

# A mineralogical perspective on the apatite in bone

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Available online 19 March 2005

## Abstract

A crystalline solid that is a special form of the mineral apatite dominates the composite material bone. A mineral represents the intimate linkage of a three-dimensional atomic structure with a chemical composition, each of which can vary slightly, but not independently. The specific compositional–structural linkage of a mineral influences its chemical and physical properties, such as solubility, density, hardness, and growth morphology. In this paper, we show how a mineralogic approach to bone can provide insights into the resorption–precipitation processes of bone development, the exceedingly small size of bone crystallites, and the body’s ability to (bio)chemically control the properties of bone. We also discuss why the apatite phase in bone should not be called *hydroxylapatite*, as well as the limitations to the use of the stoichiometric mineral hydroxylapatite as a mineral model for the inorganic phase in bone. This mineralogic approach can aid in the development of functionally specific biomaterials.

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*Keywords:* Calcium phosphates; Bioapatite; Biomaterials; Mineralogy; Crystalline structure; Raman spectroscopy

## 1. Introduction

The major constituent of bone is a calcium phosphate mineral that is similar in composition and structure to minerals within the *apatite group*, which form naturally in the Earth’s crust. Every mineral is characterized by a unique combination of compositional and structural parameters. The mineral-based nature of bone means that its properties, such as density and strength, are controlled by the formation process of the crystalline solid apatite and not merely by the flow and availability of individual elements such as calcium. For instance, in order for the mineral apatite to form, all necessary elements need to be available in the proper proportions, i.e., not only calcium, but also phosphorus, oxygen, and the appropriate channel-filling ion(s) ( $\text{Cl}^-$ ,  $\text{F}^-$ , or  $\text{OH}^-$ ). However, both the exact composition and the exact structure of a mineral are somewhat flexible. Apatite is more flexible than most other minerals, which means it is *very* accommodating to

chemical substitutions. Such substitutions slightly change the structure of a mineral and often have critical effects on mineral properties, such as solubility, hardness, brittleness, strain, thermal stability, and optical properties like birefringence [1,2]. Several types of ionic substitutions in the bone apatite lattice change the mineral’s characteristics and are critical to its crystallite size and dissolution rate. Indeed, the body seems to fine-tune the solubility properties of its different apatite minerals (i.e., bone apatite, enamel apatite, dentin apatite) via ionic substitutions, which might be viewed as the incorporation of appropriate “impurities”. In this way, the specific apatite in bone is amenable to dissolution, whereas the slightly different apatite in enamel resists dissolution. Historically, the inorganic components of both bone and enamel have been likened to the mineral hydroxylapatite [1,3–7], which is an  $\text{OH}^-$ -containing mineral with a very specific structure and composition.

In the present paper, we take a mineralogical approach to explore issues concerning geological, biological, and synthetic apatite that are applicable to biomaterials. For this perspective, we draw upon literature published by our group and others.

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## 2. The mineral hydroxylapatite and its crystal structure

The term “apatite” refers to a group of several minerals that are of multidisciplinary research interest and application, especially in the fields of (environmental) mineralogy, geology, biomineralization, medicine, and biomaterials. The pure end-member hydroxylapatite has a composition of  $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ , which often is written as  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$  to show that there are two formula units in the crystallographic unit cell. The so-called channel site in the hydroxylapatite structure can be occupied not only by  $\text{OH}^-$ , but also by the substituting ions  $\text{F}^-$  and/or  $\text{Cl}^-$ , as expressed by the general formula  $\text{Ca}_5(\text{PO}_4)_3(\text{F},\text{OH},\text{Cl})$ . Hydroxylapatite is the apatite mineral of the most interest and relevance in biological and materials sciences. The other two common minerals of the *apatite group* are chlorapatite and fluorapatite. Geological apatite, which is the most abundant phosphate mineral in the Earth’s crust, typically has various proportions of  $\text{OH}^-$ ,  $\text{F}^-$ , and  $\text{Cl}^-$  within the channel site [8,9]. Fluorapatite is the mineral that we artificially create on the outer surface of tooth enamel via fluoridated dental products. Typically, fluorapatite is also the preserved mineral in fossil teeth and fossil bones: During the burial of bones and teeth (in some cases for millions of years), fluoride in the water-bearing soil and sediments substitutes into the original bone and tooth apatite [10–12].

In a simplified sense, one could say that there are four different types of crystallographic positions (“sites”) in the apatitic unit cell: (1) tetrahedral sites for six  $\text{P}^{5+}$ -ions, each in 4-fold coordination with oxygen, (2) Ca [1] sites for four of the  $\text{Ca}^{2+}$  ions, (3) Ca [2] sites for the six other  $\text{Ca}^{2+}$  ions (arranged in such a way that they form a channel along the *c*-axis, the so-called anion-channel), and (4) the channel

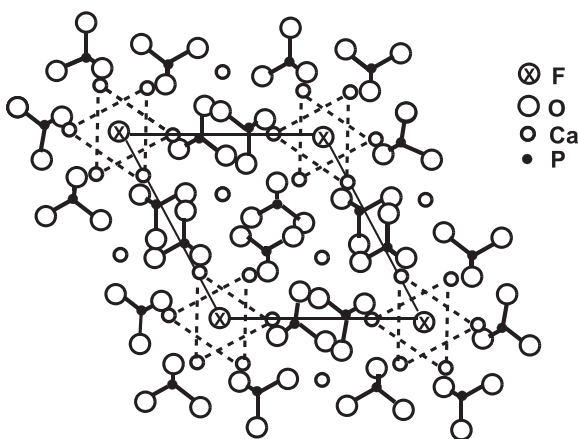


Fig. 1. Sketch of the three-dimensional structure of fluorapatite (re-drawn after [93]). View down the *c*-axis showing  $\text{PO}_4$  tetrahedral ionic groups, Ca-ions, and “channel ions.” Parallelogram indicates outline of unit cell. Six of the  $\text{Ca}^{2+}$  atoms form a six-fold site (indicated by dashed lines) in which the channel ions reside ( $\text{F}^-$  in the case of fluorapatite). These channels are oriented perpendicular to the page. Every crystallographic site (including the channel site) has a certain size, and thus not every atom or ionic group will fit into each site. (Note that the sizes of atoms in this sketch are not drawn to scale.)

site, which is typically occupied by two mono-valent anions (most commonly  $\text{OH}^-$ ,  $\text{F}^-$ , and/or  $\text{Cl}^-$ ) per unit cell (Fig. 1). Among these anions, the one that best fits into the channel site is  $\text{F}^-$ . Its ionic radius is small enough to permit  $\text{F}^-$  in the most symmetric position in the channel (i.e., on mirror planes perpendicular to the *c*-axis), and thus fluorapatite is the apatite with the highest symmetry (hexagonal space group  $\text{P6}_3/\text{m}$ ). Because the  $\text{OH}^-$  ion is not spherical, however, the two mirror planes normal to the *c*-axis channel cannot be preserved in hydroxylapatite. Thus, it has a lower symmetry than fluorapatite. Hydroxylapatite belongs to the space group  $\text{P2}_1/\text{b}$  and is therefore monoclinic rather than hexagonal [13,14]. Such differences in symmetry impact the natural growth morphology of the crystals, which is important to the bulk mechanical properties of a composite material like bone.

## 3. Ionic substitutions

The allowed composition of a mineral is not fixed, but the chemical variations that may occur must fulfill overall charge balance in the mineral and provide a geometric fit of the substituting ions within the crystal lattice. When one ion is replaced by another of the same sign but different charge (e.g.,  $\text{CO}_3^{3-}$  for  $\text{PO}_4^{3-}$ ), coupled ionic substitutions may occur. This means that charge neutrality is maintained either by a second substitution by an ion with dissimilar charge or by vacancies elsewhere in the lattice (e.g., one  $\text{Ca}^{2+}$  substituted by one  $\text{Na}^+$  plus one vacancy in place of  $\text{OH}^-$ ). Apatite has several different crystallographic sites where atomic exchanges can occur, and many different elements with different ionic charges can be accommodated in those positions [8,9]. In other words, the chemical composition of apatite in bone can be varied, but not with the same randomness and flexibility as the chemical composition of a liquid solution or a glass can be changed.

Ionic substitution in apatite is particularly well illustrated in geologic apatites. Not only does the geologic environment provide a wide range of elements (as does the human body), but temperatures also can reach hundreds of degrees Celsius, which makes the apatite structure even more accommodating to substitutions. At such high temperatures, the anions  $\text{OH}^-$ ,  $\text{Cl}^-$ , and  $\text{F}^-$  can substitute for each other in the channel sites in almost any proportion (i.e., almost complete range of substitution exists between the end-members chlorapatite (ClAp), fluorapatite (FAP), and hydroxylapatite (OHAp)). In addition, anionic complexes, such as  $\text{AsO}_4^{3-}$ ,  $\text{SO}_4^{2-}$ ,  $\text{CO}_3^{2-}$ ,  $\text{SiO}_4^{4-}$  can replace  $\text{PO}_4^{3-}$ , and a large number of metal cations, such as  $\text{K}^+$ ,  $\text{Na}^+$ ,  $\text{Mn}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Sr}^{2+}$ ,  $\text{Ba}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Y}^{3+}$ , and trivalent ions of rare-earth elements can substitute for  $\text{Ca}^{2+}$  (usually in trace concentrations). In fact, apatite is able to incorporate half of the elements in the periodic chart in its atomic structure [8,9,14]. In addition to the three phosphate apatite minerals, hydroxylapatite, fluorapatite, and chlor-

apatite (apatites *senso stricto*, i.e., the true, classical apatites), there are at least 20 other minerals that lack a phosphate component but that belong to the apatite group because they have the same structure as the phosphate apatites [8,15].

The variable chemistry of the apatite minerals can have important ramifications in the fields of medicine and environmental mineralogy. For instance, the fact that toxic metal and semi-metal ions such as  $\text{Pb}^{2+}$  and  $\text{As}^{5+}$  can be incorporated so easily into the apatite structure has clinical ramifications for bones and teeth [2,11]. Likewise, if a groundwater supply is contaminated with lead, fine-crystalline apatite may be added to the water in order to induce formation of highly insoluble lead phosphate, i.e., an inorganic salt with apatitic crystalline structure, which sequesters the toxic Pb [16,17]. The following discussions, however, are limited to the apatite minerals and other phosphate minerals of relevance to biomaterial research [1].

The effects of different ionic substitutions on the mineral OHAp are discussed in numerous articles [8,18] and in an excellent overview chapter by LeGeros [19]. The incorporation of any ion into the hydroxylapatite (OHAp) structure will result in some structural changes, which can be documented with various analytical techniques, such as X-ray diffraction (XRD) and Raman spectroscopy. For instance, the incorporation of  $\text{F}^-$  instead of  $\text{OH}^-$  will produce a better fit of the anion in the channel position, and will result in a contraction of the unit cell along the *a*-axis direction [14].

The number of ionic substitutions possible in biological apatite is smaller than in geologic apatites due to the limited number of available elements in the body. Among the substituting ions that are known and/or reported in bone and tooth mineral are  $\text{F}^-$ ,  $\text{Cl}^-$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Fe}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Sr}^{2+}$ ,  $\text{Mg}^{2+}$ , citrate, and carbonate [1–3,19,20]. Because apatite is a crystalline structure, however, there are structural limits to how much of a given ion can be incorporated. For instance, the amount of  $\text{Mg}^{2+}$  that can be incorporated into synthetic apatites has been studied in great detail [21], and some researchers have found that it is limited to a maximum of 0.4 wt.% unless  $\text{CO}_3^{2-}$  or  $\text{F}^-$  is simultaneously incorporated [22,23]. Despite the fact that there is abundant  $\text{Cl}^-$  in the human body (the  $\text{Cl}^-$  concentration in blood plasma is on the order of tenths of wt.%),  $\text{Cl}^-$  does not substitute readily for  $\text{OH}^-$  in bone and tooth apatite due to its large ionic size, which hampers its incorporation into the channel site. (As an aside, Cl-rich apatite is common in the geologic realm where temperatures for the Cl-apatite formation can be as high as 800–1000 °C [9]). In contrast, substitution of fluoride occurs so readily that it takes place rapidly even at room temperature or body temperature [24], as also demonstrated by the fluoridation imposed on tooth enamel *in vivo*. This substitution is desirable because fluorapatite is less soluble in acidic solutions (like those produced by oral bacteria or by Diet Coke®) than is the original hydroxylapatite of the tooth. The structure of fluorapatite, and

specifically how the fluoride ions substitute partially or fully for hydroxyl ions, is quite well understood [14].

Much discussion and controversy, however, still exist about how carbonate ion is incorporated into the apatite lattice. Bone apatite contains approximately 7 wt.% carbonate and tooth enamel about 3.5 wt.% carbonate [1,2,19,25]. In principle, carbonate ions can substitute in the apatite structure either in the OH-site (“A-type” substitution) or in the  $\text{PO}_4$ -site (“B-type” substitution). The nomenclature “A-type” and “B-type” was first introduced by the geologist McConnell, who studied apatites that released  $\text{CO}_2$  upon dissolution [26]. McConnell did not know at the time where and how the  $\text{CO}_2$  is incorporated into the apatite. In fact, initially it was unclear whether  $\text{CO}_3^{2-}$  was integrated into the apatite’s lattice, or whether the released  $\text{CO}_2$  came from an intermixed mineral phase [27] such as calcite ( $\text{CaCO}_3$ ). In his microscopy on geologic thin-sections under polarized light, McConnell observed distinctive optical responses among apatites that released  $\text{CO}_2$  when treated with HCl. He called the two optically different types of  $\text{CO}_2$ -containing apatites “type A” and “type B”, without proposing any specific location for the carbonate ion within the apatite crystal structure [26]. The geologic community initially used the names “francolite” and “dahllite” (or “dahllite”) to refer to carbonate-bearing fluorapatite and carbonate-bearing hydroxylapatite, respectively. The implication was that  $\text{CO}_3^{2-}$  substituted for  $\text{PO}_4^{3-}$  in both minerals. Today, however, the International Mineralogical Association does not recognize francolite and dahllite as distinct minerals that warrant their own name, because  $\text{CO}_3^{2-}$  ions are not known to be the dominant anion species substituting for the tetrahedral phosphate groups in natural apatite. Nevertheless, the names francolite and dahllite continue to be used in both the geologic and biomineralogical literature.

In the mid-1960s, based on X-ray diffraction analyses, LeGeros [28,29] recognized that biological apatite contains substantial amounts of  $\text{CO}_3^{2-}$ . For almost 40 years it has been claimed by many different researchers that  $\text{CO}_3^{2-}$  occupies two different sites within the lattice of bone apatite (e.g., [2,29–34]). Synthesis experiments, in which temperature and pressure can be elevated [32,35], have produced two different types of carbonated apatites, one in which the carbonate ion occupies the tetrahedral site in the apatite lattice, substituting for the phosphate ion (called “B-type substitution”), and another in which the carbonate ion occupies the channel, substituting for the hydroxyl ion (called “A-type substitution”).

LeGeros [29] obtained XRD and infrared absorption spectra of biological apatite and found the spectra to be different from those of OHAp. In addition to the P–O vibrational modes characteristic in infrared spectra for the phosphate tetrahedra, the biological apatite spectra also showed C–O vibrational modes characteristic for the planar carbonate ion. Presumably based on theoretical knowledge of the possibility for both A-type and B-type substitution, LeGeros [29] interpreted the observed split-

tings (i.e., multiple maxima in a complex band) of the IR peaks for the  $\text{CO}_3$  ion to represent  $\text{CO}_3$  simultaneously sited in different crystallographic environments (as in the A-type and B-type models). This interpretation of the relation between spectroscopic peaks and mineral structure, or IR “band assignment”, was inferred only from the IR spectra obtained. It apparently was never independently verified that  $\text{CO}_3^{2-}$  indeed does occur in both sites in biologic apatite. Synthetically, A-type carbonate apatite can be produced only at very high temperature (solid-state reactions at 1000 °C), whereas synthetic B-type carbonated apatite precipitates from solutions in the temperature range of 50–100 °C [19,28,32,36,37]. It is possible to produce mixed A-type/B-type carbonated apatites in the laboratory [35].

It seems now to be generally accepted that  $\text{CO}_3^{2-}$  dominantly replaces  $\text{PO}_4^{3-}$  in biological apatite [2,38]. Based on synthetic samples, it is well documented that this so-called B-type carbonate substitution causes changes in various physical properties in hydroxylapatite, such as decreases in the *a*-axial length, the overall crystallite size, and the thermal stability, and increases in the *c*-axial length, the amount of crystallographic microstrain, the solubility, and the optical birefringence. In addition to their structural disorder, nanocrystalline biologically produced apatites were observed to have atypical morphologies, i.e., their growth shapes are blocks or platelets, rather than the prisms and needles that occur most commonly in synthetically or geologically formed apatites [28,39–41]. The extent of these effects is also influenced by the simultaneous presence of other substituting ions [42]. The higher solubility of carbonate-containing apatite compared to carbonate-free apatite is in part due to the fact that the  $\text{Ca}-\text{CO}_3^{2-}$  bonds are weaker than the  $\text{Ca}-\text{PO}_4^{3-}$  bonds, thus making the carbonated apatite more susceptible to acid dissolution [2].

Various other complex ions have been inferred and/or reported to be part of the biological apatite’s crystal lattice, such as “labile  $\text{CO}_3^{2-}$ ”, “non-apatitic  $\text{CO}_3^{2-}$ ”, “labile  $\text{PO}_4^{3-}$ ”, “labile  $\text{HPO}_4^{2-}$ ”, and “non-apatitic  $\text{HPO}_4^{2-}$ ” (e.g., [30,34,43–45]). In contradiction to the claims that these ionic entities are part of the crystalline bone mineral, the descriptive terms used for these ionic associations clearly imply compositional components that are outside of the apatite structure. The terms “labile” and “non-apatitic” are difficult to interpret in a mechanistic sense. The crystallographic fact is that B-type carbonated apatite, as well as the (also plausible)  $\text{HPO}_4^{2-}$  bearing apatite, can contain variable concentrations of carbonate and thus phosphate. The deficit in negative charge caused by the replacement of  $\text{PO}_4^{3-}$  by either  $\text{CO}_3^{2-}$  or  $\text{HPO}_4^{2-}$  can be compensated by the loss of positive charge, as through removal of  $\text{Ca}^{2+}$  from the lattice. For example,  $\text{HPO}_4^{2-}$  containing apatites traditionally have been called “Ca-deficient apatites”, which are defined as those apatitic phases with a Ca/P ratio smaller than 1.67 (Table 1). Because charge balance demands in carbonated apatites

Table 1  
Possible stoichiometry for apatitic phosphates<sup>a</sup>

Chemical formula	Name	Ca/P ratio
$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$	end-member hydroxylapatite	1.67
$\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$	end-member fluorapatite	1.67
$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH},\text{F})_2$ , e.g., $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_{0.4}\text{F}_{1.6}$	mixed hydroxyl-fluorapatite	1.67
$\text{Ca}_{10}(\text{PO}_4)_6\text{Cl}_2$	end-member chlorapatite	1.67
$\text{Ca}_{10}(\text{PO}_4)_6(\text{Cl},\text{F})_2$	mixed chlor-fluorapatite	1.67
e.g., $\text{Ca}_{10}(\text{PO}_4)_6\text{Cl}_{1.2}\text{F}_{0.8}$ $\text{Ca}_{10}(\text{PO}_4)_6\text{CO}_3$	end-member A-type carbonated apatite, unhydroxylated	1.67
$\text{Ca}_{10-x}[(\text{PO}_4)_{6-2x}(\text{CO}_3)_{2x}]\text{F}_2$	end-member B-type carbonated fluorapatite old mineral name: francolite	$\geq 1.67$
$\text{Ca}_{10-x}[(\text{PO}_4)_{6-2x}(\text{CO}_3)_{2x}](\text{OH})_2$	end-member B-type carbonated hydroxylapatite old mineral name: dahllite	$\geq 1.67$
$\text{Ca}_{10-x}[(\text{PO}_4)_{6-2x}(\text{CO}_3)_{2x}]\text{CO}_3$	mixed A-type and B-type carbonated apatite	$\geq 1.67$
e.g., $\text{Ca}_{9.75}[(\text{PO}_4)_{5.5}(\text{CO}_3)_{0.5}]\text{CO}_3$ , $x=0.25$		1.77
$\text{Ca}_{10-x}[(\text{PO}_4)_{6-x}(\text{CO}_3)_x](\text{OH})_{2-x}$	Ca- and OH-deficient B-type carbonated apatite	$\geq 1.67$
e.g., $\text{Ca}_9[(\text{PO}_4)_5(\text{CO}_3)](\text{OH})$ , $x=1$		1.8
e.g., $\text{Ca}_8[(\text{PO}_4)_4(\text{CO}_3)_2](\text{empty})$ , $x=2$		2.0
$\text{Ca}_{10-x}[(\text{PO}_4)_{6-x}(\text{HPO}_4)_x](\text{OH})_{2-x}$	$\text{HPO}_4$ -containing apatite	$\leq 1.67$
e.g., $\text{Ca}_9[(\text{PO}_4)_5(\text{HPO}_4)](\text{OH})$ , $x=1$		1.5
e.g., $\text{Ca}_8[(\text{PO}_4)_4(\text{HPO}_4)_2](\text{empty})$ , $x=2$		1.33
e.g., $\text{Ca}_8[(\text{PO}_4)_4(\text{CO}_3)(\text{HPO}_4)](\text{empty})$		1.6

<sup>a</sup> Some of the listed stoichiometries have been discussed in [2,20,35,53].

actually may limit the concentration of hydroxyl ions in their lattice (Table 1), the emphasis on “hydroxyl” in the name HCA may be quite misleading.

#### 4. Calcium phosphate phases relevant to biomaterials research: distinction and nomenclature

One of the stumbling blocks to more effective interdisciplinary research in the fields of biomaterials science and biomineralization is the use of different names and nomenclature systems for the same material or process. The present mineralogical approach to bone study suggests that

some imprecise, as well as some overly restrictive, terminology be re-considered by our respective communities. One example of overly restrictive usage concerns the word “biomaterial”. Whereas many chemists and materials scientists consider a “biomaterial” to be a synthetically produced material, most biologists, geologists, and mineralogists consider materials such as bone and tooth, which are biologically produced, to be biomaterials. Of course, regardless of whether the crystalline material is synthetically or biologically produced, it will be constrained by the same needs for charge balance and structural fit.

An example of imprecise nomenclature involves the common reference to “Ca–P” in the biomaterials literature, with occasional disregard for the fact that different calcium phosphate phases have different crystalline structures. There are many phosphate minerals and phosphate salts that do not have an apatitic crystalline structure (Table 2). Different calcium phosphate phases have different structures and different compositions (including Ca/P ratios), which means they not only have different properties, but they also form under different conditions [1,3]. Such formation differences are not only of theoretical interest, but also can have some clinical ramifications. For instance, the pH-sensitivity of the individual calcium phosphate minerals destines some of them to only diseased tissue [2]. An additional nomenclature issue is that not all of the possible calcium phosphate phases relevant to biomaterials research are minerals (i.e., not all occur naturally), but rather some are synthetically produced inorganic salts. As this paper emphasizes, the word apatite refers to a very specific crystalline structure (that can have a range of different compositions). Thus, unless it is confirmed that the inorganic phosphate salt in question

indeed has the apatitic structure, it should not be called “apatite”.

Since the structure of a crystalline solid is just as important as is its chemical composition, the former should be determined whenever possible. The structures of the different Ca-phosphate phases can be characterized and distinguished from each other by means of various analytical techniques, for instance Raman spectroscopy (Fig. 2). The six different calcium phosphate phases documented in Fig. 2, all of which either have been reported in (pathological) calcifications or which are relevant to biomaterials research, easily can be distinguished from one another, because they have different bonding configurations (structures). The Raman peaks seen below  $1200 \Delta \text{ cm}^{-1}$  in Fig. 2 are due to P–O vibrations within the  $\text{PO}_4^{3-}$  tetrahedra, whereas the peaks at about  $3500 \Delta \text{ cm}^{-1}$  are due to O–H vibrations. The latter obviously are seen only in those Ca-phosphates that contain an hydroxyl ion or  $\text{H}_2\text{O}$  as part of their crystalline structure (i.e., hydroxylapatite and brushite, respectively). The exact positions and numbers of peaks in a Raman spectrum are very characteristic for a given Ca-phosphate phase, and thus can be used to unambiguously identify the phase. In addition, the spectra also show the distinction between those phases that contain  $\text{HPO}_4^{2-}$  (i.e., acidic phosphate) groups (i.e., brushite, whitlockite, and monetite) and those that contain only  $\text{PO}_4^{3-}$  groups. Whereas the strongest ( $\nu_1$  vibrational mode) peak for the tetrahedral P–O bond in monomeric calcium phosphate phases lies between  $960$  and  $990 \Delta \text{ cm}^{-1}$  (see Fig. 2b), an additional peak between  $875$  and  $925 \Delta \text{ cm}^{-1}$  occurs in those phases that also contain  $\text{HPO}_4^{2-}$  groups (i.e., brushite, whitlockite,

Table 2  
Different apatitic and non-apatitic calcium phosphates

Typical acronym	Chemical name	Chemical formula	Mineral name	Structure	Ca/P ratio
HAP, HA	tribasic calcium phosphate	$\text{Ca}_5(\text{PO}_4)_3(\text{OH})$	hydroxylapatite	apatitic	1.67
ACP	amorphous calcium phosphate	?	N.A.	N.A.	?
PCHA, PCA	poorly crystalline hydroxyapatite	$\text{Ca}_5(\text{PO}_4)_3(\text{OH})$	hydroxylapatite	apatitic	1.67
CAP	carbonated apatite, other names used: carbonate apatite, carbonated hydroxy(l)apatite	variable, see Table 1, rows 4–10	no accepted mineral name; in the past, geologic carbonated fluorapatite was called “francolite” and geologic carbonated hydroxylapatite was called “dahllite” or “dahlite”	apatitic	1.6–2.0, see Table 1
TCP	tricalcium phosphate	$\text{Ca}_3(\text{PO}_4)_2$	“whitlockite”	non-apatitic	1.50
$\beta$ -TCMP	magnesium-substituted tricalcium phosphate	$(\text{Ca},\text{Mg})_3(\text{PO}_4)_2$	“whitlockite”	non-apatitic	$\leq 1.50$
?	“tricalcium phosphate”	$\text{Ca}_9(\text{Mg},\text{Fe}^{2+})(\text{PO}_4)_6(\text{HPO}_4)$	geologically occurring whitlockite	non-apatitic	1.28
CPPD	calcium pyrophosphate dihydrate	$\text{Ca}_2\text{P}_2\text{O}_7 \cdot 2\text{H}_2\text{O}$	does not exist as geologic mineral	non-apatitic	1.0
$\gamma$ -CPP	$\gamma$ -calcium pyrophosphate	$\text{Ca}_2\text{P}_2\text{O}_7$	does not exist as geologic mineral	non-apatitic	1.0
OCP	octacalcium phosphate	$\text{Ca}_8\text{H}_2(\text{PO}_4)_6 \cdot 5\text{H}_2\text{O}$	does not exist as geologic mineral	non-apatitic	1.33
MON	dibasic calcium phosphate	$\text{Ca}(\text{HPO}_4)$	monetite	non-apatitic	1.0
DCPD	dicalcium phosphate dihydrate	$\text{Ca}(\text{HPO}_4) \cdot 2\text{H}_2\text{O}$	brushite	non-apatitic	1.0

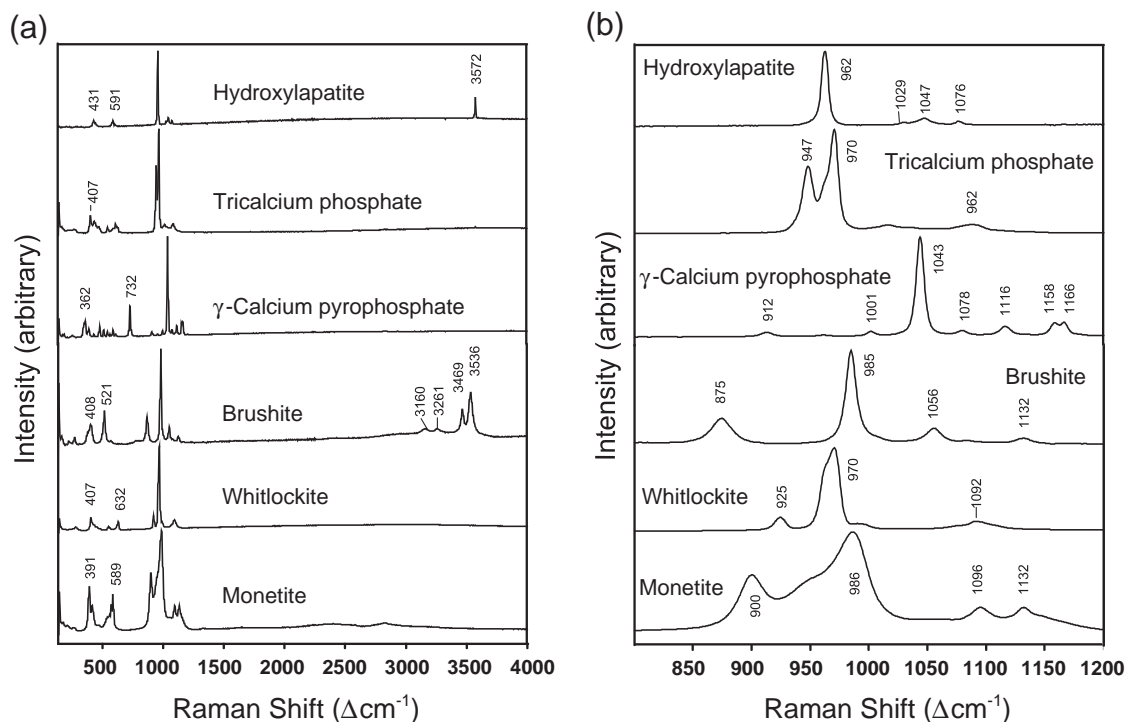


Fig. 2. (a) Raman spectra of six different calcium phosphates that have different crystalline structures (see Table 1 for chemical formulas). Spectra are  $y$ -shifted and stacked for clarity of display. Peaks above 3000  $\Delta\text{cm}^{-1}$  are caused by O–H vibrations; all other peaks are caused by P–O stretching and bending modes. See (b) for an enlargement of the P–O stretching region between 800 and 1200  $\Delta\text{cm}^{-1}$ . (b) Enlargement of the Raman spectral region from 800 to 1200  $\Delta\text{cm}^{-1}$ , which shows the peaks due to vibrations within the  $\text{PO}_4$  tetrahedra (all are P–O stretching modes) of six different calcium phosphate phases. Due to their different crystalline structures (see Table 1 for chemical formulas), the different “Ca–P materials” can be unambiguously identified and easily distinguished from one another.

and monetite) due to P–O bonds that are in the P–O–H<sup>+</sup> configuration.

Among the spectra shown in Fig. 2, it is the OHap spectrum that is most similar to spectra obtained from cortical bone (of many mammals) and tooth mineral (both enamel and dentin). It is also spectroscopically evident, however, that bone apatite is not identical to geologic or synthetic OHap (see, for example, Fig. 3). The observed finely nuanced structural and compositional differences between various natural and synthetic apatites are more than an obscure crystallographic detail, and probably are the reason for the observed differences in the osteoconductive and osteoinductive properties of various biomaterials that have been tested as bone replacements [1,46–50]. Thus, it would be desirable for the biomaterials community to understand which of the compositional–structural parameters of a calcium phosphate phase need to be tailored in order to fine-tune the desired properties of the material.

## 5. The mineral in bone and its spectroscopic puzzles

Beevers and McIntyre said in 1946 that “it is well established by X-ray crystal analysis that the mineral constituent of bone and of the enamel and dentin of teeth

is essentially hydroxy-apatite. . .” [51]. In the biomedical, orthopaedic, and biomaterials literature, the mineral component of bone is still usually referred to as “hydroxy(l)apatite” or “carbonated hydroxy(l)apatite” (note that the nomenclature with the “l” is the one accepted by the International Mineralogical Association), as if biological apatite were a well defined and well understood material. Neither, however, is true since questions still remain about both the exact chemistry and the exact crystallographic structure of bone apatite. Admittedly, the mineral in bone is structurally very similar to OHap, but there are important chemical and structural differences. In Fig. 3 the Raman spectra of synthetic OHap, geologic OHap, human enamel apatite, and cortical mouse bone apatite illustrate several differences between OHap and biological apatites.

Whereas the Raman spectra of apatite in enamel, just like those of both geologic OHap and synthetic OHap, show the O–H stretching modes for hydroxyl within the apatite structure, the spectra for apatite in bone do not. This is true of all cortical bones of different mammals that we analyzed. Thus, contrary to common statements in the literature and to general belief in the biomaterials and medical communities, bone apatite does not have a high concentration of OH<sup>−</sup> groups, which is the hallmark of the mineral hydroxylapatite. Indeed, some bone apatite may not contain any OH<sup>−</sup> groups at all. Even though the mineral in bone continues to

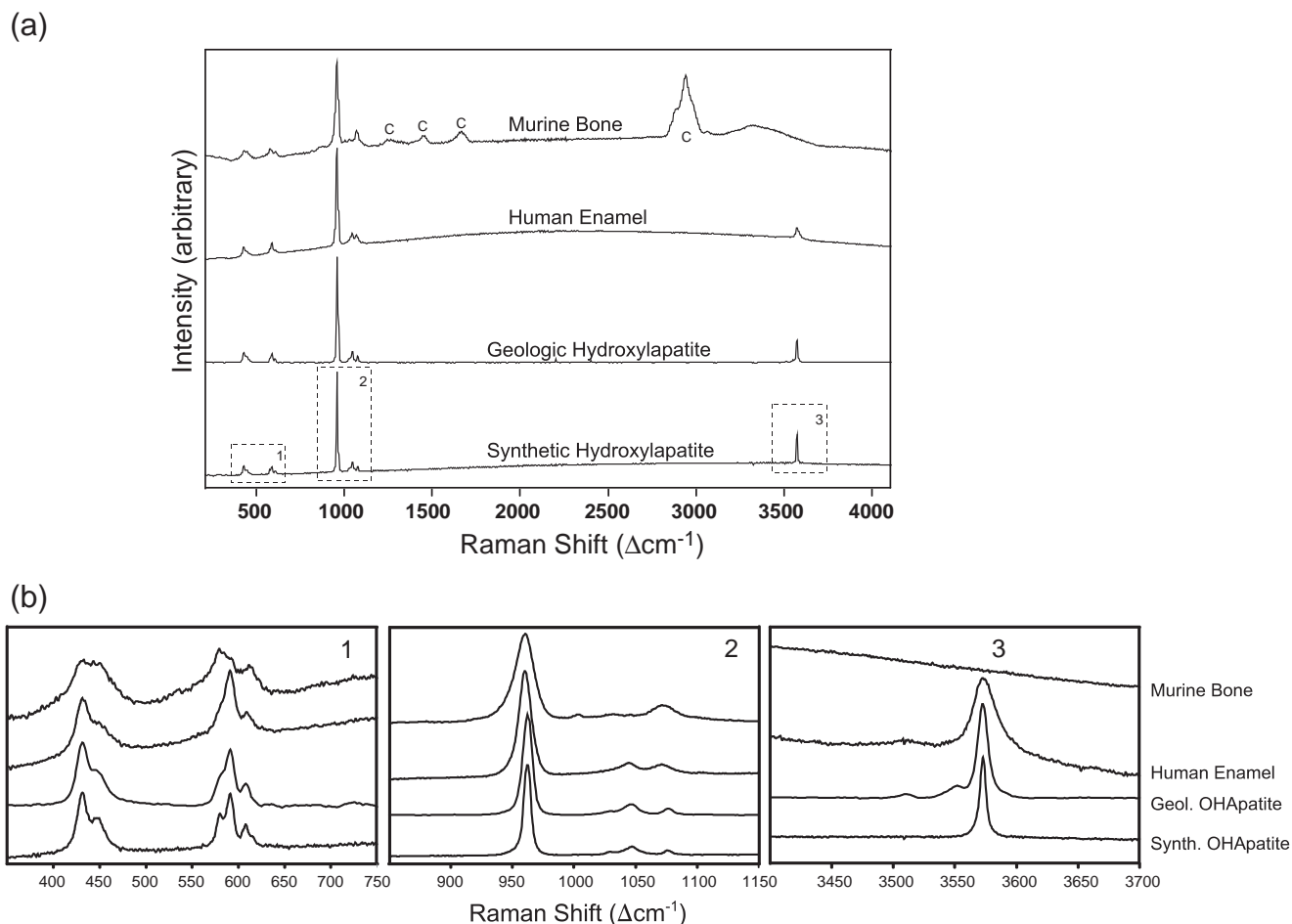


Fig. 3. (a) Representative Raman spectra ( $y$ -shifted and stacked for clarity of display) of four types of apatite, listed from top to bottom: bioapatite in a femur of a 12-month-old mouse, analyzed in cross-section; bioapatite in outside surface of deciduous molar from healthy 10-year-old girl; powdered sample of a geologic apatite (location: Holly Springs, Georgia), which is almost stoichiometric hydroxylapatite [94]; and synthetically produced hydroxylapatite from the National Institute of Standards and Technology (NIST # SRM 2910, [95]). Raman spectra were obtained on pre-selected spots while the sample was viewed in reflected light at up to  $6400\times$  magnification with a  $1\ \mu\text{m}$  spatial resolution in an optical microscope. The use of a high-magnification objective (e.g.,  $80\times$ ) with high numerical aperture (e.g., 0.75) permitted laser beam spots as small as  $1\ \mu\text{m}$  in diameter. (For more information concerning the Raman equipment and measurement conditions, see [52].) Due to the intimate spatial relationship of the nanocrystalline mineral crystals and the collagen fibers in bone, the raw Raman spectrum of bone shows both the bands for apatite and the bands for collagen (marked with the letter “C”). A background subtraction (via the use of the spectral manipulation software GRAMS) was applied to the spectrum for geologic hydroxylapatite, in order to eliminate the broad fluorescence that was caused by trace elements in this sample. See (b) for enlargements of spectral regions marked with dashed boxes. (b) Enlargements of the Raman spectral regions marked with dashed boxes in (a), which show the peaks due to vibrations of the P–O bending and stretching modes within the apatitic  $\text{PO}_4$  tetrahedra (in the spectral regions between 350 and  $750\ \Delta\ \text{cm}^{-1}$  and between 850 and  $1150\ \Delta\ \text{cm}^{-1}$ ), as well as the O–H stretching mode at  $3572\ \Delta\ \text{cm}^{-1}$  of  $\text{OH}^-$  in hydroxylapatite.

be referred to as “hydroxylapatite” in the literature, there is growing evidence for the lack of  $\text{OH}^-$  in bone apatite based not only on the results obtained via Raman spectroscopy [52], but also based on results of infrared spectroscopy, inelastic neutron scattering, and nuclear magnetic resonance spectroscopy [53–57].

The presence of trigonal planar  $\text{CO}_3^{2-}$  groups in the apatite lattice is clearly and uniquely recognizable in the distinctive peaks for C–O vibrations in the IR spectra of bone and enamel (e.g., [2]). However, neither reference to the IR spectra of biological apatites nor to spectra of analogous phases support unambiguous band assignment for the specific location of  $\text{CO}_3^{2-}$ , either in the channel location (i.e., A-type substitution) or the tetrahedral location

(i.e., B-type substitution). Vibrational spectroscopy (i.e., infrared and Raman) provides sensitive monitors of molecular structural differences among phases, but the determination of the structural mechanism behind those differences may require additional types of analyses, such as Rietveld refinement of single-crystal XRD analyses.

In summary, despite more than 40 years of spectroscopic studies of bone apatite, neither the exact nature of the carbonate substitution, nor the state of hydroxylation of the lattice is well understood. Moreover, there were some early misinterpretations of analyses of the structure and/or composition of biologic apatite, and some of these misperceptions persist. These misinterpretations are in part caused by the fact that the analysis of bone is an analytical

challenge to any instrumental technique, because of (1) the nanocrystallinity of the mineral phase and (2) the intimate association of the mineral phase with the macromolecule collagen.

## 6. Atomic disorder and nanocrystallinity

Ionic substitutions and a minute crystallite size (i.e., nanocrystallinity) are not independent of each other, and both impose some level of disorder on the mineral phase of bone. The degree of this disorder can be monitored (e.g., through increased peak widths) with various spectroscopic techniques, such as NMR or nuclear magnetic resonance [58], INS or inelastic neutron scattering [59], XRD or X-ray diffraction [35,60,61], EXAFS or X-ray absorption fine structure spectroscopy [62], ESR or electron-spin resonance [63,64], EPR or electron paramagnetic resonance [37,65], ENDOR or electron nuclear double resonance [65], FTIR or Fourier transform infrared spectroscopy [36,66], and Raman spectroscopy [2,24,67]. It is often not recognized, however, that there are various size-scales or different hierarchical levels of order/disorder within a crystalline material, and that different analytical techniques have different sensitivities to the short-range and long-range crystalline structure of a material.

In a very simplistic way, one can consider that the lowest hierarchical level of order is represented by clusters of atoms or ionic groups (i.e., the sites occupied by ionic groups such as phosphate). This short-range order within an ionic group will be affected by neighboring clusters of atoms, and thus will be influenced by, for instance, ionic substitutions. In the case of carbonated apatite, the mechanism by which the planar  $\text{CO}_3^{2-}$  ion resides within the site normally occupied by tetrahedral phosphate in the apatite structure is not yet totally clarified. Some researchers claimed that when  $\text{CO}_3^{2-}$  replaces  $\text{PO}_4^{3-}$ , the carbonate ion resides along what would have been the mirror plane of the tetrahedron, as shown in neutron diffraction experiments [68]. Other researchers have claimed that the carbonate ion can occupy either one of two different triangular sloping faces of the “tetrahedral site”, and thus that the plane of the carbonate ion will be oblique to the  $c$ -axis [61]. But no matter what the exact position of the carbonate ion in the tetrahedral lattice site is, the presence of carbonate ions in a limited number of tetrahedral sites will change the P–O bond lengths within the remaining phosphate tetrahedra, i.e., some P–O lengths will increase, and others will decrease. The variation in these lattice parameters will be a function of the amount of  $\text{CO}_3^{2-}$  incorporated, and the lattice variations will be sensed by some analytical techniques, for instance by Raman spectroscopy (Fig. 4). As documented by de Mul et al. [69], the peak width of the P–O symmetric stretching vibration in the Raman spectrum depends on the amount of the carbonate substitution in the apatitic lattice.

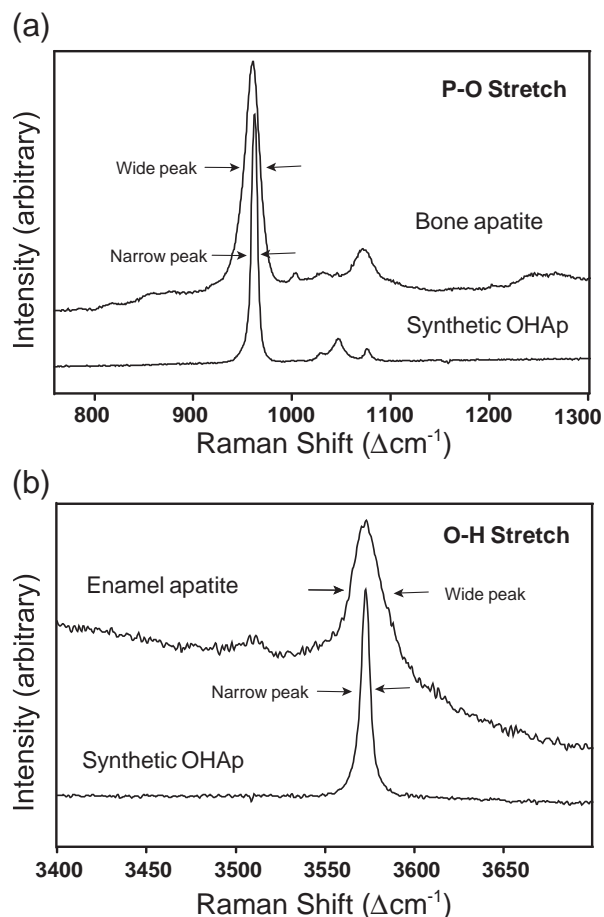


Fig. 4. Comparison of the Raman band widths in the P–O stretch region of the  $\text{PO}_4$  tetrahedra (a) and O–H stretch region (b) in synthetic hydroxylapatite (lower spectrum of each pair) and biological apatite (upper spectrum of each pair). The markedly wider bands of the biomaterials indicate more short-range disorder in these nanocrystalline, carbonated phases than in the synthetic hydroxylapatite.

Several clusters of atoms and/or ionic groups make up a unit cell (see Fig. 1 and cartoon in Fig. 5). A material is crystalline if its clusters of atoms or unit cells are repeated multiple times and are arranged in a predictable spatial pattern throughout. As mentioned above, different analytical techniques sense order/disorder on different size scales. A crystallite that produces a well-defined XRD peak appears as a coherent domain to the X-ray wavelength, because the unit-cell building blocks of the crystal are aligned very well with respect to each other in a predictable pattern. X-ray diffraction is sensitive to long-range order in a crystalline material. Essentially, the more narrow the XRD peaks, the greater is the length of continuity of atomic planes and the larger is the crystallite size [2]. As the grain or crystallite size becomes smaller, XRD analysis eventually senses the decrease in length-scale of atomic planar continuity, which would be seen in a broadening of the diffraction peaks. Over most of this range of crystallite diminution, however, the Raman peaks would retain their same width. This difference in analytical response reflects the fact that short-range order,



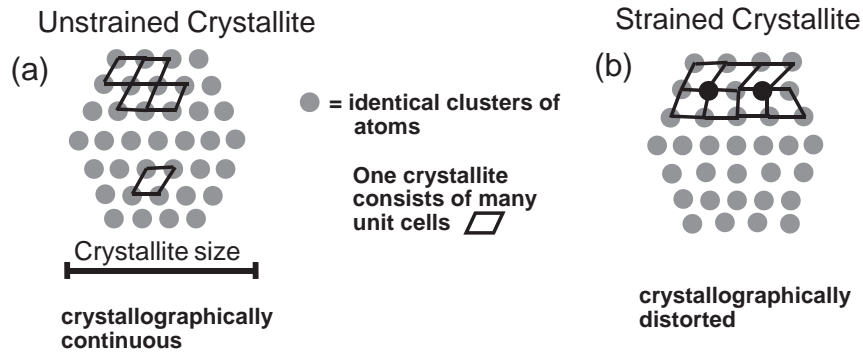


Fig. 5. Simplified representation of the repetition of the identical clusters of atoms in a coherent crystallite. (a) The length scale of continuity (“crystallite size”) extends all the way across the grain shown. (b) The length scale of continuity is shortened because a distortion in the structure disrupts its crystallographic continuity.

as detected by Raman spectroscopy, still is preserved in the smaller crystallites.

In addition to indicating the crystallite size, the widths of XRD peaks also contain some information about strain within the crystallite [70], which arises from regions of distorted unit-cell patterns that are continuous with regions of regularity/perfection (Fig. 5). If the clusters of atoms, and thus the individual unit cells, are totally identical to each other (in terms of chemistry, size, shape, charge, and location) and perfectly aligned, then the crystallite will be unstrained (Fig. 5a). The widths of its XRD bands will be the same throughout the diffractogram, and their absolute width will indicate the actual crystallite size (determined from the Scherrer formula). In contrast, a crystallite that is strained (Fig. 5b) undergoes a decrease in its long-range order; this decrease probably is different in different directions. The widths of its peaks in the XRD diffractogram therefore will not be uniform [2].

Even though a solid material is “X-ray amorphous” (i.e., does not have distinct XRD peaks), it still may have strong peaks in a Raman spectrum. This is because a Raman scattering experiment is indicative of and sensitive to the ordering within the atomic (ionic) clusters, whereas X-ray diffraction probes a higher hierarchical level (or a larger size scale) of ordering, i.e., the alignment of the unit-cells with respect to each other within a crystallite. This mechanistic difference is the reason that many amorphous materials and glasses (as well as liquids and gases) produce Raman peaks, even though they are X-ray amorphous. In other words, Raman scattering probes the lowest hierarchical level of ordering (within the unit cell), whereas X-ray diffraction probes a higher level of hierarchy, meaning a larger/coarser scale of ordering within a crystallite. Both of these scales of ordering are important to the growth and mechanical properties of the mineral.

The size of a crystallite can be in the nanometer range (as is the case for the biologic apatite crystals in bone), or it can be in the millimeter or centimeter range (typical for geologic minerals). The growth of solids with atomically disordered and strained lattices (elevated energy state, higher solubility)

is disfavored with respect to the growth of chemically identical solids from ordered and unstrained lattices (lower energy state). We believe that the high concentration of carbonate in bone apatite plays an important role in constraining bone crystallites to the nanometer scale. This proposed control on grain enlargement is also consistent with the much larger size of enamel crystallites, which have only about half the carbonate concentration that bone does. Dentin, however, which has a crystallite size very similar to that of bone, has about the same carbonate concentration as bone does. Elevated temperatures and pressures permit carbonated apatite to grow into much larger crystals

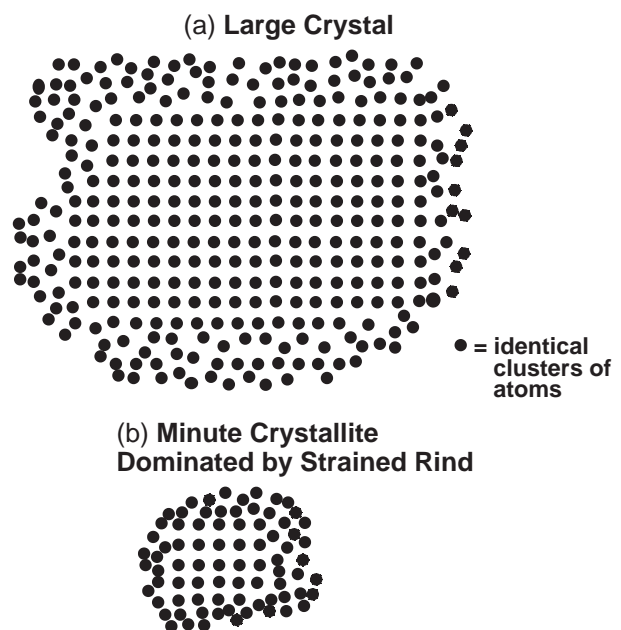


Fig. 6. Simplified representation of the repetition of identical clusters of atoms in two crystals whose central regions are identical. (a) The bonds of superficially exposed ionic units are unsatisfied, which causes the ions to modify their proportions and (remaining) bond angles. A thin distortion rind accounts for a volumetrically insignificant part of the crystal. (b) An analogous distorted, strained rind is seen. Due to the exceedingly small size of the grain, the distortion rind accounts for considerable (strained) volume of the crystal.

[1,32,71], but the low temperature of body tissue apparently does not support such growth.

On the other hand, we believe that the extremely small crystallite size of bone apatite can exert some control on the mineral's internal structure. The outer surfaces of a single-crystal grain are characterized by broken bonds, which cause distortion in the positions of nearby atoms, due to the lack of charge balance at the grain edge [72]. These edge zones are strained regions of high energy and strong distortion of the underlying atomic geometry (Fig. 6a). Continued decrease in size generates crystallites with increasing surface area/volume ratio. In a nanometer-scale grain (i.e., nanocrystal), the volume of the outer deformation rind will account for a significant proportion of the grain (Fig. 6b). Sufficient atomic distortion would be recorded by peak broadening in both the Raman spectra (short-range order disturbed) and the XRD patterns (atomic planes disrupted, truncated in the deformation rinds).

### 7. Why is the apatite in bone not hydroxylated?

X-ray diffractograms of bone apatite confirm that the lattice structure is consistent with those of standard samples of synthetic and geologic hydroxylapatite, but the diffraction peaks are much broader and less well resolved for bone than for synthetic or geologic materials [2,40,70,73–75]. XRD patterns, however, cannot give direct information about the presence or absence of hydroxyl groups. Raman and FTIR spectra also confirm that the bone mineral's structural units in principle match those of synthetic and geologic hydroxylapatite—with the important exception that neither group of spectra shows any bands for OH [52]. The IR and Raman spectra, like the XRD patterns, also show the bone mineral to have a less ordered structure than our geologic or synthetic hydroxylapatite.

From the crystallographic perspective, it is unclear in bone apatite's crystal lattice what happens to the site where the hydroxyl ion typically would reside. It is further unclear why the hydroxyl ion is missing in the structure and specifically how charge balance is maintained within the bone crystal. In principle, the lack of OH<sup>-</sup> in bone apatite could be attributed to the presence of CO<sub>3</sub><sup>2-</sup>, through direct displacement of two OH<sup>-</sup> ions by one CO<sub>3</sub><sup>2-</sup> ion in the channel site. As mentioned above, however, the plausibility of this so-called A-type substitution has become decreasingly accepted [2].

The lack of OH<sup>-</sup> in bone apatite also could be attributed to the demands of charge balance in the so-called B-type substitution. The charge imbalance created by the replacement of one PO<sub>4</sub><sup>3-</sup> tetrahedral group by one CO<sub>3</sub><sup>2-</sup> group could be counter-balanced by creating a vacancy in the channel site (see Table 1). The latter mechanism is plausible to account for the lack of OH<sup>-</sup> in bone apatite.

However, there could be yet another reason for the absence of the hydroxyl ion in bone apatite. We have

documented that synthetic nanocrystalline apatites can be deficient in OH<sup>-</sup>, even in the almost complete absence of CO<sub>3</sub><sup>2-</sup> [52]. We have observed that the degree of hydroxylation (i.e., OH-concentration) of apatite co-varies with its degree of atomic ordering (as can be documented with Raman spectroscopy) and its crystallite size (as can be documented with XRD). Based on our observations (Fig. 7), we have developed the following mechanistic model: the smaller the crystallite size and the greater the atomic disorder within the unit cells of the crystal, the less energetically favorable it is for apatite to incorporate OH<sup>-</sup> into its channel sites [52]. Even though the crystallite sizes of enamel apatite and bone apatite are both in the nanometer-range (i.e., nanocrystalline), the crystals in enamel are about 10 to 100 times larger than those in bone and dentin [1,2,25,40,76,77]. In accord with our model, the greater crystallite size of enamel apatite correlates with a significant concentration of hydroxyl (see Fig. 3). Enamel's greater crystallite size and its lower proportion of organic (protein) component compared to bone have enabled researchers to characterize and understand the structure and composition of the mineral in enamel quite well compared to the mineral in bone.

In nanocrystals, unlike in larger crystals, the absolute size of the crystal affects the material's bulk properties. As explained above, a nanocrystal's high surface area results in a large volume of distorted bonds, which becomes a significant proportion of the total crystallite (Fig. 6b). Such a distortion of the apatite crystal lattice could disfavor the incorporation of (non-spherical) hydroxyl ions into the (distorted) channel sites of the bone apatite. In other words, the extremely small size of the bone apatite crystals may structurally affect their composition above and beyond the

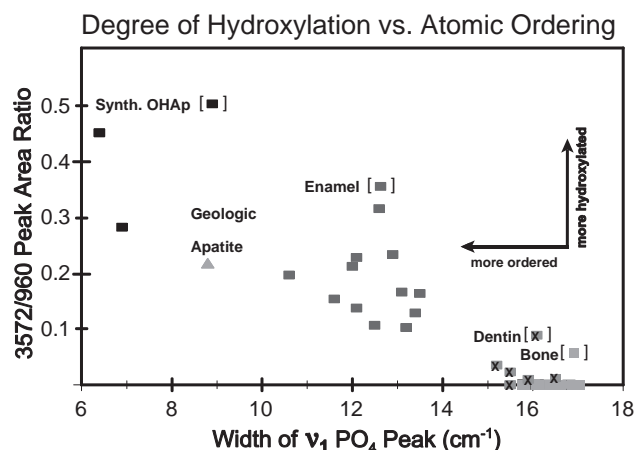


Fig. 7. Semi-quantitative assessment of the correlation between the degree of hydroxylation and the degree of atomic ordering in natural and synthetic apatite phases. Relative degree of hydroxylation represented by the ratio of the areas of the Raman peaks for the O–H stretch (at about 3572  $\Delta$  cm<sup>-1</sup>) and the P–O stretch ( $\nu_1$  at about 960  $\Delta$  cm<sup>-1</sup>) in the phosphate tetrahedra. Note that bone samples consistently show no OH-content and the highest degrees of disorder, whereas dentin can demonstrate very small concentrations of OH.

chemically induced ionic substitutions. We believe that this mechanism causes a functional relation between the composition (not only OH-concentration, but also carbonate-concentration) and grain size in apatite crystallites of nanometer scale [52].

The fact that biologically produced minerals have crystallites with sizes on the order of nanometers [7,78] suggests that either there is a biological advantage to nanocrystallinity and/or that nanocrystalline forms of a material are the easiest to precipitate at temperatures where life can exist (e.g., body temperature in mammals). Even if the latter hypothesis is true, however, it may represent only a partial explanation for these observations: The same organism may produce different crystallite sizes (still in the “nanocrystalline” size range) of the same material, for instance, bone and enamel apatite in vertebrates. There is good evidence that organisms use selected organic molecules to nucleate minerals as well as to control the specific polymorph (i.e., structural type) and growth morphology of mineral precipitates [7,79–87]. We and other mineralogists have speculated that the nanocrystalline size range also is imposed. Whereas the imposition of polymorph structural type and crystallite morphology can be attributed to (external) templating mechanisms in the organic molecules, the control on the maximum size of the crystallite may be internally controlled by mineral chemistry. It seems reasonable that, in vertebrates, (1) the body biochemically produces an environment in which the bioapatite incorporates large concentrations of carbonate, because (2) the large degree of carbonate substitution for phosphate strains the crystal lattice and thereby limits the size to which the crystallite can grow. The control on size as well as carbonate concentration in turn control the crystallites’ solubility and biological functionality.

## 8. Concluding remarks on the mineral in bone

The synthesis of more bioactive, biocompatible materials may be aided by a better understanding of the characteristics of natural biominerals and how those characteristics impart specific bulk properties to solids and to the composite materials that contain them. One of the defining characteristics of a mineral is that it is crystalline or, at least, has a well-ordered internal structure [88]. As illustrated above, among the implications of crystallinity is that the solid has limited chemical variability, the extent of which is governed by the constraints of charge balance and physical fit. Unlike in a glass, there is directionality to the properties of a crystalline solid because its atoms and bonds are distributed according to certain rules of symmetry. These attributes of crystallinity are important to the mechanical properties of composite biomaterials, both synthetic and natural [7,41,89–92]. The ramification for bone is that, although the chemical composition of bone apatite can be varied, its composition cannot be changed with the same randomness and independence as that of a liquid solution.

The nanometer size-scale of biomineralized materials permits them to exploit additional interdependences of crystalline structure. Bonds are unsatisfied at the surfaces of such particles, enhancing their chemical reactivity. These nano-scale examples of materials typically are more readily dissolved in fluids and more chemically interactive with organic molecules than are their larger, bulk counterparts. Nanocrystalline solids therefore are ideal components in biological composites that require strong interfaces between the organic and inorganic constituents (e.g., bones, teeth, mollusk shells) and where there is need for rapid, localized mineral dissolution.

The physical structure of a mineral, i.e., its underlying atomic order as well as its growth morphology, is to some degree controlled by its composition. Thus, substituting carbonate ions into hydroxylapatite changes not only its crystal lattice, but also its growth morphology—from needles to platelets. In turn, the structural distortion at the surfaces of minute particles may constrain the compositional range of the bulk solid, such as inhibiting the incorporation of OH<sup>-</sup> in nanocrystalline apatite.

Such interdependence of a mineral’s composition, structure, and properties is particularly well illustrated by the contrasts between the apatite phases in bone and tooth enamel. Bone apatite has about twice the concentration of carbonate that enamel apatite has, and bone crystallites are only about one-tenth to one-hundredth as long as enamel crystallites. Thus, bone and enamel exhibit different length scales of ordering. Both the smaller crystallite size and higher carbonate concentration account for the much greater solubility of bone apatite than of tooth enamel. The highly carbonated bone crystallites also express a platelet morphology that interfaces very effectively with collagen fibrils. The enamel crystallites are more elongated in shape than those of bone, but there is only a minor organic component with which enamel crystallites are associated. It surely is not a coincidence that the distinctive properties of these two types of apatite are so well matched with the bone’s need to be constantly resorbed and reprecipitated and with tooth enamel’s need to resist dissolution.

The systematic and detailed study of the chemistry and structure of biologic apatites will eventually lead to a better understanding of how those parameters control the apatite’s physical properties, and consequently to controlled processing parameters for producing biomaterials with desirable bioactivity and biocompatibility. A major objective in the field of biomaterials research is to derive synthetic carbonate-substituted apatite that is identical in composition, structure, and biological response to natural hard tissue.

## Acknowledgments

We thank Rui L. Reis for organizing the NATO Advanced Study Institute “Learning from Nature How to Design New Implantable Biomaterials: From Biominerali-

zation Fundamentals to Biomimetic Materials and Processing Routes” in October 2003 in Alvor, Portugal, and for making the publication of this special issue of Materials Science and Engineering possible. We also thank John J. Freeman and David Ding for the acquisition of Raman spectra. This work was supported by the US National Science Foundation under Grant No. 0210247.

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