which takes into account the liquid junction potential [11].

The experiments were carried out as follows: a fixed volume of 0.100 mol·dm^{-3} HCl was titrated with successive additions of 0.100 mol·dm^{-3} KOH until near neutrality in order to get parameters E^0 and j. Then, the volume of a stock solution of the ligands and an aliquot of the vanadium(III) stock solution were added sequentially. Finally, the titration continued with 0.100 mol·dm^{-3} KOH. The measurements were done using a total metal concentration, M_T of 2–3 mmol·dm^{-3} and a vanadium(III):H8HQ:amino acid molar ratio of R = 1:1:1, 1:2:1 and 1:1:2 respectively. The dissociation constants of H8HQ and the amino acids: aspartic acid (H_2Asp), glutamic acid (H_2Gly), cysteine (H_2Cys) and histidine (HHis), were determined (see Table 1). pK_i values in a 3.0 mol·dm^{-3} KCl ionic medium are also presented in Table 1. The obtained values are in good agreement with those previously reported in the literature [8,9].

Table 1
Acidity constants ($\log \beta$) and pK_a values of the ligands studied (3.0 mol·dm^{-3} KCl at 25 °C).

	$\log \beta_{pr}$				
Equilibrium	H8HQ	H_2Asp	H_2Glu	H_2Cys	HHis
$H_2L + H^+ \rightleftharpoons H_3L^+$		1.68(4)	2.603(8)	2.14(2)	
$H_2L \rightleftharpoons HL^- + H^+$		−3.94(4)	−4.510(6)	−8.42(2)	
$H_2L \rightleftharpoons L^{2-} + 2H^+$		−13.63(8)	−14.309(9)	−18.87(2)	
$HL \rightleftharpoons L^- + H^+$					−9.44(2)
$HL + H^+ \rightleftharpoons H_2L^+$	5.479(8)				6.63(1)
$HL + 2H^+ \rightleftharpoons H_3L^+$					8.90(2)
Dispersion(σ)	0.008	0.037	0.008	0.019	0.015
pK_i					
pKa_1	5.479	1.68	2.603	2.14	2.27
pKa_2		3.94	4.510	8.42	6.63
pKa_3		9.69	9.799	10.45	9.44

Values in parentheses are standard deviations [3$\sigma(\log \beta)$] on the last significant figure.

The V^{3+}–H8HQ–Amino acid (H_iL) systems were studied using the following reaction scheme:

$$pH_2O + qV^{3+} + rH8HQ + sHiL \rightleftharpoons [Vq(OH)p(H8HQ)r(HiL)s] + pH^+, \beta_{pqrs}$$

where (H_iL) represents the used amino acids: H_2Asp, H_2Glu, H_2Cys and HHis. In this notation i = 1 for HHis, 2 for H_2Asp, H_2Glu, H_2Cys, and [Vq(OH)p(H8HQ)r(HiL)s] is the ternary (p, q, r, s) complex with $\beta_{p,\,q,\,r,\,s}$ as the respective stability constant.

The potentiometric data were analysed using the in-house LETAGROP program [12,13], allowing to minimize the $Z_B = (h - H)/M_T$ function, where Z_B denotes the proton dissociate per mole of V(III) number, H is the total (analytical) concentration of H^+, h represents the H^+ equilibrium concentration and C the total (analytical) concentration of H8HQ.

Equilibria associated to the formation of the hydroxo complexes of vanadium(III) were considered in the calculation of the stability constants of ternary complexes. The following species were assumed present: $[V(OH)]^{2+}$, $\log \beta_{1,-1} = -3.13(8)$; $[V_2O]^{4+}$, $\log \beta_{2,-2} = -3.76(6)$; $[V(OH)_2]^+$, $\log \beta_{1,-2} = -6.86(2)$; and $[V_3(OH)_8]^+$, $\log \beta_{3,-8} = -27.47(4)$ [14]. The stability constants of binary systems were taken into account for the calculation of the stability constant of the ternary complexes; for example for the vanadium(III)–H8HQ's system the following complexes were considered: $V(OH)(L)^+$, $\log \beta_{1,1,-2} = (8.7 \pm 0.1)$; $V(OH)_2(L)$, $\log \beta_{1,1,-3} = (5.85 \pm 0.08)$; $V(L)_2^+$, $\log \beta_{1,2,-2} = (17.9 \pm 0.3)$; and $V(L)_3$, and $\log \beta_{1,3,-3} = (25.8$ max 26.1); their stability constants are given in [15]. For the vanadium(III)–H_2Asp complex the stability constants are given in [16], $V(HL)^{2+}$, $\log \beta_{1,1,-1} = (5.95 \pm 0.02)$; $V(L)^+$, $\log \beta_{1,1,-2} = (2.34 \pm 0.05)$; V(OH)L, $\log \beta_{1,1,-3} = (-1.57 \pm 0.04)$; $V(OH)_2\,L^-$, $\log \beta_{1,1,-4} = (-7.22 \pm 0.07)$; $V(HL)_2^+$, $\log \beta_{1,2,-2} = (5.18 \pm 0.03)$; V(HL)L, $\log \beta_{1,2,-3} = (1.57 \pm 0.04)$; and VL_2^-, $\log \beta_{1,2,-4} = (-2.75 \pm 0.03)$, the stability constants of the vanadium(III)–H_2Glu system are given in [17], $V(H_2L)^{3+}$, $\log \beta_{1,1,0} = (3.00 \pm 0.06)$; $V(HL)^{2+}$, $\log \beta_{1,1,-1} = (-0.11 \pm 0.05)$; $V(HL)_2^+$, $\log \beta_{1,2,-2} = (-2.50 \pm 0.08)$ and $V(HL)_3^+$, $\log \beta_{1,3,-3} = (-5.43 \pm 0.06)$. In the case of the vanadium(III)–H_2Cys the stability constants [18] are: $V(HL)^{2+}$, $\log \beta_{1,1,-1} = (6.00 \pm 0.03)$; $V(L)^+$, $\log \beta_{1,1,-2} = (1.77 \pm 0.07)$; V(L)(OH), $\log \beta_{1,1,-3} = (-2.52 \pm 0.04)$; $V(HL)_2^+$, $\log \beta_{1,2,-2} = (4.26 \pm 0.08)$; V(HL)(L)], $\log \beta_{1,2,-3} = (-0.7 \pm 0.3)$; and $V(L)_2^-$, $\log \beta_{1,2,-4} = (-5.9 \pm 0.3)$, and for the vanadium(III)–HHis system the stability constants are [19]: $V(H_2L)^{4+}$, $\log \beta_{1,1,1} = (12.59 \pm 0.07)$; $V(HL)^{3+}$, $\log \beta_{1,1,0} = (8.1 \pm 0.1)$; $V(L)^{2+}$, $\log \beta_{1,1,-1} = (3.51 \pm 0.07)$; and $V_2O(L)_4$, $\log \beta_{2,4,-6} = (-9.8 \pm 0.3)$.

The stability constants of the vanadium(III) hydroxo complexes, the stability constants of the ligands and the stability constants of the binary complexes were kept fixed during the analysis. The aim was to find the complex or set of complexes resulting in the lowest sum of the squared

Table 2
Stability constant ($\log \beta_{pqrs}$) of the vanadium(III)–H8HQ–H_iL system (3.0 mol·dm^{-3} KCl at 25 °C). According to the following reaction scheme: $pH_2O + qV^{3+} + rH8HQ + sH_iL \rightleftharpoons [Vq(OH)p(H8HQ)r(H_iL)s] + pH^+$, β_{pqrs}.

Complexes	$\log \beta_{pqrs}$			
	H_2Asp	H_2Glu	H_2Cys	HHis
$[V(8HQ)H_2L]^{2+}$	16.34(5)		16.32(7)	
$[V(8HQ)HL]^{+}$		12.71(5)	12.4 max 12.8	
V(8HQ)L	10.0(1)	10.30(5)	10.1(2)	
$[V(8HQ)L(OH)]^{-}$		7.29(5)	7.2(2)	
$[V(H8HQ)HL]^{3+}$				22.7(2)
$[V(8HQ)L]^{+}$				15.7(4)
Dispersion (σ)	0.075	0.058	0.061	0.054

Values in parentheses are standard deviations [3σ(log β)] on the last significant figure.

errors, $U = \sum (Z_B^{exp} - Z_B^{calc})^2$, in the analysis of Z_B function, by testing different (p, q, r, s) combinations.

The species distribution diagrams were generated with the HYSS computer program [20] leading to the β_{pqrs} values summarized in Table 2.

3. Results

3.1. Ionization constants of studied ligands

The ionization constants (Table 1) in the 3.0 mol·dm^{-3} KCl ionic medium are in good agreement with literature value trends taking into account the differences in ionic strength and ionic medium [8,9] used here.

3.2. Ternary vanadium(III) complexes

3.2.1. Vanadium(III)–H8HQ–H_2Asp system

Fig. 1 shows the species distribution diagrams considering the stability constants summarized in Table 2 assuming $M_T = 3$ mmol·dm^{-3} and 1:1:2 molar ratio.

3.2.2. Vanadium(III)–H8HQ–H_2Glu system

Fig. 3 presents the species distribution diagrams for this system using the stability constants summarized in Table 2, under the conditions of $M_T = 3$ mmol·dm^{-3} and 1:1:2 molar ratio.

3.2.3. Vanadium(III)–H8HQ–H_2Cys

The species distribution diagram based on the stability constants summarized in Table 2 is shown in Fig. 3. The diagram assumes $M_T = 3$ mmol·dm^{-3} and 1:1:2 molar ratio.

3.2.4. Vanadium(III)–H8HQ–HHis system

Fig. 4 shows the species distribution diagrams generated using the stability constants summarized in Table 2, assuming $M_T = 3$ mmol·dm^{-3} and 1:1:2 molar ratio.

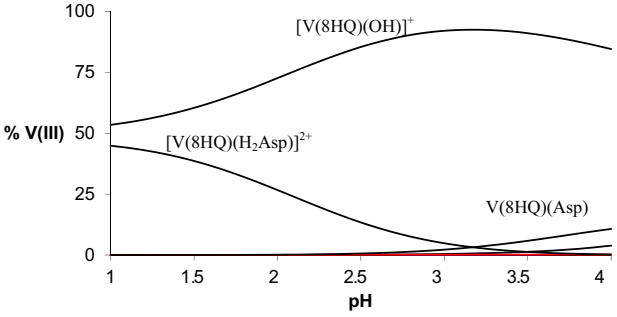

Fig. 1. Species distribution diagrams for the V(III)–H8HQ–H_2Asp system. $M_T = 3$ mmol·dm^{-3} R = 1:1:2.

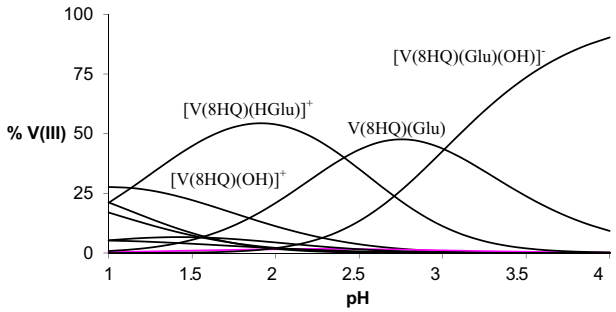

Fig. 2. Species distribution diagrams for the V(III)–H8HQ–H_2Glu system. $M_T = 3$ mmol·dm^{-3} R = 1:1:2.

4. Discussion

In the vanadium(III)–H8HQ–H_2Asp system the best fit to the experimental data was obtained considering a two species model: $[V(8HQ)(H_2Asp)]^{2+}$ and V(8HQ)(Asp). From the species distribution diagram shown in Fig. 1 for a 1:1:2 molar ratio, it is observed that the abundance of the binary $[V(8HQ)(OH)]^+$ for the entire pH range is studied. The $[V(8HQ)(H_2Asp)]^{2+}$ ternary complex is observed for pH values between 1 and 3, and the V(8HQ)(Asp) complex is formed in a very low proportion at pH = 4.

In the case of the vanadium(III)–H8HQ–H_2Glu system the best fitting to the experimental data was found considering $[V(8HQ)(HGlu)]^+$, V(8HQ)(Glu) and $[V(8HQ)(Glu)(OH)]^-$ complexes. Fig. 2 shows the species distribution diagram where it is clearly seen that the $[V(8HQ)(HGlu)]^+$ complex is predominantly present in the range $1 \leq pH \leq 2.4$. For pH values in the 2.4 to 3 range there is a predominance of the neutral species V(8HQ)(Glu), and at pH > 3 the $[V(8HQ)(Glu)(OH)]^-$ complex is dominant.

In the case of the vanadium(III)–H8HQ–H_2Cys system four complexes were detected: $[V(8HQ)(H_2Cys)]^{2+}$, $[V(8HQ)(HCys)]^+$, V(8HQ)(Cys) and $[V(8HQ)(Cys)(OH)]^-$. Fig. 3 presents the species distribution diagram where it can be seen that $[V(8HQ)(H_2Cys)]^{2+}$ species is very important in the range $1 < pH < 3$. For pH values between 2 and 3 the $[V(8HQ)(HCys)]^+$ complex is observed in a very low proportion whereas the V(8HQ)(Cys) complex is present for pH values between 2.5 and 4 but it is formed with a 20%, and the $[V(8HQ)(Cys)(OH)]^-$ complex is very abundant at pH > 3.

Finally, in the analysis of the vanadium(III)–H8HQ–HHis system, two complexes: $[V(H8HQ)(HHis)]^{3+}$ and $[V(8HQ)(His)]^+$ were detected. The corresponding species distribution diagrams are given in Fig. 4 where it is seen that the $[V(H8HQ)(HHis)]^{3+}$ complex is the most important species in the $1 < pH < 3.5$ range. The ternary complex $[V(8HQ)(His)]^+$ is abundant at pH > 3.5, and the species $[V(8HQ)(OH)]^+$ is formed in low proportion in the range of pH 3–4.

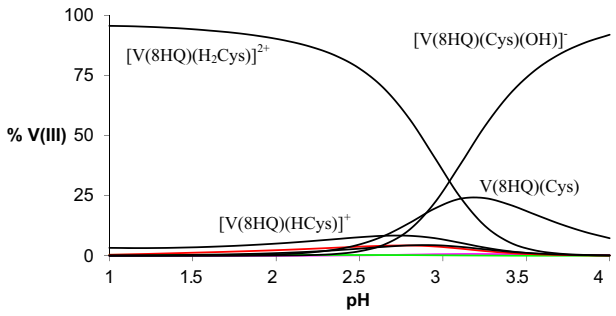

Fig. 3. Species distribution diagrams for the V(III)–H8HQ–H_2Cys system. $M_T = 3$ mmol·dm^{-3} R = 1:1:2.

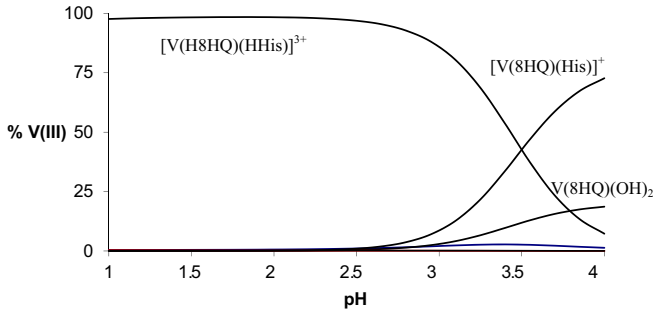

Fig. 4. Species distribution diagrams for the V(III)–H8HQ–HHis system. $M_T = 3$ mmol·dm^{-3} R = 1:1:2.

5. Conclusion

This work presents the results of a study on the speciation of the ternary complexes formed between vanadium(III), H8HQ, and the amino acids H_2Asp, H_2Glu, H_2Cys and HHis. data analysis using LETAGROP software tool indicates the formation of the $[V(8HQ)(H_2Asp)]^{2+}$ and V(8HQ)(Asp) complexes in the vanadium(III)–H8HQ–H_2Asp system, in the vanadium(III)–H8HQ–H_2Glu system where species $[V(8HQ)(HGlu)]^{+}$, V(8HQ)(Glu) and $[V(8HQ)(Glu)(OH)]^{-}$ were detected. Species $[V(8HQ)(H_2Cys)]^{2+}$, $[V(8HQ)(HCys)]^{+}$, V(8HQ)(Cys) and $[V(8HQ)(Cys)(OH)]^{-}$ were observed for the vanadium(III)–H8HQ–H_2Cys system. Finally, in the vanadium(III)–H8HQ–HHis system the complexes $[V(H8HQ)(HHis)]^{4+}$ and $[V(8HQ)(His)]^{+}$ were observed.

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