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An atomic-level look at the structure-property relationship of cerium-doped glasses using classical molecular dynamics

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ABSTRACT

Ce-containing bioactive glasses are of great interest in biomedical field since they exert antioxidant properties associated with low toxicity and a broad spectrum of bacteriostatic activities. The results obtained by classical molecular dynamics simulations allow the elucidation of the correlations between the effect of the inclusion of cerium doping ions into the structure of phosphosilicate and silicate bioactive glasses and their properties. The addition of small quantities of Ce to the silicate bioglass favours the depolymerisation of the silicate network with a positive effect on the ability to dissolve in body fluid. Moreover, the under coordination of both the Ce^{3+} and Ce^{4+} species in these glasses enhances their catalytic activity towards hydrogen peroxide. Conversely, the formation of cerium phosphate domains in the phosphosilicate glasses leads to detrimental effects for both the solubility and the catalytic activity of the glasses. Finally, a new quantitative view of the structure-activity relationships governing the macroscopic properties of these glasses has been obtained by means of structural descriptor that takes into account the fragmentation of the Si network and the consequent rearrangement of the modifier ions and the network destruction per cerium unit descriptor.

1. Introduction

The increasing popularity of Bioactive glasses is due both to their composition, chemically related to the bone tissue, and their unique dissolution properties in body fluids. The rate of dissolution can be tailored by modulation of the composition of the glass. Thus, critical concentrations of ionic species can be released in the surrounding physiological environment, promoting mineralisation and stimulating the growth and differentiation of osteoblasts at the genetic level.

Moreover, incorporation in the glass matrix of optimal amounts of specific ions with physiological activities and therapeutic properties promotes the use of bioactive glasses in a large range of novel applications for advanced therapy in the field of soft tissue regeneration, wound healing, antimicrobial effect, drug release, cancer treatment, etc.… [1,2].

Cerium doped bioglasses have gained considerable interest in the biomedical field because of their role in enhancing osteoblastic differentiation, stimulating the production of collagen, exerting a broad spectrum of antibacterial activity and exhibiting low toxicity [3].

Our interest in this element was recently arisen from its antioxidant properties. The on-going activity of our research group in the field concerns the study of the ability of Ce-containing bioactive glasses to exert antioxidant activity by promoting the decomposition of hydrogen peroxide (H_2O_2) and superoxide (O^{2-}) radicals in vitro, as the enzymes Catalase [4] and Superoxide Dismutase [5] do at the physiological level, protecting cells from oxidative stress.

We have recently showed that, as in the CeO_2 nanoparticles on which the enzyme mimetic activity was demonstrated for the first time [6], the antioxidant activity of bioglass [7] is related to the multiple valence states of Cerium, Ce^{3+} and Ce^{4+}, which are able to catalyse the dismutation reaction of hydrogen peroxide according to the following reactions:

$$2Ce^{3+} + H_2O_2 + 2H^+ \rightarrow 2H_2O + 2Ce^{4+}$$
$$2Ce^{4+} + H_2O_2 \rightarrow O_2 + 2H^+ + 2Ce^{3+}$$
$$2H_2O_2 \rightarrow 2H_2O + O_2$$

The relative amount of available Ce^{3+}/Ce^{4+} and the kinetic of redox conversion $Ce^{3+} \leftrightarrow Ce^{4+}$ depend on the chemical nature of the glass matrix constituents and environment. In particular, the phosphate units present in the glass and/or in the physiological solution, in which the leaching and catalase mimetic activity tests are usually carried out, slow the kinetics of release and of dismutation reactions, subtracting the catalyst by forming an amorphous insoluble phase ($Ce_2O_3{\cdot}CePO_4$) [8,9].

To this regards, the glass of composition $25Na_2O$ 25CaO $50SiO_2$ mol %, proposed by Kokubo et al. [10] is a more efficient catalyst [11].

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However, the additional problem of determining the maximum amount of cerium oxide that can be added to the parent Kokubo glass to imprint optimal anti-oxidant ability without negatively affecting the solubility and then the bioactivity still have to be faced.

Because of their amorphous nature, there is a lack of detailed information on the microscopic structure of the bioglasses, on how the glass network is affected by the different ions making up the glass composition, and how changes in the structure affect the dissolution behaviour and the enzyme-mimetic activity. While molecular dynamic (MD) simulations will never replace laboratory experiments, it is increasingly being used to extract measurement of material properties where existing experimental techniques are unable to or where interpretation of the results of the experiment is difficult or apparently contradictory [12].

In this paper, we review the results obtained on cerium-doped bioglasses by means of the synergic experimental-computational approach developed in our laboratory and we present a new quantitative view of the structure-activity relationships governing the macroscopic properties of these glasses.

2. The glass

2.1. Glass compositions

Two series of bioactive glasses doped with variable percentages of cerium oxide have been considered for computational simulations studies of bulk materials [4,11]. Their molar compositions are reported in Fig. 1.

The parent glass of the first series, hereafter identified as H series, is the well-known 45S5 Bioglass® [13], whereas the parent glass of the second one (hereafter referred as K series) is the phosphate free glass proposed by Kokubo et al. [10]. K_5.3 is partially crystallized therefore it has not be used for subsequent analysis.

In addition, bioactive glass nanoparticles (NP) of the same composition of the bulk H_3.6 and K_3.6 glasses have also been considered in order to investigate the effect of surface area and reduced size in the structure-property relationships with respect to the bulk glasses [14].

The relative amount of Ce^{3+} and Ce^{4+} in the two series of glasses studied was determined by XPS [4] and K-edge XANES [15]. The results obtained by the first technique suggested that the amount of the Ce^{3+} and Ce^{4+} is balanced in the K glass (Ce^{3+}/Ce^{4+} = 1.2), while it is substantially different in the H glass ($Ce^{3+}/Ce4^{+}$ = 3.5); qualitative evidences from the second technique suggest that the Ce^{+3}/Ce^{4+} ratio is not significantly dependent on the cerium doping concentration.

2.2. Glass MD simulations

The structures of the glasses have been generated through classical MD simulations by using the DL_POLY package [16]. For the molecular simulations of the bulk materials, a well-established melt-quench computational protocol, described in previous work has been used [4]. Periodic boundary conditions (PBC) were used on a cubic box of side ~ 52 Å that contains around 10,000 atoms, depending on glass density. The total number of each Ce^{3+} and Ce^{4+} species in the final box of the H_3.6 glass is 96 and 27, respectively; whereas in the K_3.6 glass is 70 and 60, respectively.

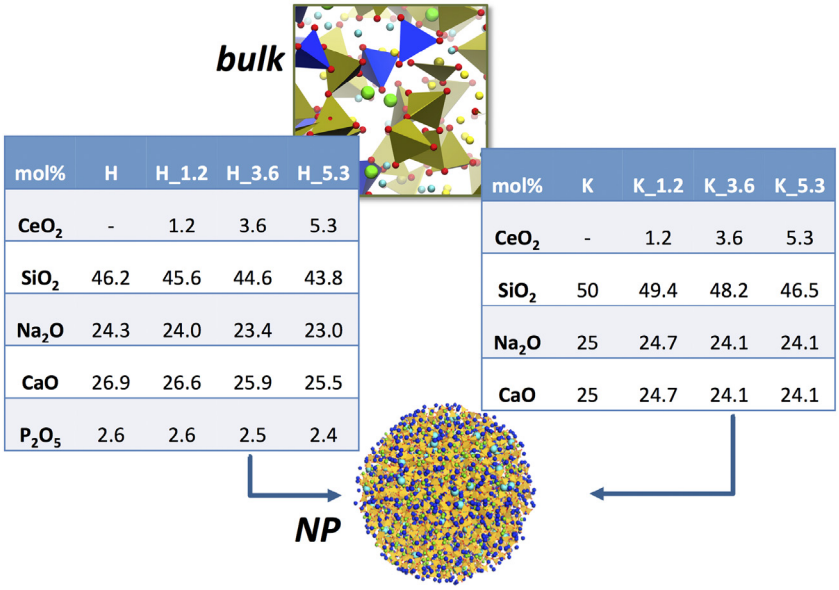
The glass nanoparticles have been obtained by removing the PBCs and imposing spherical containing potentials, while quenching from 3200 K to 300 K, until a NP with radius of about 33 Å was obtained [14].

Three independent simulations have been performed for each composition, the typical error associated to the results are on the second digit of the structural properties computed.

The Extended X-Ray Absorption Fine Structure (EXFAS) patterns were calculated for the BG_5.3 MD-derived three-dimensional structures using the FEFF 8 code [17]. Each EXAFS pattern was averaged over all the non-equivalent cerium atoms within the MD calculated shell (180 for BG_5.3 and 130 for K_3.6), including single and multi-scattering paths by atoms within a 9 Å distance from the central atom.

2.3. Force field parameters

In order to obtain a reasonable good description of the short and medium-range order of the glass structure at affordable computational costs, an adiabatic core-shell model [18] was used. In this model, the polarizability of oxygen induced by the network environment is straightforwardly included by considering the forces acting on the oxygen shell by the other ions [19]. Parameters for Ce^{3+} and Ce^{4+} compatible with this force field were derived recently by fitting on the Ce-containing crystal phases available in the literature [20]. Notwithstanding the number of experimental data available for the fitting procedure were scarce, especially for the Ce^{4+} species (5 crystalline phases containing Ce^{3+} (Ce_2O_3, CeP_5O_{14}, $Ce_2O_7Si_2$, $CePO_4$ and $Al_3CeP_2O_{14}H_6$) and 2 crystalline phases containing Ce^{4+} (CeO_2 and



mol%	H	H_1.2	H_3.6	H_5.3
CeO_2	-	1.2	3.6	5.3
SiO_2	46.2	45.6	44.6	43.8
Na_2O	24.3	24.0	23.4	23.0
CaO	26.9	26.6	25.9	25.5
P_2O_5	2.6	2.6	2.5	2.4

mol%	K	K_1.2	K_3.6	K_5.3
CeO_2	-	1.2	3.6	5.3
SiO_2	50	49.4	48.2	46.5
Na_2O	25	24.7	24.1	24.1
CaO	25	24.7	24.1	24.1

Fig. 1. The composition of the glasses studied as bulk and NP surface.