Calculations of Chemical Equilibria in Tb(NO$_3$)$_3$–H$_2$O, Tb(NO$_3$)$_3$–Heparin–H$_2$O, and CaCl$_2$–Tb(NO$_3$)$_3$–Heparin–H$_2$O Systems in Physiological Saline Solution

L. S. Nikolaeva$^a$, A. N. Semenov$^b$, M. N. Mamontov$^a$, N. A. Dobrynina$^a$, and M. A. Feofanova$^b$

$^a$ Moscow State University, Vorob’evy gory, Moscow, 119992 Russia
E-mail: cyber.1d.chem.msu.ru

$^b$ Chemistry Department, Tver State University, Tver, Russia

Received December 29, 2006

Abstract—Chemical equilibria in the heterogeneous system Tb(NO$_3$)$_3$–H$_2$O, physiological saline solutions containing terbium nitrate, and unfractionated heparin ((H$_2$L)L Tb(NO$_3$)$_3$–H$_2$L–H$_2$O–NaCl), and solutions containing calcium chloride, terbium nitrate, and unfractionated heparin (CaCl$_2$–Tb(NO$_3$)$_3$–H$_2$L–H$_2$O–NaCl) were studied by mathematical modeling and pH titration. A physicochemical model was designed for two-phase equilibria in the system Tb(NO$_3$)$_3$–H$_2$O, which consists of an aqueous solution and a solid phase of precipitated terbium hydroxide. Formation constants were calculated for terbium hydroxide ions Tb(OH)$_{3–}$ in an aqueous phase, and a correlation was found between the amount of precipitated Tb(OH)$_3$ and pH. The four-component solution Tb(NO$_3$)$_3$–H$_2$L–H$_2$O–NaCl in the range 2.3 ≤ pH ≤ 10.4 is homogeneous; as a result of its investigation, the formation constants were ascertained for significant terbium complexes with heparin: TbL, TbHL$^+$, and Tb(OH)$_2$L$^{3–}$. Chemical equilibria in the five-component solution CaCl$_2$–Tb(NO$_3$)$_3$–H$_2$L–H$_2$O–NaCl were modeled proceeding from the models developed for equilibria in the four-component solution subsystems Tb(NO$_3$)$_3$–H$_2$L–H$_2$O–NaCl and CaCl$_2$–H$_2$L–H$_2$O–NaCl. The modeling showed that the Tb$^{3+}$ ion is an efficient competitive complex former to the Ca$^{2+}$ ion, which forms complexes with heparin, and decreases tenfold the concentration of the major complex NaCaL at 6.8 ≤ pH ≤ 7.4 (the pH range of blood plasma stability).

DOI: 10.1134/S0036023608050252

The anticoagulant activity of lanthanide (Ln) salts is used in medicine [1–3]. The mechanism of the anticoagulant activity of lanthanides is yet unclear. Presumably, Ln$^{3+}$ ions force Ca$^{2+}$ ions out from the calcium-dependent blood coagulation process as a result of the competitive complexing of Ln$^{3+}$ and Ca$^{2+}$ ions with specific proteins (blood coagulation factors). The anticoagulant activity and toxicity of lanthanide complexes depend on the ligand to which the Ln$^{3+}$ ion is bound. Therefore, it is advisable to use unfractionated heparin (H$_2$L) as a bioligand: in particular, its anticoagulant activity is associated with the replacement of Ca$^{2+}$ ions from blood coagulation reactions as a result of formation of stable complexes with Ca$^{2+}$ ions [4, 5]. To understand the anticoagulant activity of lanthanide heparinates, one should study complexing of some lanthanides, e.g., terbium, an element from the middle of the lanthanide row, with heparin and the Ca$^{2+}$ and Ln$^{3+}$ ion distributions in a physiological solution of heparin at 37°C and the ionic strength 0.15 mol/L NaCl.

An equilibrated solution Tb(NO$_3$)$_3$–H$_2$L–H$_2$O–NaCl is a four-component system, whose chemical equilibria involve those observed in the subsystems H$_2$L–H$_2$O–NaCl and Tb(NO$_3$)$_3$–H$_2$O–NaCl. Heparin protonation in aqueous solution was studied in [4, 5]. It is necessary to study the formation of terbium hydroxide species in physiological saline solution Tb(NO$_3$)$_3$–H$_2$O–NaCl at 37°C and the ionic strength 0.15 mol/L NaCl.

EXPERIMENTAL

The concentrations of the lanthanide nitrate solutions used in this work were determined precisely by titration with a standard Trilon B solution in urotropin buffer. Xylenol Orange was the indicator. Lanthanide samples were of chemically pure or pure for analysis grade. A 0.1 M hydrochloric acid solution was prepared from a volumetric standard solution. All solutions were prepared from bidistilled water. The starting heparin preparation was a tetrasodium heparin pharmacological
solution packed in 5-mL vials (Ferein, Moscow). This solution contained 5 000 IU heparin per milliliter.

Aqueous solutions of the terbium salt, heparin, and hydrochloric acid were prepared and pH titration was carried out as described in [5]. The reading of an I-135 digital pH meter, which was used for pH measurements, was considered as a steady-state value if it did not change for 2 min.

When the solution opalesced at pH ≥ 7, the time drift of the pH meter stopped after 80 min. The steady-state value was set as equilibrium pH for the system of an aqueous solution and the solid phase of precipitated hydroxide.

RESULTS AND DISCUSSION

We studied the formation of terbium hydroxide ions in physiological saline solution Tb(NO₃)₃–H₂O–NaCl for the starting terbium concentration [Tb³⁺]₀ = 1.19 × 10⁻³ mol/L. Polymeric lanthanide hydroxide ions can form only in strong solutions with lanthanide concentrations of 0.1 to 1.0 mol/L [6]. On the assumption of the absence of polymeric species, the formation of terbium hydroxide ions is described by the reactions

\[
\text{Tb}^{3+} + \text{OH}^- \rightleftharpoons \text{Tb(OH)}_i^{(3-i)^+}, \quad i = 1, 2, 3. \tag{1}
\]

Opalescence observed in solution at pH ≥ 7 can be assigned to Tb(OH)₃ precipitation at pHs higher than the precipitation pH (pH ≥ pHₚₚ) [7]. Lanthanide hydroxides precipitate at pHₚₚ of 6.8–8.5; pHₚₚ decreases in transfer from lanthanum to lutetium. In the absence of an exact experimental determination of pHₚₚ for terbium in dilute solutions with the terbium concentration [Tb³⁺]₀ = 10⁻³ mol/L, we can determine 2.3 < pH < pHₚₚ, the minimum range on the titration curve in which Tb(OH)₃ is identified with an acceptable accuracy of βₙ estimation. pHₚₚ will be smaller than or equal to pHₚₚ. In the experiment in question, pHₚₚ is 7.03. This value agrees with pHₚₚ for the neighboring lanthanide (dysprosium), whose electronic configuration differs from that of terbium in one electron in the third shell: pHₚₚ(Dy) 7.0 [7].

The mathematical model of equilibria in the homogeneous system is specified by two mass-balance equations for the basis components with overall concentrations [H⁺]₀ and [Tb³⁺]₀ and with equilibrium concentrations calculated from the mass-action law for reactions (1):

\[
\begin{align*}
[H^+] - [OH^-] - [TbOH^{2+}] - 2[Tb(OH)₃^+] & = \text{[H}⁺\text{]}₀, \\
3[Tb(OH)₃] & = [H^+]₀, \\
[Tb^{3+}] + [TbOH^{2+}] + [Tb(OH)₂] & = 2[Tb(OH)₃], \\
[Tb(OH)₃] & = [Tb^{3+}]₀, \\
[OH^-] & = K_w/\text{[H}⁺\text{]}. 
\end{align*}
\]

here, \(K_w\) is the water ionic product and \(\log K_w = -13.4016\) for the ionic strength 0.15 mol/L NaCl and 37°C. The solution of the inverse problem of Eqs. (2) using AUTOEQUIL software [8, 9], which was adequate to experimental pH titration data for the test solution in the range 2.3 ≤ pH ≤ 7.03 and the starting terbium concentration [Tb³⁺]₀ = 1.19 × 10⁻³ mol/L (Fig. 1), gave estimates of the logarithmic formation constants for hydroxide ions with errors no greater than 3%: \(\log \beta_1 = 6.306, \log \beta_2 = 12.700, \log \beta_3 = 19.542\). The formation constants for hydroxide ions in the basis set OH⁻; Tb³⁺ can be calculated from \(\log \beta_i^{*} = \log \beta_i + i \log K_w\); they areas follows: \(\log \beta_1^{*} = -7.096, \log \beta_2^{*} = -14.103, \log \beta_3^{*} = -20.663\). The segment AB of the diagram in Fig. 1 refers to the homogeneous system. An estimate of \(\log \beta_3^{*} = -7.096\) well matches data in [10]: \(pK_i = 7.18\) for 30°C and the ionic strength equal to 0.1 mol/L NaCl. Importantly, when opalescence observed in the solution at pH higher than 7.03 is ignored and the single-phase model is used to describe experimental data over the entire range 2.3 ≤ pH ≤ 10,