# Speciation of the Chromium(III)−Salicylic Acid System Studied in 1.5 mol·dm$^{-3}$ KCl at 25 °C

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The complex species formed between chromium(III) and salicylic acid ($H_2$sal) were studied in aqueous solution by means of electromotive force (emf(H)) measurements at 25 °C and in 1.5 mol·dm$^{-3}$ KCl as the ionic medium. The complexes were studied by the aging solution method, which consists of the preparation of different ligand/metal molar ratios at different pH values; the solutions were maintained at room temperature [(25 ± 1) °C] for 45 days; then potentiometric measurements were done, and the data were analyzed by means of the least-squares computational program LETAGROP, from which the respective stability constants and the stoichiometric coefficients of the complexes formed in aqueous solution were obtained. The results obtained indicate the formation of Cr(sal)$^+$, Cr(sal)(OH), and Cr(sal)(OH)$_2^-$.

## 1. Introduction

In 1959 chromium was identified as the active component of the "Glucose Tolerance Factor" (GTF). In fact, the symptoms of glucose intolerance are characterized by high glucose and insulin levels, which are considered as a sign of chromium deficiency. A chromium supplement plays a nutritional role and can prevent or reduce clinical symptoms. Supplements of organic chromium(III) complexes exist that are recommended for use in the treatment of diabetes and in patients with high cholesterol levels. In 1980, the *National Research Council* and the *National Academy of Sciences* recommended a (50 to 200) $\mu$g daily consumption of chromium(III).[1]

The trispicolinatechromium(III) complex, Cr(pic)$_3$, is a known bioavailable source of chromium(III), which provides (2 to 5) % of the absorbable bioelement, where the picolinate acts as a Cr(III) transporter.[2,3] However, its safety has recently been questioned, especially with regard to its ability to act as a clastogen. At physiologically relevant concentrations, Cr(pic)$_3$ is reduced by biological reductants, including ascorbate and thiols, to Cr(II)-containing species. These species are susceptible to air oxidation, resulting in the catalytic generation of the potent DNA-damaging hydroxyl radical. In the absence of reductants, $H_2O_2$ can interact with Cr(pic)$_3$ to produce hydroxyl radicals by a second, less efficient mechanism. Cr(pic)$_3$ is extremely stable, which allows the complex to be readily absorbed but also to potentially be incorporated into cells intact. In this form, Cr(pic)$_3$ is primed by its redox potential to enter into reactions leading to the generation of hydroxyl radicals.[4]

Salicylic acid ($H_2$sal), 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 ortho position, 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 pain, and choline salicylate is used topically to relieve the pain of aphthous ulcers. As with other $\beta$-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.

Taking into account all of the salicylic acid properties we decided to investigate the reaction of the complex formation between the chromium(III) ion and the salicylic acid in aqueous solution. Because of the inertness of the chromium(III) ion,[5] complex formation reactions are slow, and options to overcome this problem are either increasing the temperature[6] or aging the solution at a certain temperature.[7]

In this paper we report the binary complexes formed between the chromium(III) and the salicylic acid, preparing mixtures of metal and ligand at differents molar ratios and aging the solution at room temperature [(25 ± 1) °C] for 45 days, after which the pH of the solutions were measured.[8] These experiments were done as a contribution to the speciation of the chromium(III) salicylic acid system in aqueous solution.

## 2. Experimental Section

***2.1. Chemicals.*** The salicylic acid was from Merck (analytical grade) and was used as received. A salicylic acid stock solution was prepared at a 25 mM (mM = mmol·dm$^{-3}$) concentration, and a 10 mM $CrCl_3$ stock solution was prepared by dissolution of $CrCl_3 \cdot 6H_2O$ in 100 mM HCl to prevent the

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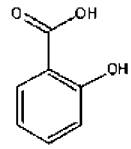
**Table 1. Acid Dissociation Constant of Salicylic Acid in Aqueous Media with $I$ = 1.5 M KCl at (25.0 ± 0.5) °C**

| Name of the Ligand | Chemical Structure (Neutral form) | $pK_{a1}$ | $pK_{a2}$ | Ref |
|---|---|---|---|---|
| Salicylic Acid ($H_2$sal) |  | 2.54 ± 0.08 | - | This work |
| | | 2.78[a] | 13.44[a] | 15 |

[a] 0.1 M KCl.

hydrolysis of the chromium(III) solution. The hydrogen ion concentration was determined by using the appropriate Gran function.[9] The HCl and KCl solutions were prepared by dissolving the respective acids and salts (Merck, analytical grade) in twice-distilled water which was previously boiled to remove dissolved $CO_2$. A carbonate-free hydroxide solution (KOH) was prepared from a Titrisol Merck ampule and standardized against potassium hydrogen phthalate. The emf(H) measurements were carried out in aqueous solution at an ionic strength of 1.5 M (M = mol·dm$^{-3}$) in KCl. Argon-free $O_2$ and $CO_2$ were used.

***2.2. Titration Procedure.*** The stability constants of the chromium(III)-salicylic acid complexes were determined by pH-potentiometric titration. The ionic strength was adjusted to 1.5 M KCl in each solution studied. In all cases, the temperature was (25.0 ± 0.1) °C. The p$K_a$ of salicylic acid was determined according to a method previously reported.[10] The total chromium(III) concentration was maintained in the range of (2 to 3) mM, and the salicylic acid/chromium(III) molar ratios ($R$) studied were 2, 4, and 10. All of the titrations were performed over the pH range 2 to 5.8 or until precipitation occurred. The solutions were kept at room temperature [(25 ± 1) °C] for 45 days. After this period the potentiometric measurements were performed. The reproducibility of the titration points included in the evaluation was within 0.005 pH units throughout the whole pH range. The pH was measured with a Thermo Orion 520 A instrument equipped with an Orion Ross 8102BN pH electrode, calibrated for hydrogen ion concentration. A p$K_w$ value of 13.75 ± 0.03 was determined and used for the calculations. Experimental data were analyzed using the Nernst program LETA,[11] a version of the least-squares program LETAGROP.[12] The data can be expressed in terms of the function $Z_C$ (pH, $H_T$, $M_T$, $L_T$), where $Z_C$ represents the average number of moles of protons dissociated per ligand mole according to eq 1.

$$Z_C = (h - H_T - K_w h^{-1})/L_T \quad (1)$$

where $H_T$, $M_T$, and $L_T$ represent the total concentrations (analytical) of $H^+$, Cr(III), and salicylic acid, respectively, $h$ represents the $H^+$ concentration in equilibrium, and $K_w$ is the ionic product of water. The complexes were studied according to the reaction scheme:

$$q\mathrm{Cr}^{3+} + r\mathrm{H_2sal} + p\mathrm{H_2O} \rightleftharpoons \mathrm{Cr}_q(\mathrm{OH})_p(\mathrm{sal})_r^{3q-2r-p} + (p + 2r)\mathrm{H}^+, \beta_{p,q,r}$$

The criterion of adjustment was to minimize the sum of least-squares (eq 2).

$$U = \sum (Z_C - Z_C^*)^2 \quad (2)$$

where $Z_C$* represents the respective values calculated by function (eq 3).

$$Z_C^*(\mathrm{pH}, H_T, M_T, L_T(p, q, r, \beta_{pqr})_{nk}) \quad (3)$$

The goodness of fit is obtained when we find a model and stability constants ($p$, $q$, $r$, $\beta_{pqr}$)$_{nk}$ which gives the lowest value of the sum of least-squares (eq 2) or a lower dispersion (eq 4):

$$\sigma(Z_C) = (U/(n - nk))^{1/2} \quad (4)$$

where $n$ is the number of experimental points and $nk$ is the number of species. During the calculations, the following Cr(III)-hydroxo complex was assumed: $Cr_6(OH)_{12}^{6+}$ (log $\beta_{6-12} = -30.3 \pm 0.1$), which was the only hydroxo-complex observed under these experimental conditions.[13] The species distribution diagrams were performed with the computer program HYSS,[14] considering the values of $\beta_{p,q,r}$ summarized in Tables 1 and 2.

## 3. Results and Discussion

***3.1. Acidity Constants of Salicylic Acid.*** In Figure 1 the $Z_C$ (pH) data of $H_2$sal are given. In the pH range studied, the $Z_C$ function takes a value of 1, indicating deprotonation of a unique proton, forming the species Hsal$^-$, with a p$K_a$ of 2.54 ± 0.08 (Table 1). This p$K_a$ value corresponds to the deprotonation of the carboxylic group, and its value is in correspondence with the values reported in the literature considering the difference in ionic strengths.[15] The other p$K_a$ value is 13.44, which corresponds to the deprotonation of the phenolic group. It is

**Table 2. Stability Constants (log $\beta_{pqr}$) of the Binary Cr(III)−$H_2$sal Complexes with $I$ = 1.5 M KCl at (25.0 ± 0.5) °C, Considering the Reaction: $q\mathrm{Cr}^{3+} + r\mathrm{H_2sal} + p\mathrm{H_2O} \rightleftharpoons \mathrm{Cr}_q(\mathrm{OH})_p(\mathrm{sal})_r^{3q-2r-p} + (p + 2r)\mathrm{H}^+$**

| reaction | log $\beta_{pqr}$ |
|---|---|
| $Cr^{3+} + H_2sal \rightleftharpoons Cr(sal)^+ + 2H^+$ | 1.2 ± 0.2 |
| $Cr^{3+} + H_2sal + H_2O \rightleftharpoons Cr(sal)(OH) + 3H^+$ | −1.9 ± 0.2 |
| $Cr^{3+} + H_2sal + 2H_2O \rightleftharpoons Cr(sal)(OH)_2^- + 4H^+$ | −5.9 ± 0.3 |
| dispersion ($\sigma$) | 0.069 |
| metal concentration (mM) | 1.43 to 2.94 |
| ligand/metal ratio $R$ | 2, 4, 10 |
| pH range | 2 to 5.8 |
| ionic medium | 1.5 M KCl |
| temperature | 25 °C |

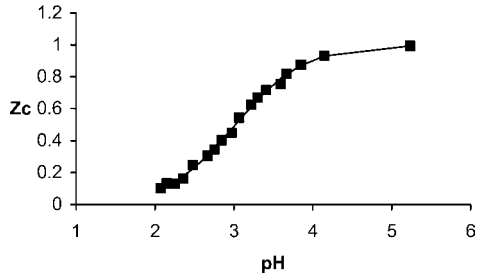



**Figure 1.** $Z_C$ (pH) data of the $H^+$ salicylic acid system.

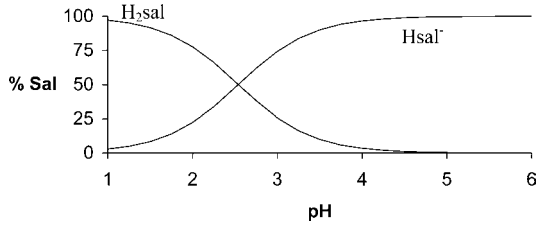



**Figure 2.** Species distribution diagram for the $H^+$ salicylic acid system.

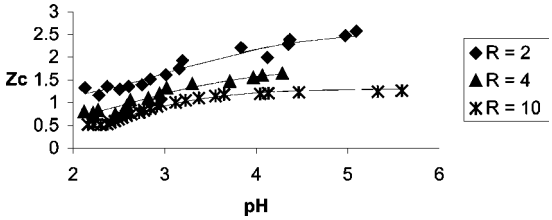



**Figure 3.** $Z_C$ (pH) data of the $H^+$−chromium(III)−salicylic acid system.

important to mention that we could not measure the phenolic dissociation because the glass electrode can only be used until pH ∼ 10 or 10.5. So it is necessary to employ a different technique to measure the phenolic p$K_a$ value. The species distribution diagram is given in Figure 2. Here we observed that at pH < 2.5 the species $H_2$sal predominates, and at pH > 2.5 $Hsal^-$ is the most important species.

***3.2. Stability Constants of the Chromium(III) $H_2$sal System.*** In Figure 3 the $Z_C$ (pH) data results of this system are given. As usual the points represent the experimental data, and the line represents the theoretical function, constructed considering the formation of the following species: $Cr(sal)^+$, Cr(sal)(OH), and $Cr(sal)(OH)_2^-$ with the stability constants summarized in Table 2. We can compare our results with the results reported by Aksoy and Özer.[16] They reported the formation of the complexes $Cr(sal)^+$, Cr(sal)(OH), Cr(sal)(Hsal), and Cr(sal)(Hsal)$(OH)^-$ studied by potentiometric titration and spectrophotometric measurements in 0.1 M $KNO_3$ at 25 °C. In our analysis we tried to included the species $Cr(sal)_2^-$, and $Cr(sal)_3^{3-}$ and the species reported by Aksoy and Özer, Cr(sal)(Hsal) and Cr(sal)(Hsal)$(OH)^-$. In our experimental data, using the aging solution method at 45 days and 25 °C in 1.5 M KCl, the best fitting obtained included the species $Cr(sal)^+$, Cr(sal)(OH), and $Cr(sal)(OH)_2^-$.

Figure 4 gives the species distribution diagram of this system for the conditions $M_T = 2$ mM and a ligand/metal molar ratio of $R = 2$. It is observed that the complex $Cr(sal)^+$ predominates at 1 < pH < 3.1; between 3.1 < pH < 4 the species Cr(sal)(OH) is formed, and at pH > 4 the hydroxo-complex $Cr(sal)(OH)_2^-$ is the most important species.

In Table 3 are summarized the stability constants of the Cr(III)−salicylic acid system considering the general reaction:

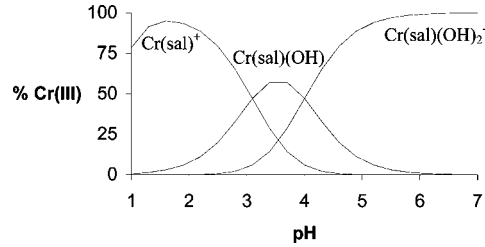



**Figure 4.** Species distribution diagram for the $H^+$−chromium(III)−salicylic acid system. Conditions $M_T = 2$ mM and ligand/metal molar ratio $R = 2$.

**Table 3. Comparative Stability Constants (log $\beta_{pqr}$*) of the Binary Cr(III)−$H_2$sal Complexes, Considering the Reaction: $qCr^{3+} + rsal^{2-} + pH^+ \rightleftharpoons Cr_q(H)_p(sal)_r^{3q+p-2r}$**

| complexes | log $\beta_{pqr}$* | log $\beta_{pqr}$* |
|---|---|---|
| $[Crsal]^+$ | 17.14 (2) | 13.27 |
| [(OH)Crsal] | 15.04 (2) | 19.17 |
| $[(OH)_2Crsal]^-$ | 11.04 (3) | |
| $[HCrsal_2]$ | | 28.50 |
| $[Crsal_2]^-$ | | 34.80 |
| reference | this work (1.5 M KCl, 25 °C) | 16 (0.1 M $KNO_3$, 25 °C) |

$$qCr^{3+} + rsal^{2-} + pH^+ \rightleftharpoons Cr_q(H)_p(sal)_r^{3q+p-2r} \quad (5)$$

We can see differences in the speciation and stability constants obtained by us and the results reported by Aksoy and Özer.[16] Because of the kinetic inertness of the Cr(III) ion, the resulting complex compounds are achieved rather slowly. They performed a potentiometric titration leaving the solutions to equilibrate overnight (24 h) after each addition of NaOH into the Cr(III)−ligand mixture. We used a batch method that we called an aging solution method consisting in the preparation of Cr(III)−salicylic acid mixtures at 25 °C and waited for 45 days to reach the equilibrium, and the potentiometric measurements were then done. It seems that the species formed in the solution change with the time and the quantities of the complexes formed must be different, and it is logical to find also differences in the stability constants observed with these two methods.

## 4. Conclusions

Chromium(III) complex formation reactions, which take place slowly, were studied by an aging solution method for 45 days at (25 ± 1) °C, which indicated that the most stable complexes formed in aqueous solution. In fact, in the Cr(III)−$H_2$sal system, only three complexes were detected: $Cr(sal)^+$, Cr(sal)(OH), and $Cr(sal)(OH)_2^-$. When we tried to include the $Cr(sal)_2^-$, $Cr(sal)_3^{3-}$, Cr(sal)(Hsal), and Cr(sal)(Hsal)$(OH)^-$ complexes, the fitting obtained was worse, corroborating that this method may give a more realistic view of the most stable complexes formed in aqueous solution.

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## Literature Cited

(1) Ding, H.; Olson, L.; Caruso. Elemental speciation for chromium in chromium picolinate products. *Spectrochim. Acta, Part B* **1996**, *51*, 1801–1812.
(2) Chakov, N.; Collins, R.; Vincent, J. A re-investigation the electronic spectra of chromium(III) picolinate complexes and high yield synthesis and characterization of $Cr_2(\mu\text{-}OH)_2(pic)_4 \cdot 5H_2O$ (Hpic = picolinic acid). *Polyhedron* **1999**, *18*, 2891–2897.
(3) Vincent, J. The bioinorganic chemistry of chromium(III). *Polyhedron* **2001**, *20*, 1–26.

(4) Speetjens, J. K.; Collins, R. A.; Vincent, J. B.; Woski, S. A. The nutritional supplement chromium(III) tris(picolinate) cleaves DNA. *Chem. Res. Toxicol.* **1999**, *12*, 483–487.
(5) Purcel, K. F.; Kotz, J. C. *Inorganic Chemistry*; W. B. Saunders Company: Philadelphia, PA, 1977; pp 694−755.
(6) Ciavatta, L.; Iuliano, M.; Vitielo, A. Stability constants of chromium(III) oxalate complexes in 1 m $NaClO_4$ at 60 °C. *Ann. Chim. (Rome, Italy)* **2000**, *90*, 169–179.
(7) Ciavatta, L.; Grimaldi, M. On the hydrolysis of the iron(III) ion, $Fe^{3+}$, in perchlorate media. *J. Inorg. Nucl. Chem.* **1975**, *37*, 163–169.
(8) Nagata, K.; Umayahara, A.; Tsuchiya, R. Formation constants of chromium(III)-oxalato complexes. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 1059–1061.
(9) Gran, G. Determination of the equivalence point in potentiometric titrations. Part II. *Analyst* **1952**, *77*, 661–671.
(10) Armas, M. T.; Mederos, A.; Gili, P.; Domínguez, S.; Hernández-Molina, R.; Lorenzo, P.; Baran, E. J.; Araujo, M. L; Lubes, V.; Brito, F. Speciation in the carnosine-oxovanadium(IV) system. *Polyhedron* **2002**, *21*, 1513–1521.
(11) Brito, F. Project 14/02.06.87; Education Council, Canary Islands Government, Tenerife, Spain, 1987. (b) Brito, F.; Gonçalves. Project S1-1228; CONICIT, Caracas, Venezuela, 1981.
(12) Sillén, L. G.; Warnqvist, B. High-speed computers as a supplement to graphical methods. VI. A strategy for two-level Letagrop adjustment of common and "group" parameters. Features that avoid divergence. *Ark. Kemi* **1969**, *31*, 315–339.
(13) Lugo, M. L.; Lubes, V. R. Ternary complex formation between chromium(III)-picolinic acid, chromium(III)-dipicolinic acid, and small blood serum bioligands. *J. Chem. Eng. Data* **2007**, *52*, 1217–1222.
(14) Alderighi, L.; Gans, P.; Ienco, A.; Peters, D.; Sabatini, A.; Vacca, A. Hyperquad simulation and speciation (HySS): a utility program for the investigation of equilibria involving soluble and partially soluble species. *Coord. Chem. Rev.* **1999**, *184*, 311–318.
(15) (a) Martell, A. E.; Smith, M.; Motekaitis, R. J. *NIST Critical stability constants of metal complexes database*; U.S. Department of Commerce: Gaithersburg, MD, 1993. (b) Powell, K. J.; Pettit, L. D. *IUPAC Stability Constants Database*; Academic Software, Otley, U.K., 1997.
(16) Aksoy, M. S.; Özer, U. Equilibrium studies on chromium(III) complexes of salicylic acid and salicylic acid derivatives in aqueous solution. *Chem. Pharm. Bull.* **2004**, *52* (11), 1280–1284.

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