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Anomalous water and ion dynamics in hydroxyapatite mesopores

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ABSTRACT

Hydroxyapatite (HAP) is the principal phase of bones, where the presence of ions in the fluids within HAP pores is critical to important phenomena such as bone remodeling, mineralization and fossilization. Classical molecular dynamics simulations of HAP pores ranging from 2 to 120 nm, containing pure water and aqueous solutions of $CaCl_2$ and of CaF_2, were conducted to quantify the effect of confinement and solution composition on the dynamic properties of water and ions. Diffusion coefficients were obtained from formulations adapted to diffusion processes parallel and perpendicular to the HAP walls. A change in diffusion mechanism is observed in the direction perpendicular to the HAP walls: after a transition period proportional to the pore size, the mean squared displacement scales with the square-root of the time instead of being linear. The presence of $CaCl_2$ and CaF_2 decelerates water and ion dynamics, and changes in ion concentration modify the in-plane dynamics more strongly than the out-plane dynamics of ions in HAP pores.

1. Introduction

The processes ontrolling the dynamics of hydrated ions in contact with hydroxyapatite (HAP) based materials is critical to important phenomena involving mineralized tissues such as bone adaptation or remodeling processes [1,2], nutrition of osteocytes that are not directly in contact with the vascular supply [3], de- and re-mineralization processes occurring in tooth enamel and dentin in response to changes in the oral fluids [4–6], and diagenetic changes and fossilization of bones [7,8]. Artificial HAP is currently used as a substitute material for damaged bones and teeth in orthopaedic and dental applications [9]. Additionally, *in situ* formation of HAP is recognized as a method for the conservation of cultural heritage, including sulphated stones, gypsum stuccoes, concrete, wall paints, archaeological bones and paper [10]. In all these cases, a fundamental understanding of the diffusion processes in HAP nanometric pores can contribute to improving the durability and effectiveness of HAP restoration and consolidation treatments.

HAP ($[Ca_{10}(PO_4)_6(OH)_2]$) is the principal phase of mineralized tissues found in mammalian bone and tooth enamel and dentin, where HAP is present in the form of thin plates with colloidal size 25–50 nm in the **a**-direction, 15–25 nm in the **b**-direction and 2.5 nm in the **c**-axis [11]. HAP platelets are stacked along **c**-direction and the interlayer space is filled with body fluid, which is rich in ions. The thickness of the resulting pores ranges from 2 to 24 nm [12], which correspond to mesopores (2–50 nm) according to IUPAC classification.

Water and ion structuration adjacent to HAP walls is recognized to impact the biomechanical response of bones [13]. Confined fluids are well-known to behave differently from bulk fluids (*e.g.* Brovchenko and Oleinikova [14]), notably in what concerns transport properties [15]. Additionally, specific (or Hofmeister) ions effects, which usually manifest at concentration above 0.01 M [16], may be associated with the concentrations of dissolved salts found in HAP pores. The confinement of electrolyte solutions in micro- or mesopores may therefore resonate into the macroscopic behavior of HAP-rich materials.

Experimental evaluation of ion effects on water dynamics within bone as well as ion dynamics *per se* may be challenging [17]. This aspect justifies the choice of *in silico* strategies to quantify the dynamic properties of water molecules and charged particles in bone mesopores [17]. Molecular Dynamics (MD) simulation is a particularly powerful tool to understand in detail the mechanisms of diffusion and quantify the interactions of aqueous solutions in contact with ionic surfaces [18], and unlike thermodynamic properties, self-diffusion coefficients can only be evaluated by means of a MD simulation [19].

In this context, recent MD simulations conducted by some authors of this work have provided molecular-level detail about the transport of water within HAP nanopores [20–23]. Di Tommaso et al. [23] showed that solvated ions in HAP pores slows the dynamics of water molecules compared to bulk liquid by enhancing the rigidity of H-bonds networks. However, the role of confinement on the mechanism of fluid and solute diffusion is still poorly understood [24–26]. For example, confinement

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may induce super- and sub-diffusion regimes and in the case of nanoporous HAP this change in diffusion mechanism is still to be identified. Moreover, the self-diffusion of ions as a function of the level of confinement within HAP nanopores is also to be quantified and the studies conducted so far have not provided an estimate of the in- and out-of-plane diffusion coefficient of ions [27,20–23]. Finally, because of periodic boundary conditions and finite size of the simulation box, it is imperative to have an estimate of these effects on the dynamics of fluid and solutes using recently proposed corrections for MD simulation in slit pores [28,29].

In this article, we examine the self-diffusion (named simply diffusion hereafter) of water and ions confined in HAP pores ranging from 2 to 120 nm by means of classical MD simulations. In particular, a numerical analysis of the finite-size effects has been conducted. The anisotropic nature of water and ion diffusion in HAP mesopores has been quantified in terms of the ensemble averaged Mean Squared Displacement (MSD) and analyzed according to various salinities. Diffusion coefficients were obtained by means of formulations adapted to dynamic processes parallel and perpendicular to HAP walls. The effects of confinement in affecting the diffusion mechanisms, leading to subdiffusion, have also been quantified. Aqueous solutions of $CaCl_2$ and CaF_2 were considered to determine the effect of specific ions because of their biological interest. In particular, Fluoride (F^-) is known to have a fundamental physicochemical role in bone cells. The results obtained in confined conditions were confronted with those of bulk solution.

2. Material and methods

2.1. Molecular model and force field

The atomic structure of HAP was derived from the cell parameters and crystallographic data of Sudarsanan and Young [30]. The resulting unit cell was hexagonal with $P6_3/m$ space group. This unit cell was replicated 3 times in each in-plane direction and 4 times in out-of-plane direction (Fig. 1). The resulting total number of atoms in the HAP solid layer is $N_{HAP} = 1584$ atoms. HAP platelets were stacked with a surface-to-surface spacing along **c**-direction varying from 2 to 12 nm. The surface of HAP considered as basal plane is {0 0 0 1}, which is reported to be the dominant surface in the thermodynamically-stable morphology [31].

The space in-between HAP platelets was filled with water molecules following the simulation protocol detailed in the next section.

The interactions between the species within HAP platelet as well HAP and electrolyte were described by the force fields developed by de Leeuw and co-workers [32,33] together with the extended single-point charge (SPC/E) water model [34]. The simulations are performed at neutral pH (water dissociation is not taken into account).

Ions resulting from $CaCl_2$ or CaF_2 dissolution were added to the system according to four concentrations C listed in Table 1. The dynamics of ions is reported to be concentration dependent [35,36]. Solutions resulting from both salts have the same ionic strength $I = (1/2)\sum_i z_i^2 c_i$, for a given concentration c_i (in mol per unit of volume), since chloride and fluoride ions own the same valence z_i. The Debye length $1/\kappa$ is the characteristic length associated with electrostatic interactions in colloids. This length can be directly computed from the ionic strength with $\kappa^2 = \frac{2Ie^2}{\epsilon\epsilon_0 kT}$, where e is the elementary charge, k is the Boltzmann constant, T is the temperature, ϵ is the dielectric constant of the medium and ϵ_0 is the vacuum permittivity.

Table 1
Concentrations, ionic strength I and Debye length $1/\kappa$ at 310 K of calcium chloride and calcium fluoride.

C (mol/kg)	M (mol/L)	I (mol/L)	$1/\kappa$ (nm)
0.1	0.104	0.311	0.926
0.5	0.519	1.557	0.414
1.0	1.038	3.114	0.293
1.5	1.583	4.748	0.237

2.1.1. Molecular dynamics simulations

MD simulations were performed using DL_POLY 4.05.1 code [37]. After filling the pore with water at 1 g/cm^3, which is close to the density of SPC/E water at ambient conditions. The system was first equilibrated in the microcanonical (NVE) ensemble for 1 ns. Then, a first isothermal-isobaric (NPT) run for 1 ns was performed to equilibrate the system under a pressure of 1 atm at 310 K to mimic the environment of *in vivo* human bone. In previous studies [20,22], simulations in the microcanonical ensemble (NVE) were performed to ensure that the rescaling of the dynamics by the thermostat did not affect significantly the dynamics. In the production phase, the system was sampled for 2 ns in NPT ensemble. The Nosé-Hoover thermostat and barostat, at relaxation time 0.5 ps for both, were employed. The long range electrostatic interactions were computed using the Smoothed Particle Mesh Ewald (SPME) method with an acceptable relative error of 10^{-6}. This MD methodology was adopted in our previous studies of HAP nanopores [21–23].

Table 2 shows the number of water molecules N_w for each target pore size H which is defined as the projection of **c** vector on **z**-direction minus the effective thickness h_{HAP} of the solid HAP. This effective thickness h_{HAP} is defined as the distance between the center of the out-most oxygen (the out-most species in HAP surface) in each exposed HAP surface projected on **z**-direction plus twice the van der Waals radius of oxygen $r_O = 0.152$ nm. Accordingly, the average pore size $\langle H\rangle_{NPT}$, sampled during the second NPT run, is computed by: $\langle H\rangle = \langle \mathbf{c}.\mathbf{z}\rangle_{NPT} - \langle h_{HAP}\rangle_{NPT}$. Similar definitions of effective thickness and pore size were used for other layered materials such as clays [38].

2.2. Quantification of self-diffusion coefficients under confinement

The dynamics of fluids can be quantified in terms of the ensemble averaged (*i.e.* an average over the number of particles, denoted $\langle . \rangle$ hereafter) of the Mean Squared Displacement (MSD):

$$\langle r_i(t)^2\rangle \approx D_{ii} t^\alpha \quad with\ i = x, y\ or\ z \tag{1}$$

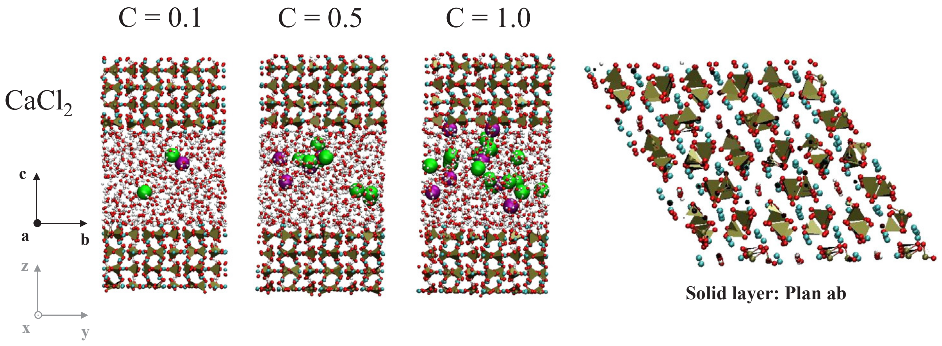

Fig. 1. At left, snapshot of configuration of HAP-aqueous solution system with $H = 2$ nm at $CaCl_2$ concentrations C (in mol/kg) considered in this article. At right, view of the HAP solid layer from **ab** plan. Ca^{2+} and Cl^- ions are depicted as purple and green van der Waals spheres, respectively. In HAP layer and water molecules, O atoms are red, H white and Ca cyan small spheres; P atoms are depicted as tetrahedra. For reference the orthogonal (**x**, **y**, **z**) and crystallographic (**a**, **b**, **c**) frames are also reported. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)