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Magnesium incorporation into hydroxyapatite

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ABSTRACT

The incorporation of Mg in hydroxyapatite (HA) was investigated using multinuclear solid state NMR, X-ray absorption spectroscopy (XAS) and computational modeling. High magnetic field ^{43}Ca solid state NMR and Ca K-edge XAS studies of a ~10% Mg-substituted HA were performed, bringing direct evidence of the preferential substitution of Mg in the Ca(II) position. ^{1}H and ^{31}P solid state NMR show that the environment of the anions is disordered in this substituted apatite phase. Both Density Functional Theory (DFT) and interatomic potential computations of Mg-substituted HA structures are in agreement with these observations. Indeed, the incorporation of low levels of Mg in the Ca(II) site is found to be more favourable energetically, and the NMR parameters calculated from these optimized structures are consistent with the experimental data. Calculations provide direct insight in the structural modifications of the HA lattice, due to the strong contraction of the M···O distances around Mg. Finally, extensive interatomic potential calculations also suggest that a local clustering of Mg within the HA lattice is likely to occur. Such structural characterizations of Mg environments in apatites will favour a better understanding of the biological role of this cation.

1. Introduction

Calcium hydroxyapatite is the main mineral component of bone tissue and teeth. Its composition differs from that of synthetic hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ (HA), due to the presence of several ionic substitutions in the lattice, such as CO_3^{2-}, F^-, Mg^{2+} and Na^+ [1]. These minor species not only alter the space group, morphology, stability, and mechanical properties of the HA structure, but also play an important role in the biological responses of bone cells. For instance, carbonates have a strong influence on the growth of apatite crystals [1], sodium plays a role in bone remodelling [2], whereas fluoride prevents the development of dental caries [3]. These ions are distributed inhomogeneously throughout the tissue, and their concentration changes according to the age and maturity of the mineral.

Magnesium is known to be an important trace element in bone and teeth. Indeed, despite its low concentration (generally between ~0.5 and 1.5 wt%), it plays a key role in bone metabolism, in particular during the early stages of osteogenesis where it stimulates osteoblast proliferation [4], and its depletion causes bone fragility and bone loss [5]. Furthermore, relationships have been suggested between the magnesium content in enamel and the development of dental caries [6].

Given the biological relevance of magnesium, many research teams have worked on the preparation of apatite and calcium-phosphate implant materials containing low levels of Mg, which has

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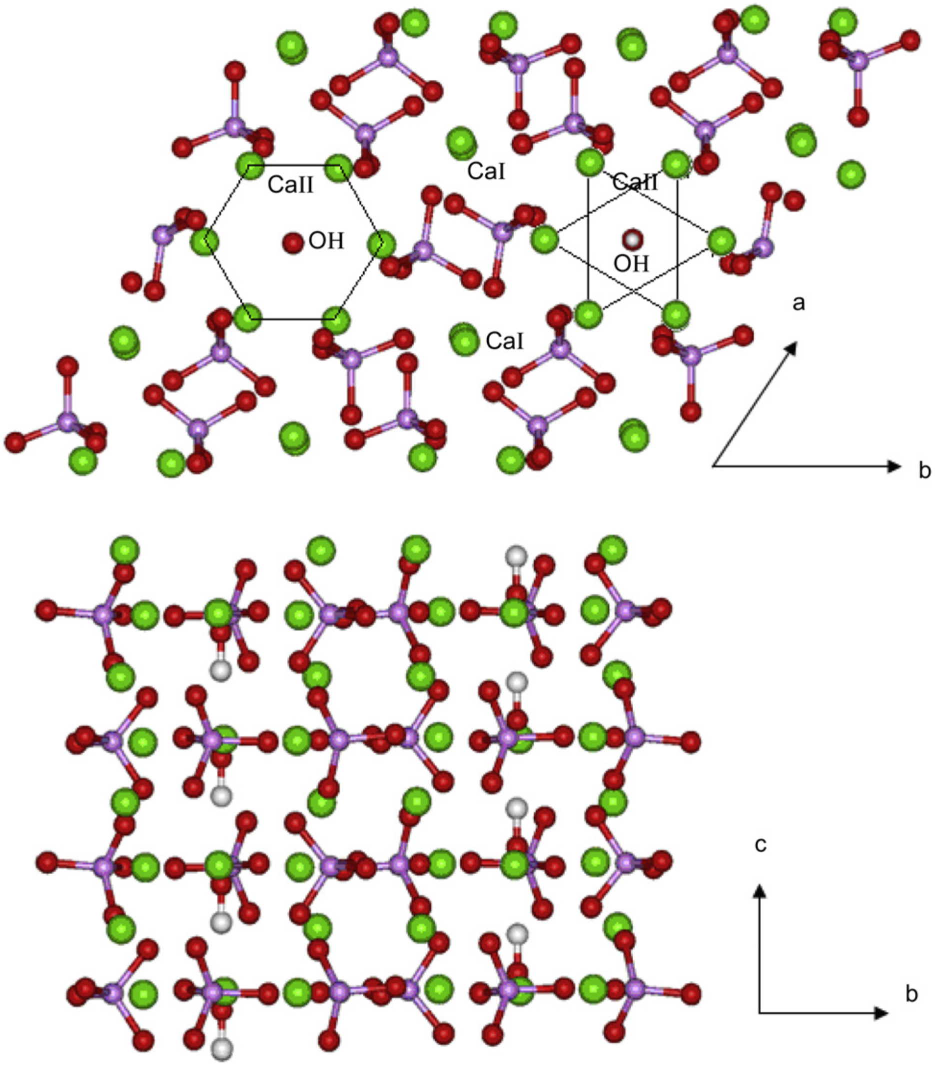

Fig. 1. Representation of the hydroxyapatite structure perpendicular to the crystallographic *c* and *a* axes, showing the OH^- channels and the different types of Ca ions (Ca = green, O = red, P = purple, H = white).

been shown to improve their bioactivity [7,8]. Moreover, much work has been done on synthetic magnesium-substituted apatites (Mg-HA), in order to try to elucidate the exact structural role of Mg in bone. According to the literature, the replacement of calcium by magnesium in HA is limited. This is related to the large size difference between Mg^{2+} and Ca^{2+} ($\sim$0.28 Å difference in radius according to the Pauling scale), which leads to strong distortions of the HA lattice and reduces its crystallinity. These changes have a direct impact on the properties of Mg-HA, compared to their non-substituted analogues [8–11]: it notably increases their solubility and biodegradability in physiological fluids and favours their thermal conversion into substituted β-tricalcium phosphate (β-$Ca_{3-x}Mg_x(PO_4)_2$). Additional studies have also shown that the co-substitution of other ions such as CO_3^{2-} in the structure may help counteract the destabilization of the apatite phase [12] and that, according to the synthetic procedure or the age of the Mg-HA material, higher Mg concentrations at the surface of the HA crystallites can be observed [13,14].

Numerous spectroscopic techniques have been used to learn more about the substitution of magnesium in HA. Nevertheless, although X-ray diffraction [15], X-Ray Photoelectron Spectroscopy [10], and cathodoluminescence spectroscopy [16] clearly indicate that Mg enters the HA lattice, several key structural characteristics remain unsolved, and little is known about how exactly Mg-incorporation affects the bulk structure of apatites. In particular, the position of Mg in the HA lattice is still an open question: does it occupy one or both of the two crystallographic calcium sites, referred to as Ca(I) and Ca(II), which present different local environments, as depicted in Fig. 1 and 2? Some authors state that Mg enters the Ca(II) site [15], whereas others the Ca(I) site [11,16,17]. The main difficulty in answering this question in the case of Mg-HA arises from the absence of high resolution spectroscopic data over an important range of composition, and the significant loss of crystallinity of Mg-HA compounds above $\sim$20% Mg. Thus, in contrast with Sr- or Ba-substituted HA [18,19], Rietveld analyses based on X-ray powder patterns are not conclusive for Mg-HA, and both Ca(I) and Ca(II) have been suggested to be the preferential site of incorporation of Mg. Such discrepancies might be due to differences in synthetic procedures (which could perhaps alter the final site for the incorporated Mg), and/or to the low quality of the XRD patterns used in the Rietveld refinements. Indeed, it is noteworthy that some of the refined distances are surprising: for a sample with $\sim$30% Mg, an average M···O bond distance was found that was almost identical to the non-substituted compound [15], which seems contradictory with the fact that average Mg···O distances are generally $\sim$0.4 Å shorter than average Ca···O distances and that there is a contraction of the HA lattice [9]. It thus appears necessary to find other analytical tools not only to help elucidate the structural and