Chinese Chemical Letters Vol. 12, No. 9, pp 809– 812, 2001
http://www.imm.ac.cn/journal/ccl.html

Tb(III) Speciation in Human Blood Plasma by Computer Simulation

Xing LU, Yue WANG, Hai Yuan ZHANG, Chun Ji NIU*, Jia Zuan NI

Key Laboratory of Rare Earth Chemistry and Physics, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022

Abstract: A multi-phase model was developed and Tb(III) speciation in human blood plasma was studied. At a concentration below 3.744×10^{-4}mol/L (or at the concentration), Tb(III) is mostly bound to phosphate to form precipitate of $TbPO_4$. As the concentration of Tb(III) increases, phosphate is exceeded and another kind of precipitate of $Tb_2(CO_3)_3$ appears. Among soluble Tb(III) species, Tb(III) mainly distribute in [Tb (Tf)] at low concentration and in [Tb (HSA)], [Tb_2 (Tf)], [Tb (IgG)], [Tb (Lactate)]$^{2+}$, [Tb (CitArgH)] and free Tb(III) at high concentration.

Keywords: Terbium (III), speciation, human blood plasma, computer simulation.

With the wide application of rare earth fertilizer and medicines[1], more and more rare earths enter into environment, and also into human body *via* food chain. Now it is very urgent to study the biological effect of rare earths on human health and environment. After entering into human body by whatever route, lanthanide ions are transported to secondary deposition sites mainly *via* the plasma in the blood stream. So it is very important to study lanthanides speciation in human blood plasma. Because of the absence of direct analysis methods, for this purpose, the computer simulation is preferred to study the distribution of species in some complicated systems, such as human blood plasma and other biological fluids[2].

Jackson *et al*. studied the *in vivo* Gd(III) speciation using single-phase model in which the insoluble species of Gd(III) were not considered[3]. Webb has published the speciation of Gd(III) and Cm(III) in the gastrointestinal tract, while the precipitated species of both metals were not considered either[4]. But such studies on Tb(III) are scarce. In this paper, we developed a multi-phase model of human blood plasma and the precipitates of Tb(III) were considered. Some reasonable results were obtained.

Methods

Multi-phase model of human blood plasma

May's single-phase model[5] was improved. PO_4^{3-} and CO_3^{2-} were added into this model because lanthanides prefer to bind them to form precipitates rather than form complexes with biological molecules[6]. The complexes of lanthanides with human serum

* E-mail: ldq@ns.ciac.jl.cn

transferrin, human serum albumin and immunoglobulin G are very stable[7], so they were included in our simulation model. In addition, the model contains almost all the important low-molecular-weight biological ligands, which consist of amino acids, carboxylic acids and hydroxy-carboxylic acids. Only a few low-molecular-weight ligands were not included because their concentrations are comparatively low and binding constants with lanthanides are relatively small. Such as histaminate, its concentration in human blood plasma is just 3.000×10^{-8} mol/L[5] and binding constant with Tb(III) is only 7.9[3]. This model is superior to the previous single-phase models because the precipitate species of Tb(III) can be calculated. The concentrations of metal ions and ligands are mainly cited from references 3 and 5.

Most of the stability constants of binary and ternary complexes of metal ions with the LMW biological ligands contained in this model were determined under physiological conditions by potentiometry in our group, and were used in this study[8~10].

Computer program

The computer program of MINTEQA2 used to simulate the speciation in human blood plasma was developed by U.S. Environmental Protection Agency in 1991.

Results and discussion

Tb(III) speciation in human blood plasma

Distribution of Tb(III) species is listed in **Table 1**. At a concentration below 3.744×10^{-4}mol/L (or at this concentration), Tb(III) is mostly bound to phosphate to form precipitate of $TbPO_4$. When the total concentration of Tb(III) increases further, the available phosphate is exceeded and another kind of precipitate of $Tb_2(CO_3)_3$ begins to form. With the increase of total concentration of Tb(III), the concentration of soluble Tb(III) increases. When the total concentration of Tb(III) increases to 1.767×10^{-2}mol/L, phosphate and carbonate are both entirely precipitated and the concentration of soluble Tb(III) reaches to a rather high value (1.007×10^{-3}mol/L). From above mention, we can conclude that in human blood plasma, Tb(III) is firstly bound to phosphate to form the precipitate of $TbPO_4$, and when the available phosphate is exceeded, another kind of precipitate of $Tb_2(CO_3)_3$ begins to form, which is in great accordance with Luckey's viewpoint[6].

Table 1 Distribution of Tb(III) species (%) (pH=7.4)

Species	Total Concentration of Tb(III) (mol/L)				
	1.000×10^{-6}	3.744×10^{-4}	1.000×10^{-2}	1.667×10^{-2}	1.767×10^{-2}
$TbPO_4$	96.1	99.0	3.7	2.2	2.1
$Tb_2(CO_3)_3$	0	0	96.0	96.7	92.2
Soluble Tb(III) species*	3.9 (3.945×10^{-8})	1.0 (3.612×10^{-6})	0.3 (3.612×10^{-6})	1.1 (1.911×10^{-4})	5.7 (1.007×10^{-3})

* The values in parentheses are concentrations of soluble Tb(III)

Distribution of soluble Tb(III) species in human blood plasma

Distribution of soluble Tb(III) species is listed in **Table 2**. At a total concentration below 3.744×10^{-4}mol/L (or at this concentration), soluble Tb(III) is mainly bound to transferrin to form [Tb (Tf)] because it is very stable[7]. As the total concentration of Tb(III) increases to 1.000×10^{-2}mol/L, percentages of [Tb_2 (Tf)], [Tb (HSA)] and [Tb (CitArgH)] increase while the percentage of [Tb (Tf)] decreases because the available transferrin is exceeded. When the total concentration of Tb(III) reaches to 1.667×10^{-2}mol/L, percentage of $[Tb (Ox)]^+$ is over 1%. Because of the high concentration of HSA in human blood plasma and the high stability of [Tb (HSA)], percentage of [Tb (HSA)] increases. For the same reason, percentages of [Tb_2 (Tf)] and [Tb (CitArgH)] also increase. As the total concentration of Tb(III) reaches to 1.767×10^{-2} mol/L when the concentration of soluble Tb(III) is about 1.000×10^{-3}mol/L, contents of free Tb(III), $[Tb (lactate)]^{2+}$ and [Tb (IgG)] increase to the values over 1%. Because available transferrin, oxalate and arginate are exceeded, percentages of their complexes with Tb(III) decrease. And at this concentration [Tb (HSA)] becomes the predominant soluble species of Tb(III).

Table 2 Distribution of soluble Tb(III) species (%) (pH=7.4)

Species	Total Concentration of Tb(III) (mol/L)				
	1.000×10^{-6}	3.744×10^{-4}	1.000×10^{-2}	1.667×10^{-2}	1.767×10^{-2}
Free Tb(III)	<1.0	<1.0	<1.0	<1.0	11.4
$[Tb (Ox)]^+$	<1.0	<1.0	<1.0	2.5	1.2
[Tb (Tf)]	99.9	99.9	88.9	3.0	<1.0
[Tb_2 (Tf)]	<1.0	<1.0	3.9	26.5	6.1
[Tb (HSA)]	<1.0	<1.0	1.2	38.1	60.7
[Tb (IgG)]	<1.0	<1.0	<1.0	<1.0	4.9
[Tb (citrate)]	<1.0	<1.0	<1.0	<1.0	<1.0
$[Tb (lactate)]^{2+}$	<1.0	<1.0	<1.0	<1.0	5.1
[Tb (CitArgH)]	<1.0	<1.0	5.7	26.4	7.3

Jackson *et al*. studied the Gd(III) speciation in human blood plasma and found that at a concentration below 1.000×10^{-4}mol/L Gd(III) was almost completely bound to transferrin, while at the concentration of 1.000×10^{-3}mol/L Gd(III) was mainly bound to low-molecular-weight ligands such as citrate, lactate[3]. However, because their single-phase model did not include human serum albumin and immunoglobulin G, also some important ternary complexes were absent, his results could not exactly elucidate the soluble Gd(III) speciation in human blood plasma. Our results show that when the concentration of soluble Tb(III) is below 1.000×10^{-4}mol/L (the total concentration of Tb(III) is below 1.625×10^{-2}mol/L), Tb(III) is mostly bound to transferrin, which is in accordance with Jackson's results. But as the concentration of soluble Tb(III) reaches to 1.000×10^{-3} mol/L (the total concentration of Tb(III) is about 1.767×10^{-2}mol/L), Tb(III) is mainly bound to human serum albumin, with some amounts of $[Tb (Ox)]^+$, [Tb_2 (Tf)], $[Tb (lactate)]^{2+}$, [Tb (CitArgH)], [Tb (IgG)] and free Tb(III). Meng *et al*. determined

the soluble rare earths in human blood plasma by ICP-MS and FPLC, and found that rare earths mainly distribute in human serum transferrin, human serum albumin and immunoglobulin G[11], which give strong support to our results.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (grant No. 29890280 and 29971029).

References

1. C. H. Evans, *Biochemistry of Lanthanide*, Plenum Press, New York, **1990**, 391.
2. J. R. Duffield, F. Marsicano, D. R. Williams, *Polyhedron*, **1991**, *10*, 1105.
3. G. E. Jackson, S. Wynchank, M. Woudenberg, *Magn. Reson. Med*. **1990**, *16*, 57.
4. L. M. Webb, D. M. Taylor, D. R. Williams, *J. Alloys and Compounds*, **1998**, *271-273*, 112.
5. P. M. May, P. W. Linder, *J. C. S. Dalton*, **1977**, 588.
6. T. D. Luckey, B. Venugopal, D. Huntcheson, *Heavy Metal Toxicity Safety and Hormology*, Academic Press, New York, **1975**, 27.
7. W. R. Harris, B. S. Yang, S. Abdollahi, Y. Hamada, *J. Inorg. Biochem.*, **1999**, *76*, 231.
8. Y. Wang, *Thesis*, Changchun Institute of Applied Chemistry, Academia Sinica, **2000**.
9. J. F. Han, *Thesis*, Changchun Institute of Applied Chemistry, Academia Sinica, **1999**.
10. Y. M. Liu, *Thesis*, Changchun Institute of Applied Chemistry, Academia Sinica, **1997**.
11. L. Meng, L. Ding, H. T. Chen, D. Q. Zhao, J. Z. Ni, *Chemical J. of Chinese Universities* (in Chinese), **1999**, *20*, 5.

Received 20 February, 2001