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Nota técnica

Ternary Complex Formation between Vanadium(III), 8-Hydroxiquinoline and Small Blood Serum Bioligands

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Resumen

A fin de evaluar el papel de los bioligandos de bajo peso molecular en el suero sanguíneo con el vanadio, se realizó un estudio de las interacciones de los complejos formados en el sistema de Vanadio(III)/8-Hidroxiquinolina (H8HQ) con diversos componentes del suero de la sanguíneo, como el ácido láctico (HLac), ácido oxálico (H_2Ox), ácido cítrico (H_3Cit) y ácido fosfórico (H_3PO_4). La especiación de los sistemas ternarios fue estudiada por potenciometría-pH a 25 °C empleando una fuerza iónica $I = 3{,}0$ mol.dm^{-3} KCl.

Palabras claves: complejos de Vanadio(III); 8-Hidroxiquinolina (H8HQ); estudios potenciométricos; especiación; complejos ternarios.

Abstract

In order to assess the role of the low molecular mass bioligands of blood serum in vanadium binding, a study was made of the interactions of the complexes formed in the Vanadium(III)/8-Hydroxyquinoline (H8HQ) system with various low molecular mass constituents of blood serum, such as lactic acid (HLac), oxalic acid (H_2Ox), citric acid (H_3Cit) and phosphoric acid (H_3PO_4). The speciation of the ternary systems was studied by pH-potentiometry at 25 °C using an ionic strength $I = 3.0$ mol.dm^{-3}KCl.

Keywords: Vanadium(III) complexes; 8-Hydroxyquinoline; potentiometric studies; speciation; ternary complexes.

Introduction

Vanadium is a trace bioelement that plays an important role in several metabolic and mitogenic processes. For deeper understanding of the biological role of vanadium it is necessary to do studies of model compounds. The coordination chemistry of the vanadium(III) compounds has been investigated far less than the corresponding chemistry of vanadium(IV) and vanadium(V). Complex compounds of vanadium(III), however, can play important role in biochemical redox processes. In addition, there are organisms such as ascidians in which the principal oxidation state of vanadium is +3[1].

The trismaltolato-vanadium(III) complex has been studied and its insulin-mimetic activity demonstrated[2], being this the first report on the insulin-mimetic activity of some vanadium(III) complex.

The idea is that after oral administration of these complexes, they may encounter many other potential vanadium(III) binding molecules present in extracellular or intracellular biological fluids. These latter ligands may partially or completely displace the original vanadium carrier molecules from the coordination sphere of the metal. Accordingly, ternary complex formation should be taken into account in a speciation description of these complexes in biological fluids. Such ternary complexes might be of great importance in the absorption and transport process of the vanadium complexes and even in their physiological activity[3].

The study of the vanadium(III) speciation has been limited, because the easy oxidation of the vanadium(III) and the high tendency to the hydrolysis of this metal ion[4].Until know, there are no reports on the speciation of ternary vanadium(III)/8-hydroxyquinoline complexes with Lactic acid (HLac), oxalic acid (H_2Ox), phosphoric acid (H_3PO_4) and citric acid (H_3Cit)[5,6].

In this work we report the results on mixed ligand complex formation in the V(III)–8-Hydroxyquinoline–ligands B systems, where ligands B were the most important low molecular mass (l.m.m.) V(III) binders presents in blood serum: HLac, H_2Ox, H_3PO_4 and H_3Cit. The pH-potentiometry technique was used to determine the stoichiometries and stability constants of the complexes formed in aqueous solution.

Experimental

Reagents and Methods

The VCl_3 (Merck p.a) and the 8-hydroxyquinoline (H8HQ) (Merck p.a.), and the HLac, Na_2Ox, Na_3PO_4 and Na_3Cit (Merck p.a.), were used without purification. The 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 the preparation of the solutions in order to remove dissolved CO_2. To prevent the hydrolysis of the VCl_3 stock solution, it contained 200 $mmol.dm^{-3}$ HCl and was maintained under a H_2 atmosphere in the presence of a Pt platinized net in order to avoid oxidation of the V(III) solution to V(IV)[7]. In this case, the H_2 cannot induce reduction to V(II), because the V(III)/V(II) standard potential is negative ($E^0 = -0.26$ V)[8]. Moreover, if there is any oxidation to V(IV), the solution is immediately reduced to V(III) because of the standard potential of the reaction:

$$VO^{2+} + H^+ + \frac{1}{2} H_2(g) \rightleftharpoons V^{3+} + H_2O(l)$$

is 366.3(3) mV[9]. Under these conditions, the V(III) solution can be maintained. The stability of the V(III) solution was checked periodically by spectrophotometric measurements and it was shown to be stable for several weeks. The 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 was used to maintain an inert atmosphere.

The emf(H) measurements were done using the following instruments: Thermo Orion model 520ApH meter, Metrohm EA 876–20 titration vessel, Lauda Brikmann RM6 thermostat bath, Shimadzu UV-1601 PC spectrophotometer, and a quartz cell with a 10.0 mm path length. The sealed 100 mL thermostatted double-walled glass titration vessel was fitted with a combined Orion Ross 8102BN pH electrode with a titrant inlet, magnetic stirrer, and an inert nitrogen atmosphere inlet with outlet tubes. The temperature was maintained at 25.0(1) ◦C by constant circulation of water from the thermostat bath.

The emf (H) measurements were carried out by means of the REF//S/GE cell, where REF = Ag, AgCl/ 3.0 $mol.dm^{-3}$KCl; S = equilibrium solution and GE = glass electrode. At 25 ◦C the emf (mV) of this cell follows the Nernst 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[10]. 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 the parameters E^0 and j. Then, aliquots of H8HQ, and the ligand B and an aliquot of the vanadium(III) stock solution were added sequentially. Finally, the titration was continued with 0.100 $mol.dm^{-3}$ KOH. The measurements were done using a total metal concentration, M_T= 2–3 $mmol.dm^{-3}$ and vanadium(III):H8HQ:ligand Bmolar ratios R = 1:1:1, 1:2:1 and 1:1:2.

The V(III)-H8HQ-ligand B systems were studied according to the reaction scheme:

$$pH_2O + qV^{3+} + rH8HQ + sH_jB \rightleftharpoons [V_q(OH)_p(H8HQ)_r(H_jB)_s] + pH^+$$

where ligand B represents the ligands: HLac, H_2Ox, H_3PO_4 and H_3Cit, and$[V_q(OH)_p(H8HQ)_r(H_jB)_s]$is the ternary (p, q, r, s) complex and $\beta_{p,q,r,s}$ is the respective stability constant.

The potentiometric data were analysed using the program LETAGROP[11,12], in order to minimize the function $Z_B = (h - H)/M_T$, where H is the total (analytical)concentration of H^+, h represents the equilibrium concentration of H^+, and M_T represents the total (analytical) concentration of V^{3+}. Equilibria corresponding to the formation of the hydroxo complexes of V(III) were considered in the calculation of the stability constants of the ternary complexes. The following species were assumed: $[V(OH)]^{2+}$, $\log\beta_{1,-1} = -3.07(3)$; $[V_2O]^{4+}$, $\log\beta_{2,-2} = -3.94(2)$; and $[V_2O(OH)]^{3+}$, $\log\beta_{2,-3} = -7.87(9)$[9]. In the case of the V(III)-H8HQ system[13] the complexes $[V(8HQ)(OH)]^+$, $\log\beta_{1,1,-2} = 8.7(1)$; $V(8HQ)(OH)_2$, $\log\beta_{1,1,-3} = 5.85(8)$; $[V(8HQ)_2]^+$, $\log\beta_{1,2,-2} = 17.9(3)$; $V(8HQ)_3$, $\log\beta_{1,3,-3} = 25.8$ max 26.1 were considered. In the binary V(III)/HLac system[14] the complexes: $[V(Lac)]^{2+}$, $\log\beta_{1,1,-1} = 0.11(4)$; $[V(Lac)(OH)]^+$, $\log\beta_{1,1,-2} = -2.29(2)$; $[V(Lac)(OH)_2]$, $\log\beta_{1,1,-3} = -7.74(3)$ were taken into account. In the V(III)/H_2Ox system[15] the complexes: $[V(HOx)]^{2+}$, $\log\beta_{1,1,-1} = 6.83(3)$; $[V(Ox)]^{2+}$, $\log\beta_{1,1,-2} = 5.16(3)$; $[V(Ox)(OH)]$, $\log\beta_{1,1,-3} = 0.97(5)$; $[V(Ox)(OH)_2]^-$, $\log\beta_{1,1,-4} = -4.76(7)$; $[V(Ox)_2]^-$, $\log\beta_{1,2,-4} = 6.37(8)$; $[V(Ox)_2(OH)]^{2-}$,$\log\beta_{1,2,-5} = 1.6(1)$; $[V(Ox)_3]^{3-}$, $\log\beta_{1,3,-6} = 7.23(6)$; $[V(Ox)_3(OH)]^{4-}$, $\log\beta_{1,3,-7} = 1.15(7)$ were considered. In the V(III)/H_3PO_4 system[14] the complexes: $[V(H_2PO_4)]^{2+}$, $\log\beta_{1,1,-1} = 1.17(4)$; $[V(HPO_4)]^+$, $\log\beta_{1,1,-2} = -1.08(7)$; $[V(HPO_4)(H_2PO_4)]$, $\log\beta_{1,2,-3} = 0.06(6)$; $[V(HPO_4)_2]^-$, $\log\beta_{1,2,-4} = -2.69(6)$ were considered. Finally, in the V(III)/H_3Cit system[14] the complexes: $[V(HCit)]^+$, $\log\beta_{1,1,-2} = -1.24(1)$; $[V(Cit)]$, $\log\beta_{1,1,-3} = -4.66(3)$; $[V(HCit)_2]^-$, $\log\beta_{1,2,-4} = -5.53(9)$; $[V(HCit)(Cit)]^{2-}$, $\log\beta_{1,2,-5} = -8.50(2)$; $[V(Cit)_2]^{3-}$, $\log\beta_{1,2,-6} = -13.26(2)$; $[V(Cit)_2(OH)]^{4-}$, $\log\beta_{1,2,-7} = -19.24(3)$ were considered.

The stability constant of the V(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 of the analysis was to find a complex or complexes giving the lowest sum of the errors squared, $U=\sum(Z_B^{\exp}-Z_B^{calc})^2$, the fittings were done by testing different (p, q, r, s) combinations. The species distribution diagrams were done with the computer program HYSS[16], yielding the β_{pqrs} values, which are summarized in Tables 2-5.

Results and discussion

Ionization constants of ligands studied

The ionization constants (table 1) in the ionic medium 3.0 mol.dm^{-3} KCl are in good agreement with the literature values, considering the differences in ionic strength and ionic medium)[5,6]. For H8HQ, only was possible to measure the pK_a of the pyridinic group, we observed precipitation problems at neutral pH, so we could not measure the corresponding pK_a of the phenolic group. For the lactic acid (HLac), only one pK_a was obtained, because the hydroxyl group has a pK_a> 14, and it is not possible to measure it in aqueous solution with a glass electrode. For the oxalic acid (H_2Ox) two pK_a values were obtained, because this ligand has two dissociable protons in the studied pH range. In the ortophosphoric acid (H_3PO_4), and citric acid (H_3Cit), three pK_a values were measured. In the case of the H_3Cit, the hydroxyl group has a pK_a > 14, it is not possible to measure it with a glass electrode.

Ternary vanadium(III) complexes

V(III)/H8HQ/HLac system:

The results of the analysis performed with the LETAGROP program, indicate the formation of an unique ternary complex $[V(8HQ)(Lac)(OH)_2]^-$. In table 2 are summarised the respective stability constants and the species distribution diagrams are depicted in figure 1.

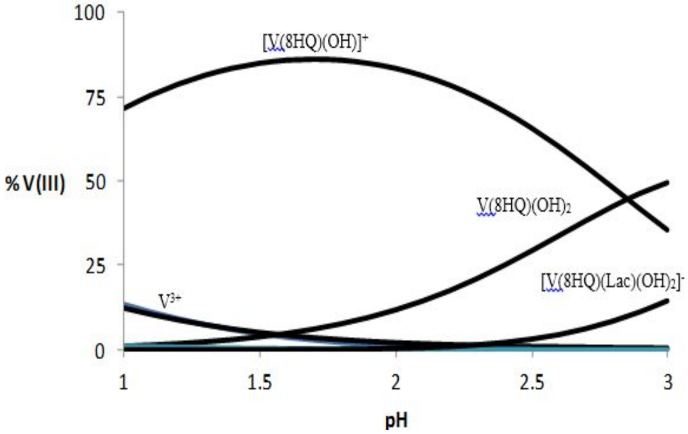

Fig. 1: Species distribution diagram of the V(III)/H8HQ/HLac system. Considering M_T= 3 mM and V^{3+}-H8HQ/HLac ratio R = 1:1:2.

V(III)/H8HQ/H_2Ox system:

The analysis obtained indicate the formation of the complexes $[V(8HQ)(Ox)(OH)]^-$ and $[V(8HQ)(Ox)(OH)_3]^{3-}$, with the stability constants given in table 3. The respective species distribution diagrams are presented in figure 2.

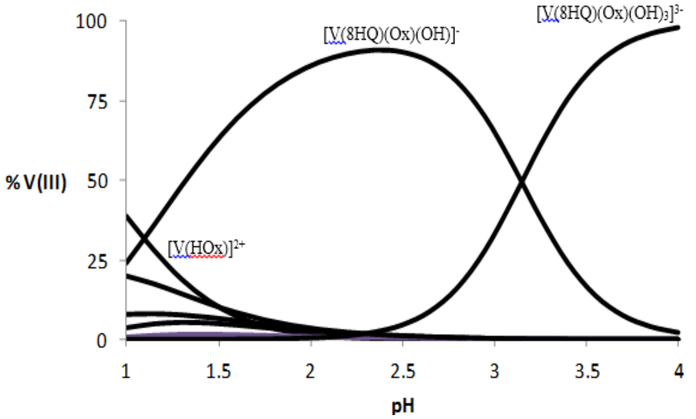

Fig. 2: Species distribution diagram of the V(III)/H8HQ/H_2Ox system. Considering M_T= 3 mM and V^{3+}-H8HQ-H_2Ox ratio R = 1:1:1.

Table 1: Ligands acidity constants (log $\beta_{p,r}$) in 3.0 mol.dm^{-3} KCl at 25 ºC.

Equilibrium	**log β_{pr}**				
	H8HQ	**HLac**	**H_2Ox**	**H_3Cit**	**H_3PO_4**
$HL + H^+ \rightleftharpoons H_2L^+$	5.39(2)				
$H_nL \rightleftharpoons H_{n-1}L^- + H^+$		-3.86(1)	-1.321(7)	-3.014(7)	-1.67(3)
$H_nL \rightleftharpoons H_{n-2}L^{2-} + 2H^+$			-5.038(7)	-7.313(7)	-8.08(3)
$H_nL \rightleftharpoons H_{n-3}L^{3-} + 3H^+$				-12.678(7)	-19.12(4)
Dispersion σ (Z)	0.021	0.015	0.009	0.009	0.030
Ligand concentration (mmol.dm^{-3})	3.0	3.0	3.0	3.0	3.0
pK_i					
H_2L^+ - HL	5.39				
HL - L^-		3.86			
H_3L - H_2L				3.014	1.67
H_2L - HL			1.321	4.299	6.41
HL - L			3.717	5.365	11.04

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

Table 2: Stability constants (log β_{pqrs}) of the V(III)/H8HQ/HLac system (KCl 3.0 mol.dm^{-3}, 25 ºC).

Equilibrium	Species	log β_{pqrs}
$V^{3+} + H8HQ + HLac \rightleftharpoons [V(8HQ)(Lac)(OH)_2]^- + 4H^+$	(-4,1,1,1)	4.8(3)
Dispersion (σ)	0.077	

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

Table 3: Stability constants (log β_{pqrs}) of the V(III)/H8HQ/H$_2$Ox system (KCl 3.0 mol.dm^{-3}, 25 ºC).

Equilibrium	Species	log β_{pqrs}
$V^{3+} + H8HQ + H_2Ox \rightleftharpoons [V(8HQ)(Ox)(OH)]^- + 4H^+$	(-4,1,1,1)	11.9(2)
$V^{3+} + H8HQ + H_2Ox \rightleftharpoons [V(8HQ)(Ox)(OH)_3]^{3-} + 6H^+$	(-6,1,1,1)	5.6(1)
Dispersion (σ)	0.090	

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

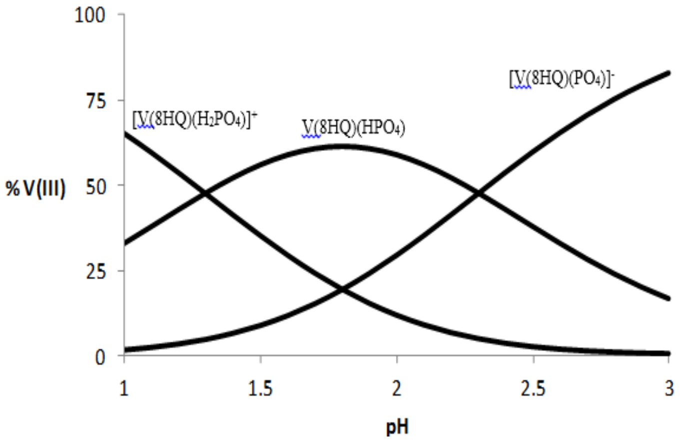

Fig. 3: Species distribution diagram of V(III)/H6Mepic/H$_3$PO$_4$ system. Considering M$_T$= 3 mM and V^{3+}-H8HQ/H$_3$PO$_4$ ratio R = 1:1:1.

V(III)/H8HQ/H$_3$PO$_4$ system

In this case the complexes obtained by the computational analysis were:[V(8HQ)(H$_2$PO$_4$)]$^+$, V(8HQ)(HPO$_4$) and [V(8HQ)(PO$_4$)]$^-$. The stability constants are summarised in Table 4 and the respective species distribution diagrams are shown in figure 3.

V(III)/H8HQ/H$_3$Cit system

Finally, the results obtained in this system considering the formation of two complexes: [V(8HQ)(H$_2$Cit)]$^+$ and [V(8HQ)(Cit)]. The stability constants are presented in table 5 and the species distribution diagrams are given in figure 4.

In the V(III)/H8HQ/HLac ternary system was detected only one complex[V(8HQ)(Lac)(OH)$_2$]$^-$. In figure 1 is given the species distribution diagram for this system taking into account the molar ratio V^{3+}:H8HQ/HLac R = 1:1:2 and M$_T$ = 3 mmol.dm^{-3}, the binary complexes [V(8HQ)(OH)]$^+$ and V(8HQ)(OH)$_2$ predominate in all the pH range studied, only it is observed a low quantity of the ternary complex [V(8HQ)(Lac)(OH)$_2$]$^-$ at pH > 2.5.

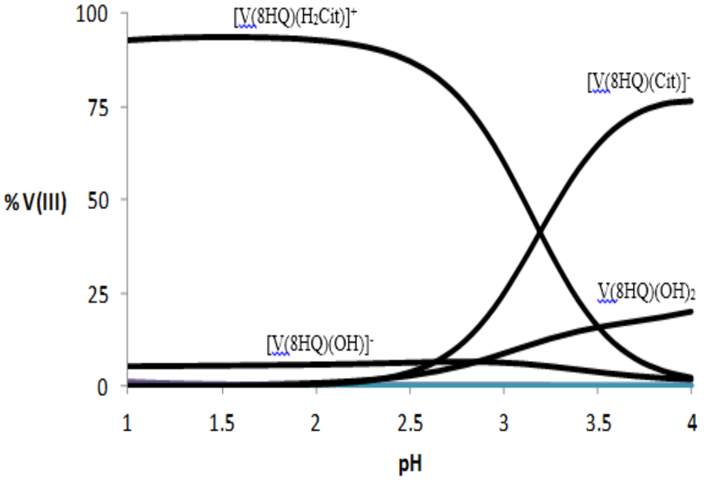

Fig. 4: Species distribution diagram of the V(III)/H8HQ/H$_3$Cit system. Considering M$_T$= 3 mM and V^{3+}-H8HQ/H$_3$Cit ratio R = 1:1:2.

Table 4: Stability constants (log β_{pqrs}) of the V(III)-H8HQ-H$_3$PO$_4$ system(KCl 3.0 mol.dm^{-3}, 25 ºC).

Equilibrium	Species	log β_{pqrs}
$V^{3+} + H8HQ + H_3PO_4 \rightleftharpoons [V(8HQ)(H_2PO_4)]^+ + 2H^+$	(-2,1,1,1)	17.0(1)
$V^{3+} + H8HQ + H_3PO_4 \rightleftharpoons V(8HQ)(HPO_4) + 3H^+$	(-3,1,1,1)	15.7(1)
$V^{3+} + H8HQ + H_3PO_4 \rightleftharpoons [V(8HQ)(PO_4)]^- + 4H^+$	(-4,1,1,1)	13.40(8)
Dispersion (σ)	0.112	

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

Table 5: Stability constants (log β_{pqrs}) of the V(III)/H8HQ/H_3Cit system(KCl 3.0 mol.dm^{-3}, 25 ºC).

Equilibrium	Species	log β_{pqrs}
V^{3+} + H8HQ + H_3Cit $\rightleftharpoons$ [V(8HQ)(H_2Cit)]$^+$ + 2H^+	(-2,1,1,1)	12.63(7)
V^{3+} + H8HQ + H_3Cit $\rightleftharpoons$ [V(8HQ)(Cit)]$^-$ + 4H^+	(-4,1,1,1)	6.24(8)
Dispersión (σ)	0.091	

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

In the V(III)/H8HQ/H_2Ox ternary system were observed the formation of two complexes [V(8HQ)(Ox)(OH)]$^-$ and [V(8HQ)(Ox)(OH)$_3$]^3. We tried to include the complex [V(8HQ)(Ox)(OH)$_2$]$^{2-}$and V(8HQ)(Ox) in the analysis using the program LETAGROP, but the fitting obtained was worse, for this reason was considered the formation of two ternary complexes. In figure 2 are presented the species distribution diagrams for the conditions R = 1:1:1 and M_T = 3 mmol.dm^{-3}. It is observed that the ternary complex[V(8HQ)(Ox)(OH)]$^-$ is very important in the range 1 < pH < 3, and the species [V(8HQ)(Ox)(OH)$_3$]$^{3-}$predominate at pH > 3.

In the case of the V(III)/H8HQ/H_3PO_4 system, the best fitting was obtained considering the formation of three ternary complexes [V(8HQ)(H_2PO_4)]$^+$, V(8HQ)(HPO_4) and [V(8HQ)(PO_4)]$^-$. In figure 3 are presented the species distribution diagrams for the molar ratio R = 1:1:1 and M_T = 3 mmol.dm^{-3}, where can be appreciated that the complex [V(8HQ)(H_2PO_4)]$^+$ is important at 1.3 < pH, in the range 1.3< pH < 2.3 the complex V(6Mepic)(HPO_4) predominate and the ternary species[V(8HQ)(PO_4)]$^-$ is abundant at pH > 2.3.

In the case of the V(III)/H8HQ/H_3Cit system the model obtained considering the formation of the ternary complexes [V(8HQ)(H_2Cit)]$^+$ and [V(8HQ)(Cit)]$^-$. We tried to include in our analysis the species V(8HQ)(H_2Cit), but the fitting was worse than the two complexes finally chosen. The respective species distribution diagrams are given in figure 4 for the conditions R = 1:1:2 and M_T = 3 mmol.dm^{-3}. In the range 1 < pH < 3 predominate the ternary complex [V(8HQ)(H_2Cit)]$^+$ and at pH >3 the most important species is [V(8HQ)(Cit)]$^-$. Are formed in a low quantities the binaries complexes [V(8HQ)(OH)]$^+$ and V(8HQ)(OH)$_2$.

Conclusions

In this work we have studied the speciation of the ternary vanadium(III)/H8HQ/Ligand B systems, where ligand B represents the lactic acid, oxalic acid, phosphoric acid and citric acid, which are small blood serum bioligand. The data analysed using the least-squares computational program LETAGROP, indicate the formation of the complex [V(8HQ)(Lac)(OH)$_2$]$^-$in the vanadium(III)/H8HQ/HLac system. In the case of the vanadium(III)/H8HQ/H_2Ox system the complexes [V(8HQ)(Ox)(OH)]$^-$ and [V(8HQ)(Ox)(OH)$_3$]$^{3-}$ were detected, in the vanadium(III)/H8HQ/H_3PO_4 system the complexes [V(8HQ)(H_2PO_4)]$^+$, V(8HQ)(HPO_4) and [V(8HQ)(PO_4)]$^-$ were detected and finally in the vanadium(III)/H8HQ/H_3Cit system the complexes [V(8HQ)(H_2Cit)]$^+$ and [V(8HQ)(Cit)]$^-$ were observed.

The complex of V(III) with the H8HQ have shown to have antimicrobial activity, particularly when they are associated to bioligand as the components of the small blood serum.

The role of mixed ligand complexes in biological processes has been well recognized. The stabilities of mixed chelates are of great importance in biological systems as many metabolic and toxicological functions are dependent upon this stability. Many attempts have been made to correlate the stability of the metal–ligand complexes with their antimicrobial activity.

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