Journal of Molecular Liquids 207 (2015) 323–326

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Stability constants of the ternary complexes formed between vanadium(III)–salicylic acid and amino acids

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ARTICLE INFO

Available online xxxx

Keywords:
Vanadium(III)
Salicylic acid
Amino acids
Potentiometric studies
Speciation
Ternary complexes

ABSTRACT

In this work, the ternary complex formation between vanadium(III), salicylic acid (H_2Sal) as primary ligand and the amino acids glycine, α-alanine, β-alanine, proline, serine, threonine, methionine and phenylalanine (HL) as secondary ligands, in aqueous solution at 25 °C using 3.0 mol·dm^{-3} KCl as the ionic medium was studied. The analysis of the potentiometric data using the least squares computational program LETAGROP indicates the formation of the species $[V(Sal)(HL)]^{+}$, $V(Sal)(L)$, $[V(Sal)(L)(OH)]^{-}$, $[V(Sal)(L)(OH)_2]^{2-}$, $[V(Sal)_2(L)]^{2-}$ and $[V(Sal)_2(L)(OH)]^{3-}$ in the ternary V(III)–H_2Sal–amino acid (HL) systems studied. The values of Δ log K'' for ternary systems involving amino acids have been evaluated and discussed. The species distribution diagrams as a function of pH were briefly discussed.

1. Introduction

Salicylic acid (H_2Sal), also known as 2-hydroxybenzoic acid, is a weak organic acid which has two acidic functional groups, a carboxylic acid and a phenol. These two acidic groups are in the orthoposition, which is important because depending on the pH this compound can act as a monodentate or bidentate ligand by (COO−, O−) coordination. Salicylic acid is known for its ability to ease aches and pains and reduce fevers. These medicinal properties, particularly fever relief, have been known since ancient times, and it has been used as an anti-inflammatory drug. In modern medicine, salicylic acid and its derivatives are used as constituents of some rubefacient products. For example, methyl salicylate is used as a liniment to soothe joint and muscle pains, and choline salicylate is used topically to relieve the pain of aphthous ulcers. As with other-hydroxy acids, salicylic acid is a key ingredient in many skin-care products for the treatment of acne, psoriasis, calluses, corns, keratosis pilaris, and warts. It works as both a keratolytic and comedolytic agent by causing the cells of the epidermis to shed more readily, opening clogged pores, and neutralizing bacteria within, preventing pores from clogging up again by constricting pore diameter, and allowing room for new cell growth. Because of its effect on skin cells, salicylic acid is used in several shampoos used to treat dandruff. Bismuth subsalicylate, a salt of bismuth and salicyclic acid, is the active ingredient in stomach relief aids such as Pepto-Bismol. Bismuth subsalicylate helps control nausea, heartburn, indigestion, upset stomach, and diarrhea. It is also a very mild antibiotic.

The vanadium(III) maltolato (ma) complex, $V(ma)_3$, showed a similar activity to normalize the glucose level in the STZ-diabetic rat to the benchmark compound, bis(maltolato)oxovanadium(IV), which is an established insulin-enhancing agent [1]. Also the vanadium(III) dipicolinate complexes [2] have shown some insulin-mimetic activity.

After oral administration of these complexes, they may encounter many other potential vanadium(III) binding molecules present in extracellular or intracellular biological fluids. These ligands may partially or completely displace the original vanadium(III) 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 V(III)–salicylic acid complexes and even in their physiological activity [3].

Sakurai et al. [4] studied in vivo coordination structural changes of a potent insulin mimetic agent, bis(picolinato)oxovanadium(IV), by electron spin-echo envelope modulation spectroscopy, and observed that the original binary complex is transformed into a ternary complex with a composition of VO(pic) (X), where pic = picolinate and X represent an amino acid. They said that the activity changes substantially by the formation of this ternary complex. Taking into account the possible application of these complexes, we decided to study the formation of the ternary complexes in the vanadium(III), salicylic acid (H_2Sal), and amino acid (HL) systems, as a contribution to the knowledge of the speciation of the vanadium(III)–H_2Sal in biofluids.

To the best of our knowledge, there are no reports on the speciation of the ternary complexes of vanadium(III)–H_2Sal and the amino acids glycine, α-alanine, β-alanine, proline, serine, threonine, methionine and phenylalanine (HL) [5,6].

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http://dx.doi.org/10.1016/j.molliq.2015.03.056
0167-7322/

Table 1
Values of log β_{pr} and pK_i for the ligands studied (25 °C. I = 3.0 mol·dm^{-3} KCl ionic medium).

	log β_{pr}				
Equilibrium	H_2Sal	HGly	HαAla	HβAla	HPro
$H_2L \rightleftharpoons HL^- + H^+$	−3.10 (4)				
$H_2L \rightleftharpoons L^{2-} + 2H^+$	−14.3 (2)				
$HL + H^+ \rightleftharpoons H_2L^+$		2.78 (2)	2.77 (2)	3.99 (2)	2.52 (2)
$HL \rightleftharpoons L^- + H^+$		−9.81 (2)	−10.02 (2)	−10.47 (2)	−11.09 (3)
Dispersion (σ)	0.025	0.027	0.027	0.019	0.022
pK_i					
pKa_1	3.10 (1.21)[a]	2.78 (2.71)[b]	2.77 (2.72)[b]	3.99 (4.03)[b]	2.52 (2.33)[b]
pKa_2	11.2 (6.32)[a]	9.81 (10.07)[b]	10.02 (10.20)[b]	10.47 (10.65)[b]	11.09 (11.09)[b]

Values in parentheses are standard deviations [3σ(log β)] on the last significant figure. [a]Reference [14] in 3.0 mol·dm^{-3} KCl. [b]Reference [14] Critical μ = 3.0 mol·dm^{-3}.

	log β_{pr}			
Equilibrium	HSer	HThr	HMet	HPhe
$HL + H^+ \rightleftharpoons H_2L^+$	2.60 (4)	2.69 (4)	2.55 (2)	2.37 (3)
$HL \rightleftharpoons L^- + H^+$	−9.17 (4)	−9.12 (4)	−9.30 (2)	−9.22 (3)
Dispersion (σ)	0.031	0.028	0.022	0.030
pK_i				
pKa_1	2.60 (2.41)[b]	2.69 (2.41)[b]	2.55 (2.70)[b]	2.37 (2.75)[b]
pKa_2	9.17 (9.64)[b]	9.12 (9.35)[b]	9.30 (9.69)[b]	9.22 (9.61)[b]

Values in parentheses are standard deviations [3σ(log β)] on the last significant figure. [a]Reference [14] in 3.0 mol·dm^{-3} KCl. [b]Reference [14] μ = 1.0 mol·dm^{-3}.

2. Experimental

2.1. Reagents

VCl_3 (Aldrich) and the amino acids glycine, α-alanine, β-alanine, proline, serine, threonine, methionine and phenylalanine (HL) (Merck, analytical grade) were used as supplied. The solutions of HCl and KCl were prepared by dissolving the respective acid and salts (Merck, analytical grade) in triply glass-distilled water that has been boiled in order to remove dissolved CO_2. A carbonate free hydroxide solution (KOH) was prepared from an ampoule of Titrisol Merck and standardized against potassium hydrogen phthalate [7]. The emf measurements were carried out in aqueous solution at ionic strength 3.0 mol dm^{-3} in KCl. Nitrogen free of O_2 and CO_2 was used.

2.2. Methods

The Emf(H) measurements were done using the following instruments: pH meter, Thermo Orion model 520A pH meter, titration vessel Methrom, and Lauda Brikmann RM6 thermostatic bath. The sealed 100 ml thermostated double-walled glass titration vessel was fitted with an Orion Ross 8102BN pH electrode and titrant inlet, magnetic stirrer, inert nitrogen atmosphere inlet and outlet tubes. The temperature was maintained at 25.00(1) °C by regular circulation of water from the thermostatic bath. The measurements have been carried out by means of the cell REF//S/GE, 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 Nernst's equation E = /E°+/Jh +/59.16 log h, where h represents the free hydrogen ion concentration, E° the standard potential and J a constant which takes into account the liquid junction potential [8]. 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° and J. Then, an aliquot of VCl_3 stock solution and an aliquot of H_2Sal and HL were added, in this order. Finally, the titration was continued with KOH 0.1000 mol·dm^{-3}.

The measurements were performed using a total metal concentration, M_T = 3 mmol·dm^{-3} and molar ratios R = 1:1:1, 1:1:2 and 1:2:1 for the V(III):H_2Sal:amino acid (HL) systems.

The V(III)–H_2Sal–amino acid (HL) systems were studied according to the reaction scheme:

$$pH_2O + qV^{3+} + rH_2Sal + sHL \rightleftharpoons [V_q(OH)_p(H_2Sal)_r(HL)_s] + pH^+, \beta_{pqrs}$$

where HL represents the amino acids studied $[V_q(OH)_p(H_2Sal)_r(HL)_s]$ that are the ternary (p, q, r, s) complexes (the charges were omitted), where β_{pqrs} are the respective stability constants.

The potentiometric data were analyzed using the program LETAGROP [9,10], in order to minimize the function $Z_B = (h - H) / M_T$, where Z_B is the average number of moles of H^+ dissociated per moles of metal, H is the total (analytical) concentration of H^+, h represents the concentration in equilibrium of H^+, and M_T represents the total (analytical) concentration of V(III).

Equilibria corresponding to the formation of the hydroxo complexes of V(III) [11] were considered in the calculation of the stability constants of the ternary complexes. The V(III)–amino acid systems were previously studied in our group [12–16]. The stability constants of the V(III) hydroxo complexes, the dissociation constants of the ligands and the stability constants of the binary complexes were kept fixed during the analysis. The aim 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.

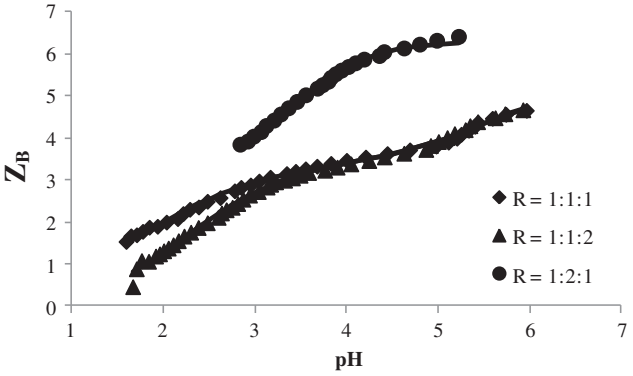

Fig. 1. Z_B vs pH data of the vanadium(III)–H_2Sal–HSer system.

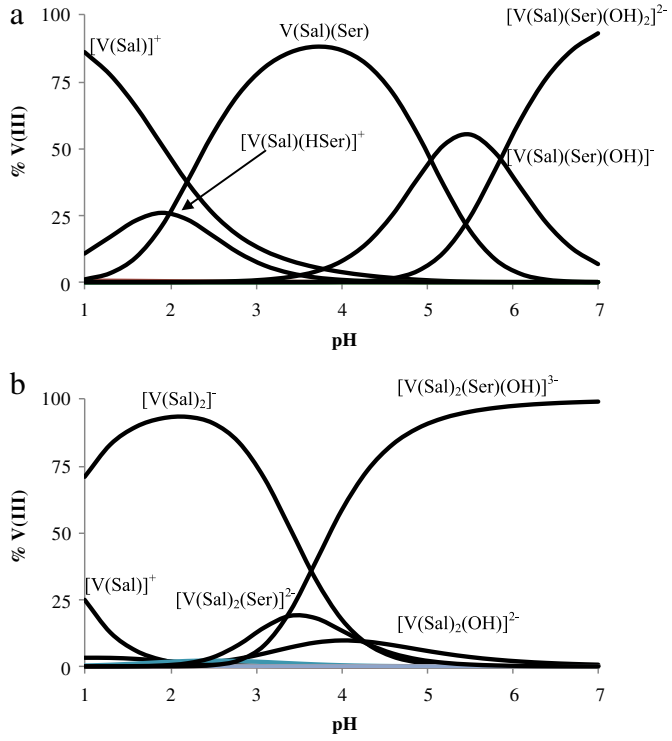

Fig. 2. Species distribution diagrams as a function of pH for the vanadium(III)–H_2Sal–HSer system in 3.0 mol·dm^{-3} KCl at 25 °C considering the conditions (a) M_T = 3 mmol·dm^{-3} and molar ratio R = 1:1:1 and (b) M_T = 3 mmol·dm^{-3} and molar ratio R = 1:2:1.

The species distribution diagrams were done with the computer program HYSS [17], yielding the β_{pqrs} values, which are summarized in Table 2.

Table 2
Equilibrium constants ($\log \beta_{pqrs}$) for the ternary V(III)–H_2Sal–amino acid (HL) systems (25 °C. I = 3.0 mol·dm^{-3} KCl ionic medium). According to the following reaction scheme:

$$pH_2O + qV^{3+} + rH_2Sal + sHL \rightleftharpoons [Vq(OH)p(H_2Sal)r(HL)s] + pH^+ \cdot \beta_{pqrs}.$$

	$\log \beta_{pqrs}$			
Species	HGly	HαAla	HβAla	HPro
$[V(Sal)(HL)]^+$	9.65 (9)	10.57 (4)	10.0 (3)	10.47 (5)
V(Sal)L	7.37 (5)	8.20 (4)	8.68 (7)	8.27 (4)
$[V(Sal)L(OH)]^-$	1.6 max 1.9	3.0 (2)	4.34 (9)	2.9 (2)
$[V(Sal)L(OH)_2]^{2-}$	−2.95 (8)	−2.31 (7)	−0.80 (9)	−2.27 (7)
$[V(Sal)_2\ L]^{2-}$	5.3 (2)	6.54 (7)	5.88 (9)	6.40 (7)
$[V(Sal)_2\ L(OH)]^{3-}$	−0.2 max 0.3	2.0 (1)	−0.3 (3)	1.6 (1)
Δ $\log_{10}$ K″	+2.08	+2.6	+2.69	+1.95
Dispersion (σ)	0.088	0.075	0.079	0.055
	$\log \beta_{pqrs}$			
Species	HSer	HThr	HMet	HPhe
$[V(Sal)(HL)]^+$	8.69 (9)	9.26 (7)	9.20 (6)	9.61 (9)
V(Sal)L	6.69 (3)	6.62 (4)	6.57 (4)	6.03 (8)
$[V(Sal)L(OH)]^-$	1.64 (9)	1.25 (9)	1.6 (1)	0.5 (1)
$[V(Sal)L(OH)_2]^{2-}$	−4.22 (7)	−4.45 (7)	−4.18 (8)	−7.2 (3)
$[V(Sal)_2\ L]^{2-}$	5.9 (2)	6.59 (9)	6.3 (2)	6.1 (1)
$[V(Sal)_2\ L(OH)]^{3-}$	2.53 (7)	2.45 (7)	2.61 (9)	0.7 (2)
Δ log K″	+0.82	+0.77	+1.06	−0.23
Dispersion (σ)	0.057	0.054	0.063	0.088

Values in parentheses are standard deviations [3σ(log β_{pqrs})] on the last significant figure.

3. Results and discussion

3.1. Dissociation constants of the studied ligands

The dissociation 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].

3.2. Ternary vanadium(III)–H_2Sal–amino acid (HL) complexes

In Fig. 1 are observed Z_B(pH) data of the vanadium(III)–H_2Sal–serine system which is similar for all the amino acids studied, the calculated Z_B versus pH curves (continuous line) indicates the correctness of the model obtained. In Fig. 2(a) and (b) the species distribution diagrams are given for the following conditions: M_T = 3 mmol·dm^{-3} and molar ratio (a) R = 1:1:1 and (b) R = 1:2:1, considering the stability constants summarized in Table 2.

In the vanadium(III)–H_2Sal–serine system the analysis of the potentiometric data made, indicated the formation of the complexes $[V(Sal)(HL)]^+$, V(Sal)(L), $[V(Sal)(L)(OH)]^-$, $[V(Sal)(L)(OH)_2]^{2-}$, $[V(Sal)_2(L)]^{2-}$ and $[V(Sal)_2(L)(OH)]^{3-}$. The good agreement between the experimental data (dotted curve) and the model (continuous line) can be observed in Fig. 1. The respective stability constants are summarized in Table 2. In all the systems studied were obtained the same speciation, so was given only the results of the vanadium(III)–H_2Sal–serine system.

It is important to mention that in all the complexes the Sal^{2-} acts as bidentate ligand, and in the case of the protonated species $[V(Sal)(HL)]^+$, the amino acids acts as monodentade ligand coordinated to the vanadium by the carboxylic group and in the rest of complexes the amino acids act as bidentate ligand by N,COO^- coordination.

The relative stability of the ternary complex, compared with the binary complexes, can be obtained considering the Δ $\log_{10}$ K″ value [18], where Δ $\log_{10}$ K″ is calculated with this equation:

$$\Delta \log_{10} K'' = \log_{10} K^{V(Sal)}_{V(Sal)(L)} - \log_{10} K^{V}_{V(L)}.$$

Also, the relative stability of the ternary complexes compared to the binary ones we can take into account the following reaction:

$$V(Sal)^+ + V(L)^{2+} \rightleftharpoons V(Sal)(L) + V^{3+},\ \Delta \log_{10} K''.$$

The Δ $\log_{10}$ K″ expresses the effect of the bound primary ligand (Sal^{2-}) toward an incoming secondary ligand (L^-). Generally, positive Δ $\log_{10}$ K″ values are obtained (Table 2) for the systems indicating favored formation of the ternary complexes over the corresponding binary complexes. This can be ascribed to interligand interactions or some cooperation between the primary and the secondary ligands such as H-bond formation. Also, Δ $\log_{10}$ K″ is negative for the vanadium(III)–H_2Sal–phenylalanine system, which is likely to be due to the smaller number of sites available for bonding on the binary $V(Sal)^+$ complex than on the aquated V^{3+} ion.

The species distribution diagrams given in Fig. 2(a), shows that the $[V(Sal)]^+$ is important at 2 < pH, in the range of 1 < pH < 3 the protonated complex $[V(Sal)(HL)]^+$ is formed in low extension, between 2 < pH < 5 the species V(Sal)(L) is very abundant, the species $[V(Sal)L(OH)]^-$ is present between 4 < pH < 5, and the formation of the complex $[V(Sal)L(OH)_2]^{2-}$ at pH > 6 is very important.

The species distribution diagrams shown in Fig. 2(b) indicate that at 1 < pH < 3.5 the most important species is the binary complex $[V(Sal)_2]^-$ and the ternary complex $[V(Sal)_2L(OH)]^{3-}$ is the most important species at pH > 3.5. The other complexes $[V(Sal)]^+$, $[V(Sal)_2\ L]^{2-}$ and $[V(Sal)_2(OH)]^{2-}$ are formed in low extension in the pH range studied.

4. Conclusions

The analysis of the potentiometric data indicates in all the V(III)–H_2Sal–HL systems the formation of the complexes $[V(Sal)(HL)]^+$, V(Sal)(L), $[V(Sal)(L)(OH)]^-$, $[V(Sal)(L)(OH)_2]^{2-}$,$[V(Sal)_2(L)]^{2-}$ and $[V(Sal)_2(L)(OH)]^{3-}$. The species distribution diagram shows that for the molar ratios R = 1:1:1 and 1:1:2 the predominance of the complexes $[V(Sal)(HL)]^+$, V(Sal)(L), $[V(Sal)(L)(OH)]^-$, $[V(Sal)(L)(OH)_2]^{2-}$ and for the molar ratios R = 1:2:1 the species and $[V(Sal)_2(L)(OH)]^{3-}$ is the most important complex at pH > 3.5.

Funding sources

The authors are grateful for financing provided by the Decanato de Investigación y Desarrollo (Project S1-IC-CB-003-07), from the Simon Bolivar University. Lino Hernández and Edgar Del Carpio thank scholarships from Simon Bolivar University.

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