

Gallium(III) Ion Hydrolysis under Physiological Conditions

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The hydrolysis of gallium(III) has been studied using potentiometric techniques under physiological conditions of temperature 37 °C and ionic strength 0.15 mol·dm⁻³ NaCl and at different metal ion concentrations. Changes in pH were monitored with a glass electrode calibrated daily in hydrogen ions concentrations. The titration data within the pH range of 2.5-9.99 were analyzed to determine stability constants of hydroxide species using the SUPERQUAD program. Several different species were considered during the calculation procedure and the following hydroxides have been characterized: Ga(OH)₃, Ga(OH)₄⁻, Ga₃(OH)₁₁²⁻, Ga₄(OH)₁₁⁻ and Ga₆(OH)₁₅³⁺. Speciation calculations based on the determined constants were then used to simulate the species distribution.

Key Words : Gallium(III), Hydrolysis, Stability constants, Potentiometry, Physiological conditions

Introduction

In aqueous solution gallium is more stable in its Ga(III) oxidation state. The oxide, hydroxide and mixed oxide-hydroxide chemistry of gallium, has been extensively studied in the last decades.¹⁻⁵

Gallium(III) plays a very important role in the diagnosis of tumor and for possible treatment of malignancies. Recently, this metal ion was approved by the FDA for i.v. administration and is used in its ⁶⁷Ga(III) salts or citrate complex to diagnose tumors.⁶

More recently, the use of complexes of Ga(III) with some ligands has emerged as a promising solution to create tumor inhibiting therapeutics.⁷⁻⁹ In physiological conditions the behavior of the system Ga(III)-citrate has been subject to debate and there is no consensus regarding the composition and the structure of the species formed.¹⁰

Numerous studies and particularly potentiometric titration and ⁷¹Ga NMR experiments^{11,12} have revealed that aluminium and gallium have a similar hydrolytic behavior. Indeed, among metals, aluminium, gallium and iron exhibit a particular hydrolytic properties as they give rise to polycationic structures in a given pH/concentration conditions.^{5,13}

Ga(III) metal ions are prone to hydrolyse within a large domain of pH including physiological pH to form mono and polynuclear hydroxide species.¹⁴ Although this phenomenon must be taken into account prior to any metal-ligand interactions.

Such studies have already been initiated concerning the hydrolysis of gallium, many of which were reviewed by Baes and Mesmer.¹⁴ More recently several reviews were devoted to gallium and other rare elements hydrolysis in aqueous solution.^{15,16} Most of the available data refer to standard conditions of temperature and pressure and at different ionic strength.

However, in spite of the numerous studies previously

carried out on Ga(III) hydrolysis, only few quantitative data are available regarding corresponding interactions in solution, and none of these refer to the physiological conditions of temperature and ionic strength.

This study thus reports a potentiometric determination of the stability constants of Ga(III) hydroxydes under physiological conditions. Although made difficult by the occurrence of precipitates in the case of higher metal ion concentrations, this study led to definite conclusions as to the number and stoichiometry of hydroxides formed under physiological conditions (0.15 mol·dm⁻³ NaCl, 37 °C). In particular mononuclear Ga(OH)₃ and Ga(OH)₄⁻ species could be characterized beside polynuclear Ga₃(OH)₁₁²⁻, Ga₄(OH)₁₁⁻ and Ga₆(OH)₁₅³⁺ (M represents metal ion).

Experimental

Reagents. Solutions of gallium(III) chloride prepared from Sigma pure anhydrous crystals were slightly acidified to prevent metal hydrolysis. It was titrated for its metal contents using complexometric¹⁷ titrations whereas its exact final acid titre was deduced from potentiometric measurements using Gran titrations.¹⁸

Sodium hydroxide solutions were prepared by diluting the contents of BDH concentrated volumetric solutions vials with freshly boiled doubly deionized water, which was saturated with purified nitrogen before use. These solutions, standardized against potassium hydrogenophthalate (Prolabo, Normapur) and proved to be carbonate-free from the features of the corresponding Gran titration plots,¹⁹ were stored under nitrogen atmosphere.

Experimental Conditions. Sodium chloride (0.15 mol·dm⁻³) was chosen as a background electrolyte to maintain constant activity coefficients and to ensure isotonicity with blood plasma.

Potentiometric titrations were performed using a Beckmann glass electrode opposed to a saturated NaCl Corning

calomel electrode, fitted in a thermostated Metrohm 20 cm³ cell unit. E.m.f. variations were monitored by a Beckman model 4500 digital mV-meter. The temperature of the reaction vessel was maintained at 37 ± 0.02 °C by circulating water and all titrations were carried out under a constant bubbling of purified and thermostated nitrogen. The above electrode system was calibrated in the concentration scale,²⁰ the ionic product of water being found equal to 10^{-13.24} under the present conditions. The value of *K_w* was estimated using acid-base titration curves and the refined value was obtained using the SUPERQUAD²¹ computer program. Accordingly, the symbol pH used throughout actually represents -log[H⁺]. The slope *s* from the Nernst equation, $E = E_0 - s \cdot pH$ was determined using acid-base titration.²⁰ The electrode slope was found equivalent to the expected theoretical one (61.54 mV·pH⁻¹). In these conditions, the value of the standard electromotive force, *E*₀ takes into account the liquid junction potential and activity coefficient terms. With a view to avoid the day-to-day drift of *E*₀, the *E* of 0.01 mol·dm⁻³ HCl was measured at the beginning of each titration.

Successive aliquots of sodium hydroxide 0.1 mol·dm⁻³ were delivered from a Radiometer ABU 12 Autoburette equipped with a 25 cm³ glass cylinder, both titrate and titrant containing 0.15 mol·dm⁻³ NaCl.

As may be noted in Table 1, where titration data are summarized and whose results are given in the supplementary data, metal ions concentration were varied significantly over the set of these experiments in view to allow the formation of different metal-hydroxide stoichiometries.

It is well known that hydrolytic complexation largely depends on the experiment conditions, which have a strong influence on the nature and relative concentrations of the formed species.^{22,25} The main technical difficulty arises from the very slow reaction process. This phenomenon was already mentioned in the case of Al(III) hydrolysis investigated under the same conditions of temperature and ionic strength.²⁶

In view of this, it was decided to select the same operational protocol as detailed in reference.²⁶ It consists in experiments with the smallest aliquots of hydroxide with potentials been read every 2 min.

Calculation Procedures. Potentiometric data were treated following our usual approach^{27,28} involving optimization and simulation in successive steps.

For a general complex formula corresponding to $M_p(OH)_q^{3p-q}$ (*M* = Ga(III) metal ion, OH = hydroxide ion,

the reaction for the hydrolysis can be written:



The numerical treatment of the data was performed by the program SUPERQUAD. To be in agreement with the notations of this program, the cumulative stability constant of the equilibrium (1) is given by the equation (2) where charges and molecules of water have been omitted for the sake of simplicity:

$$\beta_{p,q} = \frac{[M_p(OH)_q]}{[M]^p [H]^{-q}} \quad (2)$$

According to SUPERQUAD notations, the hydroxo-complexes are referred to as (p, -q) pairs and the hydroxide ion is thus (0, -1).

The experimental hydroxylation curves were plotted using equation (3). These curves represent the average number of hydroxides bound to each metal ion:

$$\bar{q} = \frac{C_{OH} - C_H - [OH^-] + [H^-]}{C_M} \quad (3)$$

with *C*_{OH} and *C*_H = total concentrations of strong hydroxide and acid, respectively, as a function of pOH. From the shape of these curves, estimates of some formation constants can be made. They were consequently used as an input data and refined with the help of the SUPERQUAD computer program. Then the final discrimination between sets displaying similar SUPERQUAD analyses was based on the two parameters: σ (connected with the objective function) and χ^2 statistics. The critical values are assumed as $\sigma < 3$ and $\chi^2 \leq 12.60$ at the 0.95 confidence level. Graphical comparisons between calculated curves and the corresponding simulated data were taken into account too.

Results and Discussion

It is worth noting that for pH values above *ca.* 5 and independently of Ga³⁺ concentration, a slight opacity was observed in the titration cell, indicative of the initiation of a precipitation process which can be assigned to the neutral hydroxide Ga(OH)₃. Titrations were not stopped in view to collect data beyond the true equilibrium which may sometimes be useful in defining the stoichiometry of hydroxides predominating under such conditions.²⁶ The study of the Ga(III)-OH⁻ system was thus conducted in two steps: (i) all the measurement data shown in figure 1 were first considered for examination and (ii) when the set of stability constant representing the best model was established with the help of SUPERQUAD program, it was then used for the interval of data pairs limited to pH 5.

Figure 1 represents the experimental hydroxylation curves as defined in equation (3) of the Ga(III)-hydroxide system for the reactant concentrations shown in Table 1.

One can notice that our experimental hydroxylation curves are strikingly similar to that of aluminium hydrolysis carried out in the same conditions.²⁶ Indeed, the two sets of curves are superimposable with a relative shift to higher pOH in the

Table 1. Summary of the Titration Data Used for this Study^a

System	<i>C</i> _M	<i>C</i> _H	pH range	Exp.	<i>n</i>
Ga(III)-hydroxide	3.242	2.570	2.71-8.03	+	50
	4.539	3.675	2.47-9.99	×	67
	5.187	4.138	2.42-5.62	□	44
	6.484	5.199	2.28-7.23	△	53
	6.484	5.140	2.28-7.94	▽	44

^aInitial total concentration (mmol·dm⁻³) of metal (*C*_M), hydrochloric acid (*C*_H) and number of experimental observations (*n*). Exp.: Experiment.

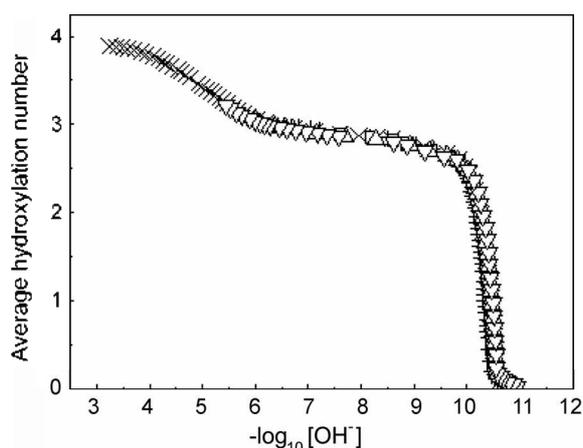


Figure 1. Experimental hydroxylation curves relative to Ga(III); key to symbols as in Table 1.

case of Ga(III), which means that Gallium(III) hydroxydes are relatively more stable than those of Aluminium(III) obtained in the same conditions.²⁶ Indeed, in the latter study, G. Berthon *et al.* have mentioned the beginning of the precipitation which was attributed to the neutral $\text{Al}(\text{OH})_3$ above $\text{pH} = 8$.

Since the stoichiometry of the species present cannot be easily predicted, different hydroxides $\text{M}_p(\text{OH})_q$ were systematically selected for examination. In general, the initial choice of a base model was guided by the literature and 'chemical judgment'.²⁹

Moreover, interaction between Ga^{3+} and Cl^- has been neglected in our analysis. Indeed, as pointed out in the literature, this complexation becomes significant only at very high chloride ion concentrations.³⁰ This was not the case for our study, since 0.15 mol dm^{-3} NaCl can be considered as relatively a low ionic strength medium.

Several gallium hydroxydes species were tried during the SUPERQUAD calculations procedure in the first step of this protocol. As may be seen, the set of the constants represent-

ing the 'best' model whose results are gathered in Table 2, includes mononuclear $\text{M}(\text{OH})_3$, $\text{M}(\text{OH})_4$ and polynuclear species $\text{M}_3(\text{OH})_{11}$, $\text{M}_4(\text{OH})_{11}$ and $\text{M}_6(\text{OH})_{15}$. Our results concerning the existence of the trimeric and tetrameric hydroxydes are in fair agreement with a recent study on Gallium(III), which used ^{71}Ga NMR and EXAFS techniques.⁵ Other polynuclear species such as the particular tridecamer $\text{M}_{13}(\text{OH})_{24}$ known as Keggin-ion observed in the case of Ga(III)⁵ and Al(III)²² hydrolysis was systematically rejected by SUPERQUAD in the totality of the combinations used.

It is worth mentioning, that polynuclear hydroxydes were necessary to enhance the graphical fit and the SUPERQUAD statistical parameters. For example, the omission of the hexameric species $\text{M}_6(\text{OH})_{15}$ from the best model relative to the case (i) of Table 2 produces a significant increase of the parameter σ from 2.073 to 7.167 as well as χ^2 , which varies from 8.74 to 185.18. Moreover, there is a drastic loss of the graphical fit between experimental and simulated data almost in the whole domain of the pH investigated.

As far as the monomeric species such as $\text{M}(\text{OH})$ and $\text{M}(\text{OH})_2$ are concerned, any attempt to refine their constants alone or in presence of our polynuclear hydroxydes and in various combinations was unsuccessful. Therefore, as may be noted in Table 3, our results reveal poor agreement with many literature data based on potentiometric, colorimetric, and solubility measurements at various ionic strengths,^{31,32} which confirm the presence of the mononuclear hydroxides in their respective conditions. However, because Ga^{3+} can generate polynuclear hydroxide species, Baes and Mesmer¹⁴ have underlined the difficulty to produce reliable stability constants relative to monomeric species.

The pseudo-experimental curves for the whole pH range are shown in Figure 2. They were computed with the help of our SIMDIS program³³ on the basis of constants from Table II and analytical conditions from Table 1. A quite satisfactory coincidence may be observed between this figure and the experimental one (see Figure 1), which confirms the

Table 2. Logarithm of the Formation Constants for Gallium (III) Hydroxides in Aqueous Solution at 37°C and $I = 0.15 \text{ mol dm}^{-3}$ NaCl. (i) for the entire titration pH interval, and (ii) for data limited to $\text{pH} < 5.50$

System	p	q	$\log_{10}\beta_{pq}$	σ	χ^2	n
Ga(III)-hydroxide (i)	1	-3	-9.52 ± 0.01	2.073	8.74	257
	1	-4	-18.06 ± 0.01			
	3	-11	-40.18 ± 0.04			
	4	-11	-25.20 ± 0.04			
	6	-15	-30.45 ± 0.06			
(ii)	1	-3	-9.53 ± 0.01	1.838	17.13	184
	4	-11	-25.17 ± 0.03			
	6	-15	-30.46 ± 0.05			

$\beta_{pq} = \frac{\text{M}_p(\text{OH})_q}{[\text{M}]^p[\text{OH}]^{-q}}$ where σ = sample standard deviation, χ^2 = statistical parameter given by SUPERQUAD; n = number of experimental observations.

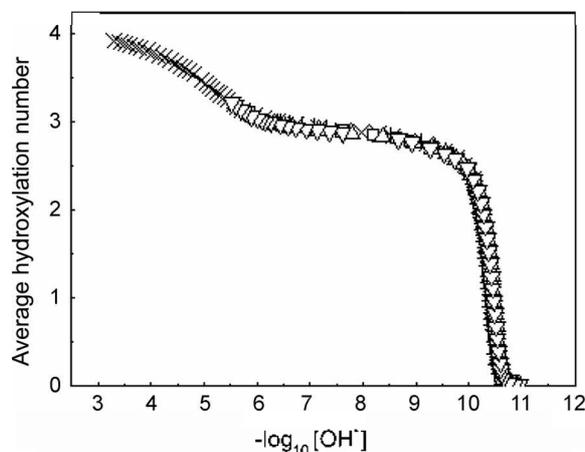


Figure 2. Simulated hydroxylation curves relative to Ga(III) as obtained by means of SIMDIS program using results in Table 2 (i); key to symbols as in Table 1.

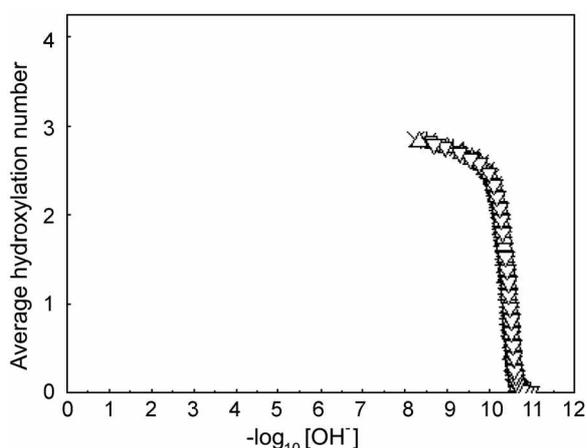


Figure 3. Simulated hydroxylation curves relative to Ga(III) as obtained by means of SIMDIS program using results in Table 2 and data pairs limited to pH *ca.* 5.0; key to symbols as in Table 1.

Table 3. Logarithm of the formation constants for some selected monomeric gallium hydroxydes in aqueous solution at different conditions taken from the literature.

Medium	Temp. (°C)	$\log_{10}\beta_{1n}$				Ref.
		(1, -1)	(1, -2)	(1, -3)	(1, -4)	
0.15 M NaCl	37	–	–	-9.52	-18.06	This study
0.10 M KNO ₃	25	-3.16	-7.07	–	–	25
0.10 M NaCl	25	-2.90	-6.60	-11.00	–	31
0.10 M NaClO ₄	25	-2.87	-6.55	-11.07	–	32

validity of the approach used.

Concerning the data limited to pH range defined above (see figure 1), the 'best' model shown in Table 2 (ii) was obtained according to the same procedure relative to the whole pH interval. As may be noted, the species $M(OH)_4$ and $M_3(OH)_{11}$ are not formed in this restricted pH range. Nevertheless, one may note the existence of $M(OH)_3$ beside polynuclear hydroxides $M_4(OH)_{11}$ and $M_6(OH)_{15}$. Moreover,

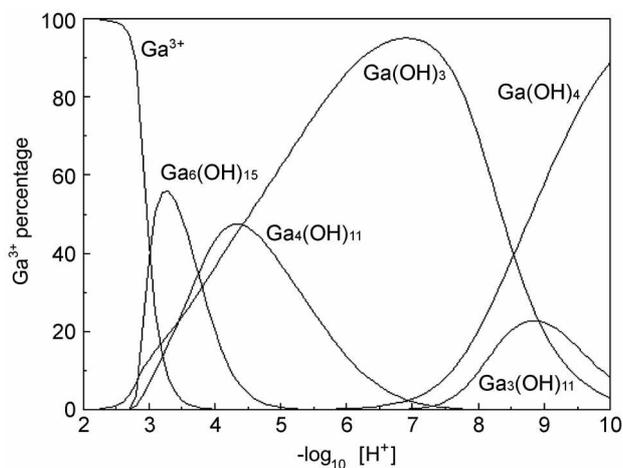


Figure 4. Simulated distribution of the Ga(III) into its free and hydroxylated species as a function of pH, with Ga(III) = 2 mmol·dm⁻³.

the stability constants obtained in this case benefit almost from the same accuracy as in case (i).

Figure 3 shows the pseudo-experimental curves based on this set of constants and analytical conditions of Table 1. A quite satisfactory coincidence may be observed when compared to the restricted pH range of the experimental curves shown in Figure 1.

SIMDIS program³³ calculations based on the constants from Table 2 led to the distribution of the Ga(III) into its free, and Ga(III)-hydroxo species as a function of pH for a solution containing 2 mmol of metal ions (see figure 4). Clearly, the polymeric species $M_4(OH)_{11}$ and $M_6(OH)_{15}$ dominate the distribution until pH *ca.* 4.5. From pH 4.5 to 8.4, the neutral hydroxide $M(OH)_3$ becomes predominant to reach 90% around pH 7.0. The $M(OH)_4$ appears around pH 6 and reaches its maximum at pH 10.0. The $M_3(OH)_{11}$ is formed at pH around 7 to attain 23% at pH 8.8.

Conclusion

The aim of this study was to make a contribution towards the hydrolysis of Gallium(III) in aqueous medium and near physiological conditions. This was done using potentiometric techniques assisted by computer calculations.

From the overall presented study, it is concluded that in physiological conditions (37 °C, 0.15 mol·dm⁻³ NaCl) and for the range of concentrations used, gallium(III) ions gives rise to monomeric hydroxydes $M(OH)_3$ and $M(OH)_4$ along with polycationic species $M_3(OH)_{11}$, $M_4(OH)_{11}$ and $M_6(OH)_{15}$. Our results are in good agreement with the prediction of Baes and Mesmer¹⁴ who indicate the tendency of Ga(III) to engender polycationic hydroxides and the difficulty to determine mononuclear species. Indeed, our speciation calculations show that $M_6(OH)_{15}$ is formed around pH = 2.8. Moreover, our results confirm the resemblance of Ga(III) and Al(III) regarding aqueous hydrolysis, since the latter produces monomeric and polymeric hydroxides under the same conditions of temperature and ionic strength.²⁶ Nevertheless, there is a poor concordance with many literature data obtained at different conditions,^{31,32} which confirm exclusively the presence of mononuclear hydroxides.

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