Chinese Chemical Letters Vol. 12, No. 2, pp. 161–162, 2001

Study on Effect of Gd (III) Speciation on Ca (II) Speciation in Human Blood Plasma by Computer Simulation

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Abstract: Ca (II) speciation and effect of Gd (III) speciation on Ca (II) speciation in human blood plasma were studied by computer simulation. $[CaHCO_3]^+$ is a predominant compound species of Ca (II). Gd (III) can compete with Ca (II) for biological molecules. The presence of Gd (III) results in a increase of concentration of free Ca (II) and a decrease of concentration of Ca (II) compounds.

Keywords: Speciation, blood plasma, computer simulation, calcium (II), gadolinium (III).

Lanthanide with excellent spectroscopic and magnetic properties can compete for Ca (II) binding sites in biological systems, which makes them very appealing as probes of Ca (II). Moreover, the Ca (II) displacement by lanthanide is closely related to biological effects of lanthanide. Therefore investigation on effect of the presence of the lanthanide on speciation of Ca (II) is very important to application of the lanthanide probes and study on biological effects of the lanthanide[1, 2]. Jackson *et al.* published the speciation of biological metal ions and Gd (III) ions *in vivo* by computer simulation[3]. Because insoluble species of metal ions could not be considered due to using single-phase model, the single-phase model could not be applied to study on effect of lanthanide speciation on Ca (II) speciation. In this article, Ca (II) speciation and effect of Gd (III) on Ca (II) speciation were studied using multi-phase model. Reasonable results were obtained.

We improved May's model and constructed a multi-phase computer model of blood plasma[4]. In this model, 22 ligands (including PO_4^{3-}, CO_3^{2-}, transferrin, HSA, IgG and some important low-molecular-weight ligands), three metals (Ca (II), Zn (II), Gd (III)) and hundreds of complexes were added. A lot of accurate stability constants of binary and ternary complexes of metal ions with biological ligands were determined under physiological conditions in our group, and were used in the computer simulation by means of computer program MINTEQA2.

The percentage distribution of Ca (II) in human blood plasma at pH 7.40 is shown in **Table 1**. It shows that 72.1% of Ca (II) ions are free, ~10% distribute in carbonate and phosphate and the rest form several kinds of complexes with histidinate, aspartate and so on. The species and their percentage distribution of Ca (II) in blood plasma in the presence of Gd (III) are also listed in **Table 1**. The data in **Table 1** show that at the concentration of

1.000 E-7 mol/L, Gd (III) ions are completely bound to phosphate to form precipitate of $GdPO_4$. However, the consumption of phosphate ions by Gd (III) ions is exceedingly small, so the presence of Gd (III) has little effect on species of Ca (II) ions. When the total concentration of Gd (III) increases, available phosphate ions are exceeded and the surplus are bound to carbonate to form another kind of precipitate of $Gd_2(CO_3)_3$, which causes the Ca (II) redistribution that the contents of $CaHPO_4$, $CaCO_3$ and $[CaHCO_3]^+$ decrease and the content of free Ca (II) ions increases. When the concentration of Gd (III) ions increases further, the concentration of soluble Gd (III) species increases. The soluble Gd (III) species can compete with Ca (II) for low-molecular-weight ligands, which would result in a decrease in contents of complexes of Ca (II) with low-molecular- weight ligands. From mentioned above, Gd (III) ions can compete with Ca (II) ions for biological ligands. In the presence of Gd (III), the concentration of free Ca (II) ions increases while Ca (II) compounds decreases.

Table 1 * Main species and distribution of Ca (II)** in the presence of Gd (III) (%)

Species	Total Concentration of Gd (III) (mol/L)					
	0	1.000E-7	3.744E-4	1.000E-2	1.650E-2	5.000E-2
Free Ca (II)	72.1	72.1	73.2	77.6	81.0	83.1
$[CaHCO_3]^+$	7.6	7.6	7.7	3.4	<1.0	<1.0
$CaCO_3$	1.0	1.0	1.1	<1.0	<1.0	<1.0
$CaHPO_4$	1.3	1.3	<1.0	<1.0	<1.0	<1.0
$[CaPO_4]^-$	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
$[CaLac]^+$	6.2	6.2	6.3	6.6	6.9	6.8
$[CaCit]^-$	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
$[CaHisThrH_3]^{3+}$	2.4	2.4	2.4	2.4	2.7	3.6
$[CaAspArgH_3]^{2+}$	~1.0	~1.0	1.0	1.1	1.0	<1.0
$[CaAspIleH_2]^+$	1.0	1.0	1.1	1.0	<1.0	<1.0
$[CaCitHisH_2]$	2.4	2.4	2.4	2.4	2.0	<1.0
$GdPO_4$	0	~100	~100	3.8	2.3	2.3
$Gd_2(CO_3)_3$	0	~0	~0	96.2	97.3	31.0
Soluble Gd (III) species	0	~0	~0	~0	0. 4	66.7

* Cit=citrate, His=histidinate, Asp=aspartate, Arg=arginate, Ile=isoleucinate, Thr=threoninate, Lac=lactate

** [Ca (II)]= 1.460 E-3 mol/L

Acknowledgment

We thank the NSFC for financial support of this work (Project Nos.29890280, 29971029).

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Received 7 July, 2000