Theoretical Calculations of Segregation Behavior of Zinc and Magnesium at Hydroxyapatite Surface in Contact with Water

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Density functional theory (DFT) calculations were performed to investigate atomic structures and segregation behavior of Zn2+ and Mg2+ ions at a (1010) surface of hydroxyapatite (HAp). In order to take account of aqueous solution environment surrounding the HAp surface, the conductor-like screening model (COSMO) was used. Ionic exchange energies of Zn2+ and Mg2+ at Ca sites around the surface were evaluated, under an assumption of chemical equilibrium between HAp and aqueous solution. It was found that Zn2+ can segregate energetically more favorably at the HAp surface, as compared to Mg2+. This may correspond to Zn2+ effects on inhibition of HAp crystal growth, as suggested by experiment. 

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1. Introduction

Mammalian bones are composed of hydroxyapatite (HAp, Ca10(PO4)6(OH)2) crystals and collagen fibers. It is well known that HAp components play important roles in human bodies, such as good mechanical strength, protection of internal organs and control of calcium concentrations in body fluids. Bones are also subjected to bone metabolism, in which HAp crystals in bones are repeatedly absorbed and reformed together with collagens by activation of osteoclasts and osteoblasts. Bone metabolism is closely related to osteoporosis, which is one of recent severe health problems worldwide, and it is desirable to find a way to control bone resorption and promote bone reformation. In this regard, one of possibilities is doping of metal ions (e.g., Mg2+, Zn2+, Sr2+).1-6) For example, Rude et al. showed that Mg2+ deficiency results in bone mass reduction due to decreased osteoclasts and increased osteoclasts.7) In contrast, it was also reported that Zn2+ can stimulate osteoblast activity, leading to promoted bone formation.8-11) Sr2+ doping was also expected to have the similar effect of increased osteoclast activity and increased osteoblasts activity.3)

In addition to the biological effect of doped metal ions, it is also likely that the doped ions significantly affect crystallography and growth of HAp crystals in vivo and in vitro. Fuierer et al. and Kanzaki et al. investigated effects of Zn2+ and Mg2+ on mineralization kinetics, and showed that these cations can inhibit HAp crystal growth and especially Zn2+ is more effective than Mg2+.12,13) In contrast, Hayakawa et al. reported that Zn2+ doping into HAp particles promotes protein adsorption.14) It is considered that protein adsorption as well as HAp growth is an important step for bone formation. These results indicate that these cations likely play their roles at HAp crystal surfaces. In order to obtain physical and chemical insights into the doping effect, therefore, it is necessary to clarify chemical environments of these cations, when they are located at HAp crystal surfaces.

In the present study, density functional theory (DFT) calculations were performed to reveal electronic and atomic structures of Mg2+ and Zn2+ at HAp surfaces. In particular, it is important to treat HAp surfaces in contact with water, because biological phenomena during bone metabolism occur under aqueous solution environments. Previously, a number of groups performed DFT calculations of HAp surfaces. Rulis et al. reported an atomic structure of pure HAp (0001) surface and its surface energy.15) Ma and Ellis investigated surface defects of Zn2+ on the HAp in a first principles manner.16) However, these calculations treated free HAp surfaces, namely the surfaces in contact with vacuum. In contrast, the present study performed DFT calculations of HAp surfaces and Zn2+ and Mg2+ ions therein in contact with water, with a dielectric continuum model to mimic water environments. For analyses of thermodynamic stability of the dopants, ionic exchange energies with Ca2+ were evaluated. A possibility of surface segregation of the dopants and their electronic and atomic level characteristics will be discussed.

2. Computational Method

2.1 Electronic structure calculation

DFT calculations of HAp surfaces and dopants therein were performed with the DMol3 code.17-19) The generalized gradient approximation of the Perdew-Burke-Ernzerhof form for the exchange correlation function was used.20) k-point sampling was performed by using a Γ-centered Monkhorst-Pack (MK)21) 2 × 2 × 2 mesh for a hexagonal HAp unit cell, the Γ point for supercells of bulk HAp, and a 2 × 3 × 1 MK mesh for HAp surface supercells described later. As a basis set, the double numeric basis with polarization was used, and a real-space cutoff radius was set to be 0.55 nm, which results in total-energy convergence of 1 meV/atom.

2.2 Supercells

In this study, atomic and electronic structures of HAp surfaces with/without substitutional Zn2+ and Mg2+ ions
were calculated. In order to examine a possibility of dopant segregation on HAp surfaces, as a first step, it is necessary to obtain formation energies of the dopants in bulk. Before going to the surface calculations, therefore, substitutional Zn$^{2+}$ and Mg$^{2+}$ ions in bulk HAp were calculated by using bulk supercells. Although our group already performed such dopant calculations in bulk HAp,$^{22-25}$ a different kind of basis set to describe wave functions (previously, a plane-wave basis had been used) was employed here, and thus similar calculations of dopants in bulk were again carried out. Based on the computational conditions described above, the calculated lattice constants of $a = 0.954$ nm and $c = 0.697$ nm for the hexagonal unit cell with a space group of $P6_3/m$ were obtained (within an error of less than 1.2% from experiment).$^{26}$ For calculations of dopants in bulk, the optimized hexagonal unit cell was repeated by $2 \times 2 \times 2$, and the resultant supercell of perfect HAp contained 352 atoms. A divalent cation of Zn$^{2+}$ or Mg$^{2+}$ was substituted for Ca$^{2+}$ in the bulk supercell. In the bulk case, it is noted that there are four kinds of inequivalent Ca$^{2+}$ sites in HAp, Ca-1a, Ca-1b and Ca-2. These are shown in Fig. 1.

In contrast, surface calculations require detailed information on surface orientation. In this regard, a (1010) surface of hexagonal HAp was selected in the present study. This is because recent experiments by Pareek et al. using the grazing incidence X-ray diffraction method revealed detailed atomic arrangements of the wet HAp (1010) surface.$^{27}$ Their results indicate that H$_2$O molecules adsorbed on the HAp surface exhibit an ordering arrangement parallel to the surface and at least two ordered H$_2$O layers are present on the HAp surface. H$_2$O molecules above the third layer show rather disordered arrangement, as expected from H$_2$O-molecule networks in bulk water. Based on their result, a surface slab model of HAp (1010) sandwiched with two adsorbed water-molecule layers was constructed, and was further sandwiched with a vacuum layer of 2.0 nm thickness in the surface supercell. The atomic arrangement of the surface supercell is displayed in Fig. 2. The two adsorbed water layers in our computed supercell contained six H$_2$O molecules on each HAp surface, in which four oxygen atoms in the first layer were denoted as $O_{w1}$, $O_{w2}$, $O_{w5}$ and $O_{w6}$ while those in the second layer as $O_{w3}$ and $O_{w4}$. The resulting number of atoms in the supercell was 140, including twelve H$_2$O molecules in total. It is noted here that the outermost Ca sites (Ca-A and Ca-B) correspond to Ca-2 sites in bulk HAp, which are located adjacent to the OH$^-$ group column along the $c$ axis.

In order to take into account an effect of H$_2$O molecules above the third layer from the HAp surface, the conductor like screening model (COSMO)$^{28}$ was used. COSMO is a
continuum solvent model approximation, where solvent molecules are treated as dielectric continuum of permittivity, \( \varepsilon \), with a cavity around a solute molecule. Charge distribution of a solute polarizes the dielectric continuum. The response of the dielectric continuum is described by the generation of screening charges on the cavity surface. These charges are scaled by a factor \( f(\varepsilon) = (\varepsilon - 1)/(\varepsilon + 0.5) \), to obtain a rather good approximation for the screening charges in a dielectric medium. The dielectric constant of water was used to \( \varepsilon = 78.4 \) in this study.20

### 2.3 Ionic exchange energy

In order to evaluate stability of the substituted cations, ionic exchange energies at the HAp surface were evaluated. Ion exchange energies (\( \Delta E \)) of \( \text{Zn}^{2+} \) and \( \text{Mg}^{2+} \) in HAp were evaluated from total energies \( E_i \) of HAp supercells. Here the following ion exchange reaction was considered:

\[
\text{Ca}^{2+} (s, \text{HAp}) + \text{M}^{2+} (aq) = \text{M}^{2+} (s, \text{HAp}) + \text{Ca}^{2+} (aq) \tag{1}
\]

By using total energies of HAp supercells, the ion exchange energy can be written as

\[
\Delta E = E_i (\text{M}^{2+} \text{ in HAp}) - E_i (\text{HAp}) + \mu_{\text{Ca}^{2+}, aq} - \mu_{\text{M}^{2+}, aq} \tag{2}
\]

Where \( \mu_{\text{M}^{2+}, aq} \) is an ionic chemical potential of the ionic species \( \text{M}^{2+} \) in aqueous solution. In a dilute solution, the ionic chemical potential can be written in terms of a standard chemical potential (\( \mu^{\circ} \)) and a concentration of ionic species in solution (\( [\text{M}^{2+}] \)) as

\[
\mu_{\text{M}^{2+}, aq} = \mu^{\circ}_{\text{M}^{2+}, aq} + k_B T \ln [\text{M}^{2+}] \tag{3}
\]

In this equation, \( k_B \) is the Boltzmann constant, and \( T \) is a temperature (\( T = 298.15 \) K throughout this study). Then eq. (2) can be rewritten as

\[
\Delta E = E_i (\text{M}^{2+} \text{ in HAp}) - E_i (\text{HAp}) + \mu_{\text{Ca}^{2+}, aq} - \mu_{\text{M}^{2+}, aq} + 2.303 k_B T \log \frac{[\text{Ca}^{2+}]}{[\text{M}^{2+}]} \tag{4}
\]

In order to calculate \( \Delta E \), it is necessary to evaluate the third, fourth and fifth terms of right hand side of eq. (4). The third and fourth terms of the standard Gibbs formation energies of \( \text{Ca}^{2+} \) and \( \text{M}^{2+} \) in aqueous solution (\( \Delta G_i^{\circ} \)) can be written as follows:22–24

\[
\mu^{\circ}_{\text{Ca}^{2+},aq} - \mu^{\circ}_{\text{M}^{2+},aq} = \Delta G_i^{\circ} (\text{Ca}^{2+}, aq) - \Delta G_i^{\circ} (\text{M}^{2+}, aq) + \mu_{\text{Ca}^{2+}} - \mu_{\text{M}^{2+}} \tag{5}
\]

For \( \Delta G_i^{\circ} (\text{M}^{2+}, aq) \), the experimental thermodynamic data at \( T = 298.15 \) K was used in this study.22–25 Also, \( \mu_{\text{Ca}^{2+}} \) and \( \mu_{\text{M}^{2+}} \) are chemical potentials of solid Ca and M metals. These quantities were considered to correspond to total energies per atom of fcc Ca, hcp Zn and Mg, which were separately calculated in the first-principles manner.

Remaining quantities to be prepared for eq. (4) are ionic concentrations in aqueous solution. Here it was assumed that HAp is in chemical equilibrium with aqueous solution, and then the ionic concentration of \( \text{Ca}^{2+} (\text{aq}) \) was obtained from the one in aqueous solution saturated with respect to HAp. This can be evaluated from the solubility constant of HAp, the acid dissociation constants of phosphate ions, and so on. Furthermore, the concentration of \( \text{M}^{2+} \) in the saturated solution was assumed to be \( 1.0 \times 10^{-4} \) mol/L. The [Ca\(^{2+}\)] in the saturated solution against pH thus obtained is displayed in Fig. 3. It can be seen that the [Ca\(^{2+}\)] value varies depending on pH so that the ionic exchange energy from eq. (4) also exhibits the pH dependence. Further details can be seen elsewhere.22–25

### 3. Results and Discussion

#### 3.1 Atomic structures

Figure 4 displays a calculated atomic structure of the HAp (1010) surface with the two adsorbed H\(_2\)O layers. Basically, the outermost Ca atoms (Ca-A and Ca-B) have bonding mainly with oxygen atoms below the surface plane (belonging to OH\(^{-}\) groups or PO\(_4^{3-}\) groups in HAp). It is noted, however, that Ca-A involves bonding with Ow1 in the first adsorbed H\(_2\)O layer (see Fig. 5(a)). Bond lengths of Ca-A and Ca-B with the first neighboring oxygen atoms range from 0.23 to 0.26 nm, and their coordination numbers are six, as displayed in Fig. 5. As stated in Sec. 2.2, these Ca atoms correspond to Ca-2 in bulk hexagonal HAp, which has a coordination number of six with oxygen within the first nearest neighbor atomic shell (within a bonding distance of 0.25 nm). It can be said that the outermost Ca-A and Ca-B have the similar atomic coordination with Ca-2 atoms in bulk and yet Ca-A involves direct bonding with an oxygen atom of adsorbed H\(_2\)O.

Regarding an atomic configuration of adsorbed H\(_2\)O molecules above the HAp surface, H\(_2\)O molecules in the two adsorbed layers tend to make hydrogen-bonding like networks with oxygen ions of other H\(_2\)O molecules and at the HAp surface (O–H–O). As listed in Table 1, calculated distances between oxygen ions of H\(_2\)O molecules and their nearest neighboring oxygen ions at the HAp surface are in the range of 0.26–0.28 nm, which is within a typical atomic distance between oxygen atoms as found in bulk water.29 This is also the case on the basis of experimental data by Pareek \textit{et al.}\textsuperscript{27} and yet the bond-length variation of 0.24–0.30 nm for different oxygen atoms of H\(_2\)O molecules is slightly larger than that by the present calculation. Such a difference is also expected from a comparison of the atomic structures between theory and experiment (see Figs. 2 and 4),
showing the different arrangement of H2O molecules apparently. In this regard, strictly speaking, the H2O-molecules arrangement above the HAp surface cannot be fully reproduced by the present calculation. This may be mainly because the present calculations deal with only two adsorbed H2O layers. As stated in Sec. 2.2, it is experimentally reported that H2O molecules above the third adsorbed layers exhibit rather disordered arrangement. The H2O effect above the third layer is approximated by COSMO in the present calculation. Introduction of H2O molecules above the third layers in the supercell may further improve computational accuracy, but such calculations are also demanding. On the other hand, previous theoretical calculations of ions in aqueous solution suggested that inclusion of H2O molecules within the second nearest neighboring atomic shell, together with the COSMO model, results in good accuracy of hydration energies of solvated ions in water.30) It is thought, therefore, that the present calculations reasonably take account of quantum-mechanical and electrostatic interactions between ions at the HAP surface and H2O adsorbed molecules to some extent, and the supercell can be expected to be appropriate for investigating dopant segregation on the surface in contact with water.

When Zn2+ and Mg2+ are introduced at the outermost Ca sites, it appears that their coordination environments become different from those of the outermost Ca atoms at the undoped surface. In the case of Zn2+ (see Fig. 6), Zn2+ also has fivefold coordination with oxygen at the Ca-A site, while that at Ca-B is fourfold coordinated. An average bonding distance of Zn–O at Ca-A and Ca-B was 0.21 nm, which is close to the ZnO bond length 0.20 nm in ZnO. In contrast, Mg2+ has fivefold coordination with oxygen atoms at the

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Table 1 Bond lengths between oxygen belonging to H2O and their nearest neighboring oxygen belonging to HAp (in nm).
Ca-A and Ca-B site. Their bond lengths range from 0.20 to 0.23 nm, which corresponds with the Mg-O bond length of 0.21 nm in solid MgO. Therefore, these doped cations tend to have smaller coordination numbers than Ca ions at the surface. This is due to smaller ionic radii of Mg$^{2+}$ (0.072 nm) and Zn$^{2+}$ (0.074 nm) than Ca$^{2+}$ (0.10 nm).\textsuperscript{31)

3.2 Ionic exchange energy

Figure 7 shows calculated ionic exchange energies of Zn$^{2+}$ and Mg$^{2+}$ with Ca$^{2+}$ in bulk and at the HAp surface, as a function of pH. In the bulk case, as already reported in our previous study,\textsuperscript{24) these cations favor Ca-2 substitution, and Zn$^{2+}$ has a smaller ionic exchange energy with Ca$^{2+}$, as compared to Mg$^{2+}$. This is partly because Zn$^{2+}$ at the Ca-2 site can take fourfold coordination with oxygen as found in the oxide material of ZnO, although original Ca sites in bulk HAp have sixfold coordination with oxygen. Moreover, substitutional Zn in HAp exhibits covalent like bonding with oxygen in HAp, which may also contribute to stabilization of substitutional Zn.\textsuperscript{24)}
The similar situation can also be seen at the surface. Ionic exchange energies of Zn$^{2+}$ and Mg$^{2+}$ at the HAp surface (Ca-A or Ca-B site) become smaller than those in bulk, which indicates that these cations tend to segregate on the HAp surface. However, Mg$^{2+}$ at Ca-A of the surface shows a much higher energy than Zn$^{2+}$ on the surface. Moreover, the ionic exchange energy of Zn$^{2+}$ is negative at around the neutral pH. Since the negative energy indicates spontaneous substitution of Zn$^{2+}$ at Ca-A, Zn$^{2+}$ can more effectively segregate at the HAp surface than Mg$^{2+}$.

As stated above, the present calculations clearly showed that Zn$^{2+}$ can more favorably segregate on the HAp surface, as compared with Mg$^{2+}$. This is closely related to the experimental result that crystal growth of HAp can be more effectively inhibited by Zn$^{2+}$ doping, as compared with Mg$^{2+}$ doping. More intense segregation of smaller sized Zn$^{2+}$ ions at the surface may correspond to Zn$^{2+}$ ions at the surface may favorably segregate the HAp surface, as suggested by experiment.

4. Conclusion

Atomic structures and segregation behavior of Zn$^{2+}$ and Mg$^{2+}$ at the HAp (1010) surface were theoretically investigated by DFT calculations. The COSMO model was used to approximately describe interactions between ions in HAp and aqueous solution. From total energies of undoped and doped supercells for the HAp surface, ionic exchange energies of Zn$^{2+}$ and Mg$^{2+}$ were found that Zn$^{2+}$ can favorably segregate on the HAp surface, and may correspond to Zn$^{2+}$ effects on inhibition of HAp crystal growth, as suggested by experiment.

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REFERENCES