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# Complex Formation between Aluminum(III) and Hydroxysalicylic Acid Derivatives in Aqueous Solution

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Equilibria between aluminum(III) and hydroxysalicylic acids, ($H_3L$), (2,X-DHBA, X = 4–6) were investigated in 0.1 M (NaCl) medium at 25.0 ± 0.1°C. pH-potentiometric solution speciation measurements were performed within the limits $2 \leq pH \leq 10$ and Al(III) to ligand ratios were within the ranges 1 : 1 to 1 : 10. The stoichiometries of the formed complexes between Al(III) and these hydroxysalicylic acids were defined by means of spectroscopy. The results of potentiometric titrations were analyzed with two different computer programmes: BEST and RANA. All data can be explained with the occurrences of binary $Al(HL)^+$ and Al(HL)(OH) mixed hydroxo complexes and their formation constants were found as: $\log \beta = 8.67 \pm 0.02$, $9.24 \pm 0.02$, $10.87 \pm 0.01$ and $\log \beta = 5.16 \pm 0.04$, $4.69 \pm 0.04$, $4.73 \pm 0.04$, respectively. The formation constants and the stoichiometries of Al(III)-2,X-DHBA complexes were compared to the values resulted in earlier studies of aluminium(III)-2,X-DHBA systems.

**Key Words: Aluminum(III), Formation constant, 2,X-Dihydroxy benzoic acid, Mixed hydroxo complex.**

## INTRODUCTION

The advances in understanding the chemistry and *in vitro* biochemistry of aluminum(III) have been steady. Aluminum bioavailability and overload have been interest, especially in the last two decades, since Al(III) was considered to be toxic and affecting neurological functions[1–7]. The aqua Al(III) is smaller than other commonly encountered trivalent metal ions. The free Al(III) and other trivalent metal ions are not accumulated in measurable concentrations in cells, because they may form complexes with potential binding sites of organisms. Therefore, the chemistry of aluminum to biological systems concerns the binding of Al(III) to organic molecules, the stabilities of its complexes and the ease of release of Al(III) from its complexes[1].

In the last two decades, the investigations of solution equilibria, especially connected with speciation researches, have been revived. Several authors carried out studies on aluminum speciations[3–11], some of them were interested in speciation particularly in biological fluids. Desroches *et al.*[5] especially investigated Al(III) complex equilibria with two catechol derivatives, two pyridones, including desferrioxamine-B (desferol, DFO), in order to substitute to DFO in the clinical treatment of aluminum intoxication. Kiss *et al.*[8] reviewed the studies related with the solution states of Al(III) in organisms and the biospeciation of Al(III) ion in its transport.

We have already determined the formation constants of the complexes formed between Al(III) and some catechol derivatives[11]. We were also interested in the protonation constants (log K) of hydroxysalicylic acids ($H_3L$), (2,X-dihydroxybenzoic acids, 2,X-DHBA, X = 4, 5 or 6), which contain additional phenolate besides salicylate sites[12]. Then we continued on studies on the stabilities of complexes formed between Cr(III)[13], Sc(III)[14], Y(III)[14] and 2,X-DHBA. In spite of rather high coordination abilities of 2,X-DHBA ligands, they have been scarcely studied; only the affinities of these ligands to some first row transition metal ions, like oxovanadium(IV)[15], copper(II)[16] and iron(III)[17], were investigated. However, Kiss *et al.*[7] determined the protonation constants of these ligands and the formation constants (log β) of their Al(III) complexes[7]. Although they accepted the speciation model proposed by Öhman *et al.*[10] for the aluminum (III)-salicylate (SA) system, but their corresponding formation constants of the binary and ternary complexes of the same system were not in agreement with the results of Öhman *et al.*[10] Besides these discrepancies, Kiss *et al.*[7] have not checked rigorously thermodynamic equilibrium in the potentiometric titrations which reported the corresponding data base of Al(III)-(2,X-DHBA) systems. It is worthwhile that the reliability of a given simulation model crucially depends on that of the parameters fed into the corresponding data base[6]. When the experimental conditions of Kiss *et al.*[7] are evaluated, it is noticed that the reported results of Al(III)-2,X-DHBA systems were found from pH values which were read in 1–3 min. But they have investigated the coordination abilities of Al(III) with several ligands in the last decade[18–20]. They controlled rigorously thermodynamic equilibrium and selected the data for computer evaluation, especially described in detailed pH-potentiometric solution speciation measurements of bioactive complexes and different Al(III)-ligand systems[8, 18–20]. Due to the rather sluggish ligand-exchange kinetics of Al(III), Kiss *et al.*[20] applied a strict criterion; when equilibration could not be reached in 10 min, the corresponding titration points were omitted from the calculations. Therefore, the present work is concerned about Al(III)-(2,X-DHBA) systems in 0.1 M (NaCl) ionic medium in order to: (i) apply two different computer programmes to deal with chemical equilibria for speciation calculations and for the simulation of Al(III)-(2,X-DHBA) systems, (ii) ascertain the stoichiometries and the stabilities of species under experimental conditions by potentiometry and spectroscopy, since Kiss *et al.*[7] have not applied UV spectroscopy, (iii) compare the protonation and formation constants with the results of the previous study of Kiss *et al.*[7].

## EXPERIMENTAL

All the chemicals were of analytical-reagent grade and were used as received. All solutions were made with bi-distilled, deionized and $CO_2$-free water. 2,4-DHBA were purchased from Fluka and 2,5-DHBA with 2,6-DHBA were purchased from Aldrich. The purities of these ligands were periodically checked by Gran method[21]. The aluminum stock solution (0.1 M) was prepared by dissolving $AlCl_3 \cdot 6H_2O$ (99%, Merck) in a small excess of HCl (Merck, 37%, d = 1.18) in order to avoid hydrolysis and it was standardized by back titration with EDTA[22]. The concentration of free acid in the Al(III) solution was systematically checked by potentiometric titration before each series of experiments. Sodium hydroxide (0.1 M) (Merck, preanalyse) solution was prepared as carbonate-free solution and was

standardized against potassium hydrogen phthalate (99.9%, Merck). Sodium chloride (Merck, proanalyse) was the supporting electrolyte to maintain constant activity coefficients and to obtain the formation constants to be used in computer simulation models referring to blood plasma.

### pH-Metric measurements

pH-metric measurements of 50.0 $cm^3$ samples were carried out under an inert atmosphere of water-NaOH saturated nitrogen in a water-jacketed vessel maintained at 25 ± 0.1°C and 0.1 M ionic strength with (NaCl). Four potentiometric titrations were carried out for each ligand studied; the first one was performed with the ligand alone to determine its protonation constant, the others took place in the presence of ligand and Al(III) ion. Al(III) to ligand ratios were 1 : 1, 1 : 2, 1 : 3 and 1 : 10. The titrations were performed within the limits $2 \leq pH \leq 10$, except 1 : 1 mole ratio; at least 10 ± 2 min was waited for pH readings to reach thermodynamic equilibrium in 1 : 1 mole ratio; when equilibration could not be reached, the titration was ended, since the drifts on pH values were started due to the precipitation reactions. But the time necessary for thermodynamic equilibrium in 1 : 2, 1 : 3, 1 : 10 mole ratios were around 4 ± 2 min. pH-metric titrations were performed with Schott automatic piston burette to deliver the titrant, NaOH standard and the pH values were directly measured with a Schott model pH-meter (Hofheim, Germany), fitted with combined electrode. The electrode system was calibrated for hydrogen ion concentration according to Irving *et al.*[23] The corresponding logarithmic value of the ionic product of water was determined to be 13.71 under the present conditions. In the calibration step of the pH-meter, the pH reproducibility is < 0.005 units at acidic pH region and < 0.015 units at basic pH region.

### Spectroscopic measurements

On a Shimadzu GDU-20C spectrophotometer (Kyoto, Japan) the absorption spectra of ligands alone and Al(III)-2,X-DHBA systems in different mole ratios were recorded at defined pH values and wavelength ranges. Thus the stochiometries of the complexes were determined by Job's method of continuous variation[24]. The solutions were allowed to equilibrate in the nitrogen atmosphere at 25.0 ± 0.1°C.

### Data treatment

The data obtained in the potentiometric titrations were treated by two different computer programmes RANA and BEST. The first programme RANA consists of several sections and it was developed previously[12] by dealing multiple chemical equilibria. It was written for the computation and refinement with least squares of the protonation constants and corresponding formation constants that "best" fit the experimental data. This programme can find the concentrations of the species, draw also their speciation diagrams and the formation curves of the defined species. The second program BEST[25] calculates the set of known and estimated constants of equilibria which involve the formation of $H^+$ and Al(III) complexes of hydroxosalicylates and computes the concentrations of $H^+$ ion for each equilibrium and the quantity of added base. This corresponding equilibrium constants that BEST fit the experimental data were determined by minimizing the squares sum.

In order to apply these programmes to each Al(III) 2,X-DHBA system, 60 and 99

experimental point titrations were introduced into RANA and BEST, respectively. Thus the mathematical analysis of the data comprising 12 titrations was performed and the averages of constants obtained from these programmes are tabulated in Table-1.

Two groups of equilibria were treated in this work: the first group of equilibria included the protonation of $HL^{2-}$ and $H_2L^-$ ions of those occurred from $H_3L$ ligands; the second group were Al(III)-2,X-DHBA complex formation equilibria; thus log K and log β values were defined for these equilibria.

## RESULTS AND DISCUSSION

### Proton complexes

2,X-DHBA ligands have three dissociable protons, but OH group *ortho* to $COO^-$ ion cannot be titrated until pH *ca.* 13.0, since there is very strong hydrogen bonding between $COO^-$ and OH group. Therefore, only one inflection at m = 1.0, where m is moles of base per mole of $H_3L$ ligand, was observed in the potentiometric titrations of 2,X-DHBA ligands (Fig. 1, Curve I; for simplicity, only the potentiometric titration curve of 2,4-DHBA is given). The protonation constants log K are in good agreement with those reported previously[7, 13, 14], especially if the differences between experimental conditions are taken into account (Table-1). Also the values obtained by RANA and BEST are in full agreement within 0.01%.

### Al(III)-2,X-DHBA complexes

In 1 : 1 Al(III)-2,X-DHBA systems, the potentiometric titration curves have two distinct inflections at m = 2.0 and m = 3.0 (where m is moles of base per mole of Al(III), only for one concentration and for Al(III)-2,4-DHBA system the titration curves are given in Fig. 1), since they are superimposable for each mole ratio. The neutralization of two protons from COOH and adjacent OH group can be consid-

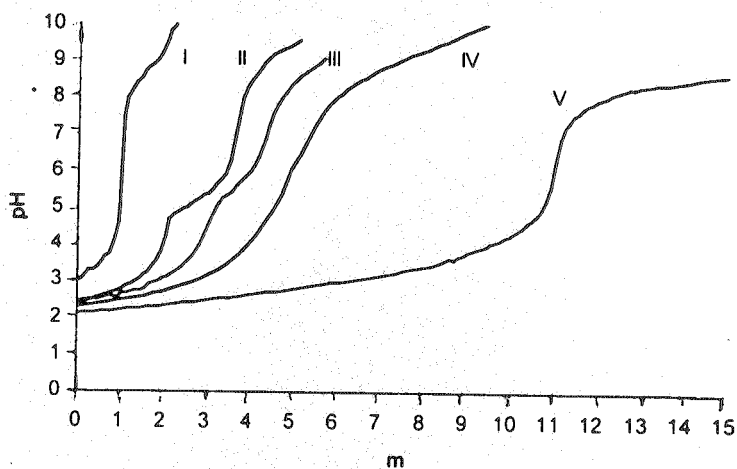


Fig. 1. Potentiometric titration curves of Al(III) complexes of 2,4-DHBA in 0.1 M NaCl at 25.0 ± 00.1°C: I. 2,4-DHBA alone ($T_L = 9.60 \times 10^{-1}$ M); II. (1 : 1) Al(III)-2,4-DHBA ($T_{Al} = 9.60 \times 10^{-2}$ M, $T_L = 9.60 \times 10^{-2}$ M); III. (1 : 2) Al (III)-2,4-DHBA ($T_{Al} = 9.60 \times 10^{-2}$ M, $T_L = 1.92 \times 10^{-1}$ M); IV. (1 : 3) Al (III)-2,4-DHBA ($T_{Al} = 9.60 \times 10^{-2}$ M, $T_L = 2.89 \times 10^{-1}$ M); V. (1 : 10) Al III)-2,4-DHBA ($T_{Al} = 9.60 \times 10^{-2}$ M, $T_L = 9.60 \times 10^{-1}$ M)

ered and the coordination of 2,X-DHBA from its salicylate sites ($COO^-$, $O^-$), but not from the phenolic OH group in position X, may be supposed. On the basis of our earlier experiments the coordination abilities of 2,X-DHBA ligands to trivalent metal ions like, Sc(III)[14], Cr(III)[13] and Y(III)[14] strongly support this assumption; thus the formation of $Al(HL)^+$ type complex in the m = 0.00–2.00 range by equilibrium (4) and the deprotonation of $Al(HL)^+$ to form Al(HL)OH in m = 2.0–3.0 range by equilibrium (5) were assumed (Table-1).

TABLE-1
PROTONATION CONSTANTS (log K) AND Al(III) COMPLEX FORMATION CONSTANTS (log β) FOR 2,X-DIHYDROXYBENZOIC ACID (X = 4, 5, 6) AT 25.0 ± 0.1°C AND I = 0.1 M NaCl

| Row | Equlibrium | 2,4-DHBA | 2,5-DHBA | 2,6-DHBA |
|---|---|---|---|---|
| | Proton complexes | > 14[7] | > 14[7] | > 14[7] |
| 1 | 2-OH $L^- + H^+ \rightleftharpoons HL^{2-}$ | 13.37 ± 0.03* | 13.74 ± 0.02* | 13.28 ± 0.04* |
| 2 | X-OH $HL^{2-} + H^+ \rightleftharpoons H_2L^-$ | 8.64[7] | 10.06[7] | 13.1[7] |
| | | 8.80 ± 0.01[14] | 10.18 ± 0.02[14] | 11.03 ± 0.04[14] |
| | | 8.95 ± 0.01* | 10.14 ± 0.02* | 10.39 ± 0.01* |
| | | 8.94 ± 0.02† | 10.13 ± 0.03† | 10.38 ± 0.02† |
| 3 | COOH $H_2L^- + H^+ \rightleftharpoons H_3L$ | 3.09[7] | 2.75[7] | 1.00[7] |
| | | 3.56 ± 0.01* | 2.85 ± 0.01* | 1.25 ± 0.04* |
| | | 3.55 ± 0.02† | 2.84 ± 0.01† | 1.24 ± 0.05† |
| 4 | Al(III) Complexes $Al^{3+} + HL^{2-} \rightleftharpoons Al(HL)^+$ | 8.71[7] | 9.74[7] | 12.79[7] |
| | | 8.67 ± 0.01* | 9.24 ± 0.01* | 10.87 ± 0.01* |
| | | 8.66 ± 0.02† | 9.23 ± 0.02† | 10.86 ± 0.01† |
| 5 | $Al(HL)^+ + OH \rightleftharpoons Al(HL)(OH)$ | 5.16 ± 0.04† | 4.69 ± 0.06† | 4.73 ± 0.04† |

*The values are the averages of BEST program.
†The values are the averages of RANA program.

It is worthwhile to notice that OH groups of X positions cause the acidity differences between salicylic acid and 2,X-DHBA derivatives; as a result in 2,6-DHBA the carboxylic group of 2,4-DHBA is much more acidic than either 2,5-DHBA or 2,4-DHBA; therefore its dissociation occurs at much lower pH, below that for any Al(III) complexation.

The potentiometric titration curves of Al(III)-2,X-DHBA systems in 1 : 2 and 1 : 3 mole ratios showed only one inflection at m = 3.0 and m = 4.0, respectively. In the case of 1 : 10 mole ratio also only one inflection was observed at m = 11.0. However, since no precipitation was noticed when the limits of titration were $2 \leq pH \leq 10$ and the range of mole ratios was 1 : 2 to 1 : 10 mole ratios can be fully explained, so that the coordination of only one mole of 2,X-DHBA to Al(III) occurs, therefore the titrations of uncoordinated one, two and nine moles of 2,X-DHBA ligands were carried out for 1 : 2, 1 : 3 and 1 : 10 mole ratios, respectively. As a result the occurrence of only mono-nuclear species $Al(HL)^+$ can be proposed. Thus,

the data obtained from different mole ratios (1 : 1, 1 : 2, 1 : 3 and 1 : 10) were treated by RANA and BEST programmes, so that they were introduced into the equations for equilibrium (4) to calculate the formation constant of Al $(HL)^+$ complex (Table-1). They are in accordance with the values obtained by Kiss *et al.*[7]

Moreover, the formation of bis complexes could not be concluded from 1 : 1 up to 1 : 10 mole ratios in our study. Although Kiss *et al.*[7] proposed the occurrence of bis complexes for Al(III)-2,X-DHBA systems, but they could conclude the presence of bis complexes of phosphorylated amino acid and Al(III) in 1 : 10 mole ratio. The similar behaviour and conditions can be valid for $Al(HL)^+$ type complex of 2,X-DHBA ligands. Since their formation constants are in comparable ranges with phosphorylated amino acids, therefore one cannot expect the occurrence of $Al(HL)_2$ and $Al(HL)_2(OH)$ type complexes also for 2,X-DHBA ligands; so it means the second mole of deprotonated 2,X-DHBA cannot compete with water molecules in the coordination sphere of $Al(HL)^+$.

Spectroscopic investigations were carried out to show the complex formation and to find the stoichiometries of the above mentioned complexes. The electronic absorption spectra of solutions of each 2,X-DHBA ligand were investigated in the absence and presence of Al(III); as an illustration, the spectra of 2,4-DHBA and Al(III)-2,4-DHBA system at pH = 4.1 and different mole ratios are given (Fig. 2). The maximum absorbances were observed at defined pH values, so that they were at $\lambda = 310$ nm for 2,4-DHBA, $\lambda = 345$ nm for 2,5-DHBA and $\lambda = 350$ nm for 2,6-DHBA at defined pH values. The shift of maximum absorbance to longer wavelength indicates its coordinations to Al(III) and the increases in absorbances of Al(III)-2.4-DHBA system in 1 : 1, 1 : 2, 1 : 3 mole ratios were noticed; these observations prove that only one type of complex occurs (Fig. 2). Then Job's plots were drawn at the defined wavelengths from their spectra (Fig. 3); as an example

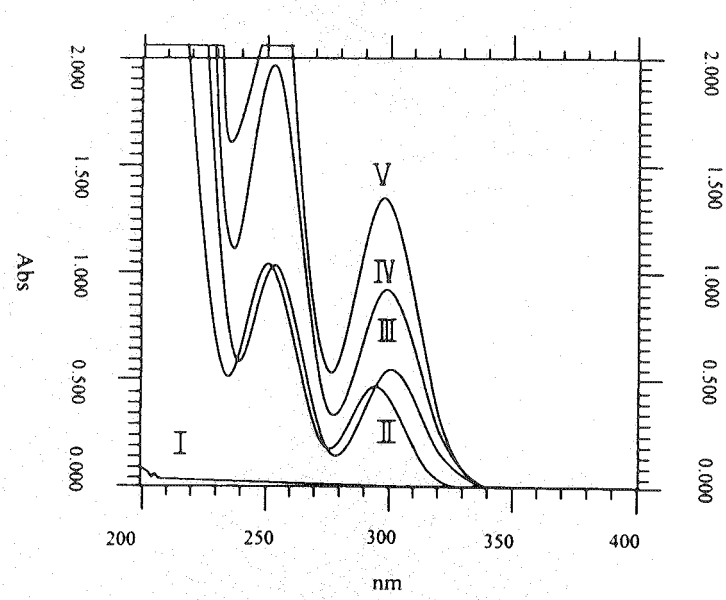


Fig. 2. Absorption spectra of Al(III) complex of 2,4-DHBA in 0.I M NaCl at 25°C (pH = 4.1) (a: mole fraction): I. Al(III) alone ($T_{Al} = 1 \times 10^{-4}$ M); II. 2,4-DHBA alone ($T_L = 1 \times 10^{-4}$ M); III. (1 : 1) Al(III)-2,4-DHBA ($T_{Al} = 1 \times 10^{-4}$ M, $T_L = 1 \times 10^{-4}$ M); IV. (1 : 2) Al(III)-2,4-DHBA ($T_{Al} = 1 \times 10^{-4}$ M, $T_L = 2 \times 10^{-4}$ M); V. (1 : 3) Al(III)-2,4-DHBA ($T_{Al} = 1 \times 10^{-4}$ M, $T_L = 3 \times 10^{-4}$ M)

Job's plot of Al(III)-2,4-DHBA system is given (pH = 4.1, $\lambda$ = 310 nm); the stochiometry of the formed complex ion corresponds to $X_M = 0.5$ which means 1 : 1 complex at pH = 4.1–4.5 range is formed.

The species distributions for Al(III)-2,X-DHBA systems are depicted in Figs. 4, 5 and 6. They are drawn for 1 : 1 mole ratios. The complex formation starts

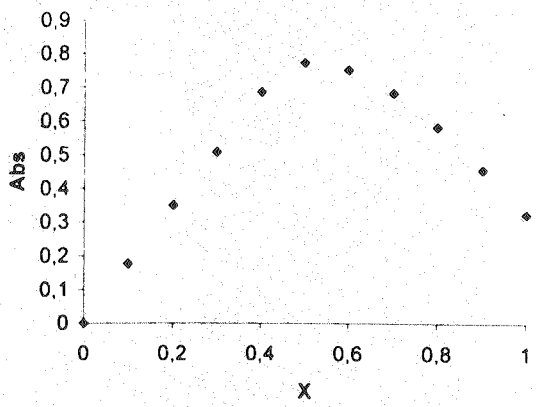


Fig. 3. Job's plot for Al(III)-2,4-DHBA in pH = 4.1 at $\lambda$ = 310 nm

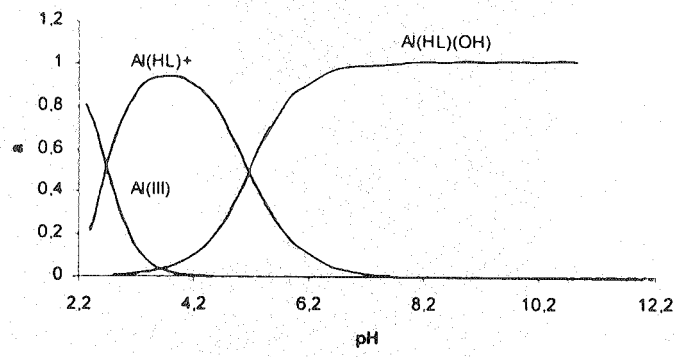


Fig. 4. Species distribution curves of the Al(III) ion and 2,4-DHBA system as a function of –log [$H^+$] (a: mole fraction)

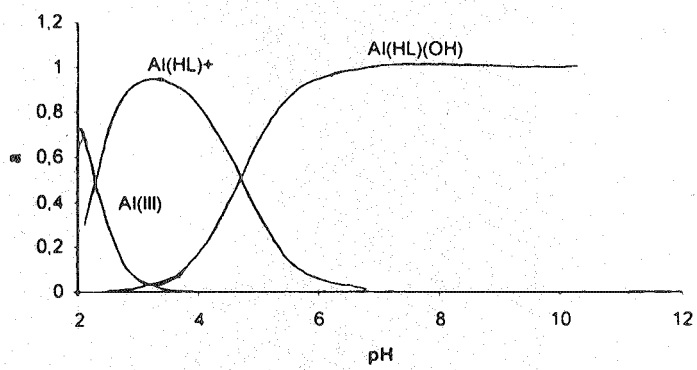


Fig. 5. Species distribution curves of the Al(III) ion and 2,5-DHBA system as a function of –log [$H^+$]

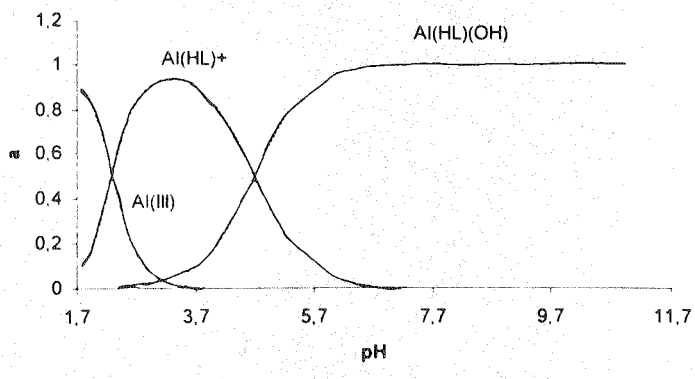


Fig. 6. Species distribution curves of the Al(III) ion and 2,6-DHBA system as a function of $-\log [H^+]$

with $H_3L$ ligands at the ($COO^-$, $O^-$) sites; the resulting major species has a stoichiometry of $Al(HL)^+$ that has OH group at X position in the protonated form) in the acidic pH range. Then $Al(HL)^+$ undergoes deprotonation from a water molecule in the coordination sphere on the increase of the pH only in 1 : 1 mole ratio.

The formation curves (–log ligand concentration *vs.* the degree of formation, $\bar{n}$) were also drawn to verify the potentiometric data for Al(III)-2,X-DHBA systems (Fig. 7). It reaches up to n = 1.0, that means Al(III) ion coordinates only one mole of $H_3L$ ligand.

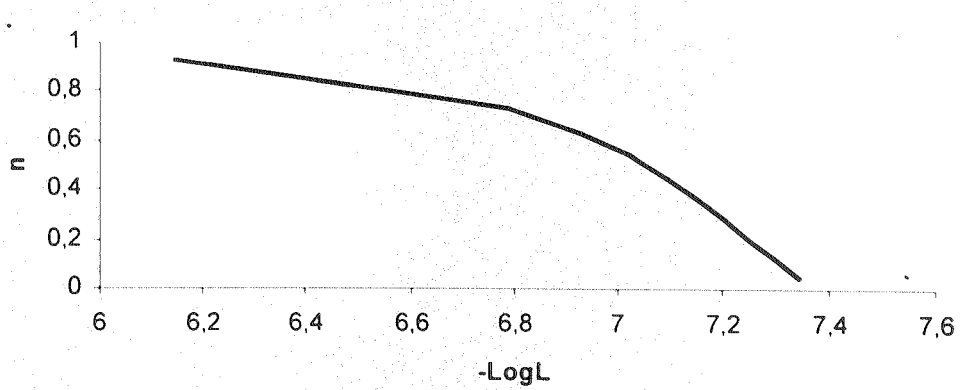


Fig. 7. Degree of formation for Al(III)-2,4-DHBA system, $\bar{n}$, as a function of log L

## Conclusion

1. 2,X-DHBA ligands act as bidentate towards Al(III), they are coordinated to Al(III) ion from their salicylate sites ($COO^-$, $O^-$) and they form only $Al(HL)^+$ type complexes in all mole ratios of Al(III) to ligand.
2. The stabilities of the Al(III) complexes of 2,X-DHBA decrease in the order of 2,6-DHBA > 2,5-DHBA > 2,4-DHBA which coincides with the decreasing overall basicity of the ligands.

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