



# Speciation of the ternary complexes formed between copper(II), salicylic acid and small blood serum bioligands



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## ABSTRACT

In this work we present the speciation of the ternary complexes formed between the copper(II)-salicylate ( $\text{Sal}^{2-}$ ) system and the small blood serum bioligands, such as lactate ( $\text{Lac}^-$ ), oxalate ( $\text{Ox}^{2-}$ ), citrate ( $\text{Cit}^{3-}$ ) and phosphate ( $\text{PO}_4^{3-}$ ). The speciation of the ternary systems were studied by pH-potentiometry at 25 °C and using an ionic strength  $I = 1.0 \text{ mol} \cdot \text{dm}^{-3} \text{ KNO}_3$ . In the Cu(II)- $\text{Sal}^{2-}$ – $\text{Lac}^-$  system the complexes  $[\text{Cu}(\text{Sal})(\text{Lac})(\text{OH})]^{2-}$ ,  $[\text{Cu}(\text{Sal})(\text{Lac})(\text{OH})_2]^{3-}$  and  $[\text{Cu}(\text{Sal})_2(\text{Lac})]^{3-}$  were detected. In the case of the Cu(II)- $\text{Sal}^{2-}$ – $\text{Ox}^{2-}$  system the complexes  $[\text{Cu}(\text{Sal})(\text{Ox})]^{2-}$ ,  $[\text{Cu}(\text{Sal})(\text{Ox})(\text{OH})]^{3-}$  and  $[\text{Cu}(\text{Sal})(\text{Ox})(\text{OH})_2]^{4-}$  were observed. In the Cu(II)- $\text{Sal}^{2-}$ – $\text{Cit}^{3-}$  system the species  $[\text{Cu}(\text{Sal})(\text{H}_2\text{Cit})]^-$ ,  $[\text{Cu}(\text{Sal})(\text{HCit})]^{2-}$ ,  $[\text{Cu}(\text{Sal})(\text{Cit})]^{3-}$  and  $[\text{Cu}(\text{Sal})(\text{Cit})(\text{OH})]^{4-}$  were detected and in the Cu(II)- $\text{Sal}^{2-}$ – $\text{PO}_4^{3-}$  system the complexes  $[\text{Cu}(\text{Sal})(\text{H}_2\text{PO}_4)]^-$ ,  $[\text{Cu}(\text{Sal})(\text{HPO}_4)]^{2-}$  and  $[\text{Cu}(\text{Sal})(\text{PO}_4)]^{3-}$  were observed.

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## 1. Introduction

Copper is one of essential elements required for normal human metabolism. Copper(II) is known to play a significant role in biological systems and also as a pharmaceutical agent. Its antibacterial properties have been known for thousands of years. Synthetic copper(II) complexes have been reported to act as a potential anticancer and cancer inhibiting agents and a number of copper complexes have been found to be active both in vitro and in vivo [1].

From the coordination chemistry point of view, salicylic acid ( $\text{H}_2\text{Sal}$ ) is a versatile ligand, since it offers two hard and strongly basic donor centers in a ligand geometry facilitating chelation and/or metal bridging for a medium- to large-size cation. Furthermore, hydroxyl group in salicylate ligand can entertain intra- and/or intermolecular hydrogen bonding and assist the formation of multidimensional assemblies [2].

Salicylate copper(II) complexes are of growing interest from both structural and biological point of view. Salicylic acid itself and its healing properties have been known for centuries. It is well known that salicylic acid and its derivatives are non-steroidal anti-inflammatory, anti-pyretic and analgesic drugs [1].

Taking into account the possible application in medicine of the copper(II)-salicylate complexes, it is considered that after the administration of these complexes, they may encounter many other potential copper(II) binding molecules present in extracellular or intracellular biological fluids. These latter ligands may partially or completely displace

the original copper(II) carrier molecules from the metal coordination sphere. 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 Cu(II)-Salicylate complexes and even in their physiological activity [3].

Until now, there are no reports on the speciation of the ternary Cu(II)-Salicylate complexes with the small blood serum bioligands: Lactate ( $\text{Lac}^-$ ), Oxalate ( $\text{Ox}^{2-}$ ), phosphate ( $\text{PO}_4^{3-}$ ) and Citrate ( $\text{Cit}^{3-}$ ) [4, 5].

In this work we report the results on mixed ligand complexes formation in the Cu(II)-Salicylate system with the ligands B, where ligands B were the most important low molecular mass (l.m.m.) Cu(II) binders presents in blood serum [6,7]:  $\text{Lac}^-$ ,  $\text{Ox}^{2-}$ ,  $\text{PO}_4^{3-}$  and  $\text{Cit}^{3-}$ . The pH-potentiometry technique was used to determine the stoichiometries and stability constants of the complexes formed in aqueous solution.

## 2. Experimental

### 2.1. Reagents

$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  (Merck p.a.), the ligand salicylic acid ( $\text{H}_2\text{Sal}$ ) (Merck p.a.), and the HLac,  $\text{Na}_2\text{Ox}$ ,  $\text{Na}_3\text{PO}_4$  and  $\text{Na}_3\text{Cit}$  all also Merck p.a., were used without purification.  $\text{Na}_2\text{EDTA} \cdot 2\text{H}_2\text{O}$  (Merck p.a.), and murexide (Merck p.a.) as indicator were used in order to standardize the Cu(II) stock solution. The  $\text{HNO}_3$  and KOH solutions were prepared using  $100.0 \text{ mmol} \cdot \text{dm}^{-3}$  Titrisol Merck ampoules. The KOH solution was standardized against potassium hydrogen

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phthalate. The solutions were prepared using triple glass-distilled water, boiled before the preparation of the solutions in order to remove dissolved CO<sub>2</sub>. The Cu(II) stock solution was standardized using a Na<sub>2</sub>EDTA·2H<sub>2</sub>O solution (0.01 mol·dm<sup>-3</sup>) in a buffer media... (pH = 10) using murexide as indicator [8].

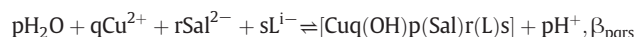
The emf (H) measurements were carried out in aqueous solution at an ionic strength of 1.0 mol·dm<sup>-3</sup> in KNO<sub>3</sub>. Nitrogen free O<sub>2</sub> and CO<sub>2</sub> was used to maintain an inert atmosphere.

## 2.2. Methods

The potentiometric measurements were done using the following instruments: Thermo Orion model 520A pH meter, Metrohm EA 876–20 titration vessel, Lauda Brikmann RM6 thermostatic bath. 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 ± 0.1) °C by constant circulation of water from the thermostatic bath.

The emf (H) measurements were carried out by means of the REF//S//GE cell, where REF = Ag/AgCl/3.0 mol·dm<sup>-3</sup> 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 [9]. The experiments were carried out as follows: a fixed volume of 0.100 mol·dm<sup>-3</sup> HNO<sub>3</sub> was titrated with successive additions of 0.100 mol·dm<sup>-3</sup> KOH until near neutrality in order to get the parameters  $E^0$  and  $j$ . Then, aliquots of the Sal<sup>2-</sup> and the Ligand B under study were added and finally an aliquot of the copper(II) stock solution was added sequentially. The titration was continued with 0.100 mol·dm<sup>-3</sup> KOH. The measurements were performed using a total metal concentration,  $M_T = 2\text{--}3 \text{ mmol}\cdot\text{dm}^{-3}$  and molar ratios  $R = 1:1:1, 1:1:2$  and  $1:2:1$  for the Cu(II):Sal<sup>2-</sup>:Ligand B system.

The Cu<sup>2+</sup>–Sal<sup>2-</sup>–Ligands B (L<sup>-</sup>) systems were studied according to the reaction scheme:



where L<sup>-</sup> represents the small blood serum bioligands, such as lactate (Lac<sup>-</sup>), oxalate (Ox<sup>2-</sup>), citrate (Cit<sup>3-</sup>) and phosphate (PO<sub>4</sub><sup>3-</sup>) and [Cu<sub>q</sub>(OH)<sub>p</sub>(Sal)<sub>r</sub>(L)<sub>s</sub>] are the ternary (p, q, r, s) complexes (the charges were omitted), where  $\beta_{pqrs}$  are the respective stability constants.

The potentiometric data were analysed using the program LETAGROP [10,11], in order to minimize the function  $Z_b = (H - h) / M_T$ , where  $Z_b$  is the average number of moles of H<sup>+</sup> associated per moles of metal,  $H$  is the total (analytical) concentration of H<sup>+</sup>,  $h$  represents the concentration in equilibrium of H<sup>+</sup>, and  $M_T$  represents the total (analytical) concentration of Cu(II).

Equilibria corresponding to the formation of the hydroxo complexes of Cu(II) [12] were considered in the calculation of the stability constants of the ternary complexes. The Cu(II)–Ligands B systems were previously studied in our group [13]. The stability constants of the Cu(II) hydroxo complexes, the protonation 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,  $U = \sum (Z_b^{\text{exp}} - Z_b^{\text{calc}})^2$ , the fittings were done by testing different (p, q, r, s) combinations.

The species distribution diagrams were done with the computer program HYSS [14], yielding the  $\beta_{pqrs}$  values, which are summarised in the Tables 2–5.

**Table 1**  
Ligands protonation constants (log  $\beta_{pr}$ ) in 1.0 mol·dm<sup>-3</sup> KNO<sub>3</sub> at 25 °C.

Equilibrium	Sal <sup>2-</sup>	log $\beta_{pr}$ Lac <sup>-</sup>	Ox <sup>2-</sup>	Cit <sup>3-</sup>	PO <sub>4</sub> <sup>3-</sup>
L + H <sup>+</sup> = HL	11.88(1)	3.64(1)	3.637(7)	5.51(1)	11.051(8)
L + 2H <sup>+</sup> = H <sub>2</sub> L	14.83(1)		4.95(2)	9.77(2)	17.42(1)
L + 3H <sup>+</sup> = H <sub>3</sub> L				12.75(2)	19.18(6)
Dispersion $\sigma$ (Z)	0.012	0.010	0.006	0.016	0.012
pK <sub>i</sub>					
H <sub>2</sub> L–HL	2.95		1.31		
	2.78 <sup>a</sup>		1.321 <sup>b</sup>		
HL–L <sup>-</sup>	11.88	3.64	3.637		
	11.72 <sup>a</sup>	3.86 <sup>b</sup>	3.717 <sup>b</sup>		
H <sub>3</sub> L–H <sub>2</sub> L				2.98	1.76
				3.014 <sup>b</sup>	1.67 <sup>b</sup>
H <sub>2</sub> L–HL				4.26	6.37
				4.299 <sup>b</sup>	6.41 <sup>b</sup>
HL–L				5.51	11.051
				5.365 <sup>b</sup>	11.04 <sup>b</sup>

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

<sup>a</sup> 1.0 mol·dm<sup>-3</sup> KNO<sub>3</sub>, 25 °C [15].

<sup>b</sup> 3.0 mol·dm<sup>-3</sup> KCl, 25 °C [16].

## 3. Results and discussion

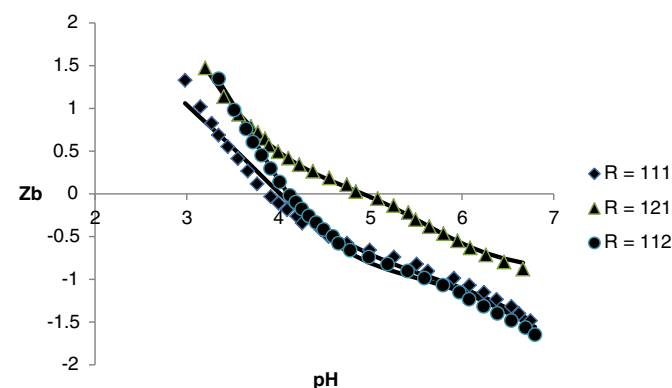
### 3.1. Ionization constants of ligands studied

The protonation constants (Table 1) in the ionic medium 1.0 mol·dm<sup>-3</sup> KNO<sub>3</sub> are in good agreement with the literature values, considering the differences in ionic strength and ionic medium [4, 5]. For the lactate (Lac<sup>-</sup>), only one pK<sub>a</sub> was obtained, because the hydroxyl group has a pK<sub>a</sub> > 14, and it is not possible to measure it in aqueous solution with a glass electrode. For the oxalate (Ox<sup>2-</sup>) and salicylate (Sal<sup>2-</sup>) two pK<sub>a</sub> values were obtained, because these ligand has two dissociable protons in the studied pH range. In the phosphate (PO<sub>4</sub><sup>3-</sup>) and citrate (Cit<sup>3-</sup>), three pK<sub>a</sub> values were measured. In the case of the Cit<sup>3-</sup>, the hydroxyl group has a pK<sub>a</sub> > 14, it is not possible to measure it with a glass electrode.

### 3.2. Ternary copper(II) complexes

#### 3.2.1. Cu(II)–Sal<sup>2-</sup>–Lac<sup>-</sup> system

Fig. 1 shows the Z<sub>b</sub> vs pH results of the analysis performed with the LETAGROP program, a good agreement is observed between the experimental data and the model considered which indicates the formation of the ternary complexes [Cu(Sal)(Lac)(OH)]<sup>2-</sup>, [Cu(Sal)(Lac)(OH)<sub>2</sub>]<sup>3-</sup> and [Cu(Sal)<sub>2</sub>(Lac)]<sup>3-</sup>. If we considered the denticity of salicylate is clear that this primary ligand is acting as a bidentate ligand by O<sup>-</sup>, COO<sup>-</sup> coordination. The lactate ligand is probably acting as a monodentate ligand, we can observe from Table 2 that there is no



**Fig. 1.** Z<sub>b</sub> vs pH data of the Cu(II)–Sal<sup>2-</sup>–Lac<sup>-</sup> system.

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