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Calcium orthophosphates

Occurrence, properties, biomineralization, pathological calcification and biomimetic applications

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The present overview is intended to point the readers' attention to the important subject of calcium orthophosphates. This type of materials is of special significance for human beings, because they represent the inorganic part of major normal (bones, teeth and antlers) and pathological (i.e., those appearing due to various diseases) calcified tissues of mammals. For example, atherosclerosis results in blood vessel blockage caused by a solid composite of cholesterol with calcium orthophosphates, while dental caries and osteoporosis mean a partial decalcification of teeth and bones, respectively, that results in replacement of a less soluble and harder biological apatite by more soluble and softer calcium hydrogenphosphates. Therefore, the processes of both normal and pathological calcifications are just an in vivo crystallization of calcium orthophosphates. Similarly, dental caries and osteoporosis might be considered an in vivo dissolution of calcium orthophosphates. Thus, calcium orthophosphates hold a great significance for humankind, and in this paper an overview on the current knowledge on this subject is provided.

Introduction

Due to their abundance in nature and presence in living organisms, calcium apatites[a] and other calcium orthophosphates remain the chemical compounds of a special interest in many fields of science, including geology, chemistry, biology and medicine. Due to big problems with access to the scientific literature published in the 19th century and before, a historical description of the subject appears to be very brief. Namely, according to the accessible literature,[1] as early as the end of the 18th century, French chemist Joseph-Louis Proust (1754–1826) and German chemist Martin Klaproth (1743–1817) proposed that calcium apatite was the major inorganic component of bones. In the middle of the 19th century, attempts to establish the chemical composition of calcium apatites and other calcium orthophosphates were performed by J. Berzelius,[2] R. Warington Jr.[3] and R. Fresenius.[4] The chemical formula of perfectly transparent crystals of natural fluorapatite (FA) as $Ca_5(PO_4)_3F$ was established in 1873,[5] while the crystallographic faces of a natural calcium apatite were described in 1883.[6] Furthermore, a paper on a behavior of an undisclosed calcium orthophosphate in organisms of carnivores was published in 1883.[7] Further, the quantitative analysis of a calcium orthophosphate was performed in 1884,[8] followed by remarks by C. Glaser in 1885.[9] In the 1880s, occurrence of a calcium apatite[10] and another calcium orthophosphate[11-13] in a metallurgical slag was discovered. Chemical reactions between calcium orthophosphates and other chemicals were investigated in 1891.[14] Research papers on bone repairing are known since at least 1892,[15] while the earliest well-documented systematic studies of calcium orthophosphates were performed at the beginning of the 20th century by F.K. Cameron with coworkers[16-20] and H. Bassett.[21-24] The majority of the aforementioned researchers already operated with individual chemical compounds.

By definition, all calcium orthophosphates consist of three major chemical elements, calcium (oxidation state +2), phosphorus (oxidation state +5) and oxygen (reduction state -2), as a part of orthophosphate anions. These three chemical elements are present in abundance on the surface of our planet: oxygen is the most widespread chemical element of the Earth's surface (~47 mass%), calcium occupies the fifth place (~3.3–3.4 mass%) and phosphorus (~0.08–0.12 mass%) is among the first 20 of the chemical elements most widespread on our planet.[25] In addition, the chemical composition of many calcium orthophosphates includes hydrogen, as an acidic orthophosphate anion (for example, HPO_4^{2-} or $H_2PO_4^-$); hydroxide [for example, $Ca_{10}(PO_4)_6(OH)_2$] and/or incorporated water (for example, $CaHPO_4{\cdot}2H_2O$). Diverse combinations of CaO and P_2O_5 (both in the presence of water and without it) provide a large variety of calcium phosphates, which are distinguished by the type of the phosphate anion: ortho-(PO_4^{3-}), meta-(PO_3^-), pyro-($P_2O_7^{4-}$) and poly-[$(PO_3)_n^{n-}$]. In the case of multi-charged anions (orthophosphates and pyrophosphates), calcium phosphates are also differentiated by the number of hydrogen ions attached to the anion. Examples include mono-[$Ca(H_2PO_4)_2$], di-($CaHPO_4$), tri-[$Ca_3(PO_4)_2$] and tetra-($Ca_2P_2O_7$) calcium phosphates (here, prefixes "mono," "di," "tri" and "tetra" are related to the amount of hydrogen ions replaced by calcium).[26-28] However, only calcium orthophosphates will be considered and discussed in this review. The names, standard abbreviations, chemical formulae and solubility values are listed in **Table 1**.[29,30] Since all of them

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Table 1. Existing calcium orthophosphates and their major properties[30,31]

Ca/P molar ratio	Compound	Formula	Solubility at 25°C, -log(K_s)	Solubility at 25°C, g/L	pH stability range in aqueous solutions at 25°C
0.5	Monocalcium phosphate monohydrate (MCPM)	$Ca(H_2PO_4)_2·H_2O$	1.14	~18	0.0–2.0
0.5	Monocalcium phosphate anhydrous (MCPA or MCP)	$Ca(H_2PO_4)_2$	1.14	~17	[c]
1.0	Dicalcium phosphate dihydrate (DCPD), mineral brushite	$CaHPO_4·2H_2O$	6.59	~0.088	2.0–6.0
1.0	Dicalcium phosphate anhydrous (DCPA or DCP), mineral monetite	$CaHPO_4$	6.90	~0.048	[c]
1.33	Octacalcium phosphate (OCP)	$Ca_8(HPO_4)_2(PO_4)_4·5H_2O$	96.6	~0.0081	5.5–7.0
1.5	α-Tricalcium phosphate (α-TCP)	$α\text{-}Ca_3(PO_4)_2$	25.5	~0.0025	[a]
1.5	β-Tricalcium phosphate (β-TCP)	$β\text{-}Ca_3(PO_4)_2$	28.9	~0.0005	[a]
1.2–2.2	Amorphous calcium phosphates (ACP)	$Ca_xH_y(PO_4)_z·nH_2O$, n = 3 - 4.5; 15 - 20% H_2O	[b]	[b]	~5–12[d]
1.5–1.67	Calcium-deficient hydroxyapatite (CDHA or Ca-def HA)[e]	$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$ ($0 < x < 1$)	~85	~0.0094	6.5–9.5
1.67	Hydroxyapatite (HA, HAp or OHAp)	$Ca_{10}(PO_4)_6(OH)_2$	116.8	~0.0003	9.5–12
1.67	Fluorapatite (FA or FAp)	$Ca_{10}(PO_4)_6F_2$	120.0	~0.0002	7–12
1.67	Oxyapatite (OA, OAp or OXA)[f]	$Ca_{10}(PO_4)_6O$	~69	~0.087	[a]
2.0	Tetracalcium phosphate (TTCP or TetCP), mineral hilgenstockite	$Ca_4(PO_4)_2O$	38–44	~0.0007	[a]

[a]These compounds cannot be precipitated from aqueous solutions. [b]Cannot be measured precisely. However, the following values were found: 25.7 ± 0.1 (pH = 7.40), 29.9 ± 0.1 (pH = 6.00), 32.7 ± 0.1 (pH = 5.28).[236] The comparative extent of dissolution in acidic buffer is: ACP >> α-TCP >> β-TCP > CDHA >> HA > FA.[107] [c]Stable at temperatures above 100°C. [d]Always metastable. [e]Occasionally, it is called "precipitated HA (PHA)." [f]Existence of OA remains questionable.

belong to calcium orthophosphates, strictly speaking, all abbreviations in **Table 1** are incorrect; however, they are extensively used in the literature, and there is no need to modify them.

The atomic arrangement of calcium orthophosphates is built up around a network of orthophosphate (PO_4) groups, which gives stability to the entire structure. The majority of calcium orthophosphates are sparingly soluble in water; however, all of them are easily soluble in acids but insoluble in alkaline solutions. All chemically pure calcium orthophosphates are crystals of white color and moderate hardness. However, natural minerals of calcium orthophosphates are always colored due to impurities, the most widespread of which are ions of Fe, Mn and rare earth elements.[33,34] Biologically formed calcium orthophosphates are the major component of all mammalian calcified tissues,[35] while the natural ones are the major raw material to produce phosphorus-containing fertilizers.[36-39]

Geological and Biological Occurrences

Geologically, natural calcium orthophosphates are found in different regions mostly as deposits of apatites (belong to igneous rocks), mainly as natural FA or phosphorites (a sedimentary rock).[37-40] Some types of sedimentary rocks can be formed by weathering of igneous rocks into smaller particles.[41] Other types of sedimentary rocks can be composed of minerals precipitated from the dissolution products of igneous rocks or minerals produced by biomineralization (**Fig. 1**).[42] Thus, due to a sedimentary origin, both the general appearance and the chemical composition of natural phosphorites vary a great deal.[43,44] It is common practice to consider francolite (or carbonate-hydroxyfluorapatite regarded as its synonym) as the basic phosphorite mineral.[40,45-49] A cryptocrystalline (almost amorphous) variety of francolite (partly of a biological origin) is called collophane (synonyms: collophanit, collophanita, collophanite, grodnolite, kollophan).[50-52] It occurs in natural phosphorites predominantly as fossil bones and phosphatized microbial pseudomorphs: phosphatic crusts of chasmolithic biofilms (or microstromatolites) and globular clusters with intra-particular porosities.[53-56] Natural phosphorites (therefore, francolite and collophane as well) occur in various forms, such as nodules, crystals or masses. Occasionally, other types of natural calcium orthophosphates are found as minerals, for example, clinohydroxylapatite,[57] staffelite (synonyms: staffelit, staffelita) belonging to carbonate-rich fluorapatites (chemical formula: $Ca_5[(F,O)(PO_4,CO_3)_3]$) [4,58] and DCPD.[59] Furthermore, calcium orthophosphates were found in meteoric stones.[60] The world deposits of natural calcium orthophosphates are estimated to exceed 150 billion tons, out of which approximately 85% belong to phosphorites and the remaining ~15% belong to apatites.[40]

Natural calcium orthophosphates occur in most geological environments, usually as accessory minerals (<5%). Concentrations sufficient for economic use (>15%) are also

available. The largest world deposits of natural apatites are located in Russia (the Khibiny and Kovdor massifs, Kola peninsula[61,62]), Brazil and Zambia, while the largest world deposits of natural phosphorites are located in Morocco, Russia, Kazakhstan, USA (Florida, Tennessee), China and Australia, as well as in the oceans.[36-40] Most of natural calcium orthophosphates occur as small polycrystalline structures (spherulitic clusters). Larger crystals are rare.[63] They usually have the crystal structure of apatites (hexagonal system, space group $P6_3/m$). Giant crystals, including "a solid but irregular mass of green crystalline apatite, 15 feet long and 9 feet wide"[64] and a single euhedral crystal from the Aetna mine measuring 2.1 x 1.2 min with an estimated weight of 6 tons,[65] were found. None of them are pure compounds; they always contain admixtures of other elements. For example, ions of calcium might be partially replaced by Sr, Ba, Mg, Mn, K, Na, Fe; ions of orthophosphate may be partly replaced by AsO_4^{3-}, CO_3^{2-} and VO_4;[2-30,33-66] ions of hydroxide, chloride, bromide, carbonate and oxide may, to a certain extent, substitute for fluoride in the crystal lattice of natural apatites.[48] Furthermore, various organic radicals have been found in natural apatites.[67,68] In principle, the crystal structure of apatites can incorporate half of the periodic table in its atomic arrangement. In medicine, this property might be used as an antidote for heavy metal intoxication.[69] Ease of atomic substitution for apatite leaves this mineral open to a wide array of compositions. This might be related to the fact that the apatite structure type displays porous properties.[70] The substitutions in apatites are usually in trace concentrations, but large concentrations and even complete solid solutions exist for certain substituents (e.g., F^- and OH^-). To make things even more complicated, some ions in the crystal structure may be missing, leaving crystallographic defects, which leads to formation of non-stoichiometric compounds. **Figure 2** shows examples of polycrystalline and single-crystalline samples of natural FA.

Manufacturing of elementary phosphorus (white and red),[71,72] phosphoric acids,[37,73-76] various phosphorus-containing chemicals and, especially, agricultural fertilizers (namely, superphosphate,[77-79] ammonium orthophosphates[80]) are the major industrial applications of natural calcium orthophosphates. The annual consumption of a phosphate rock has approached ~150 million tons, and about 95 percent of this production is utilized in the fertilizer industry.[81,82]

In biological systems, many organisms, ranging from bacteria and isolated cells to invertebrates and vertebrates, synthesize calcium orthophosphates.[42] Formation of calcium orthophosphates in primitive organisms is believed to enable the storage and regulation of essential elements, such as calcium, phosphorus and, possibly, magnesium. The morphology of precipitates in these organisms (small intracellular nodules of ACP often located in mitochondria) complies with the necessity for rapid mobilization and intracellular control of the concentration of these elements.[83] In vertebrates, calcium orthophosphates occur as the principal inorganic constituent of normal (bones, teeth, fish enameloid, deer antlers and some species of shells) and pathological (dental and urinary calculus and stones, atherosclerotic lesions, etc.) calcifications.[26,84-89] Except for small portions of the inner ear, all hard tissue of the human body is formed of calcium

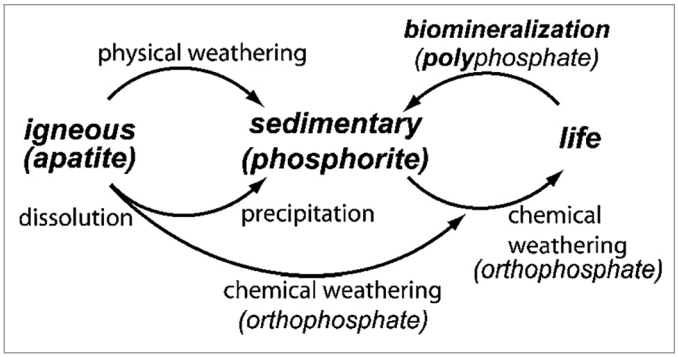

Figure 1. Simplified schematic of the phosphorus cycle from apatitic igneous rock to phosphorite sedimentary rock through chemical or physical weathering. Life forms accumulate soluble phosphorus species and can produce apatite through biomineralization. Reprinted from reference 42 with permission.

orthophosphates. Structurally, they occur mainly in the form of poorly crystalline, non-stoichiometric, calcium-deficient, Na-, Mg- and carbonate-containing HA [often called "biological apatite"[90-94] (which might be abbreviated as BAp[95,96]), bioapatite[97-100] or dahllite.[b],[101] The main constituents of human bones are calcium orthophosphates (~60–70 wt%), collagen[c] (~20–30 wt%) and water (up to 10 wt%).[32,88,97-99,101,102] Detailed information on the chemical composition of the most important human normal calcified tissues can be found in **Table 2**. One should note that the values mentioned in **Table 2** are approximate; the main constituents can vary by one percent or more.[106]

The Members of the Calcium Orthophosphate Family

In the ternary aqueous system $Ca(OH)_2$-H_3PO_4-H_2O (or CaO-P_2O_5-H_2O),[107-109] there are 12 known non-ion-substituted calcium orthophosphates with the Ca/P molar ratio ranging between 0.5 and 2.0 (**Table 1**). An anhydrous phase diagram CaO-P_2O_5 at temperatures within 200–2,200°C is shown in **Figure 3**.[110,111] **Table 3** comprises crystallographic data of the existing calcium orthophosphates.[27,112-114] The most important parameters of calcium orthophosphates are the ionic Ca/P ratio, basicity/acidity and solubility. All these parameters strongly correlate with the solution pH. The lower the Ca/P molar ratio is, the more acidic and water-soluble the calcium orthophosphate is.[26-28] One can see that the solubility ranges from high values for acidic compounds, such as MCPM, to very low values for basic compounds, such as apatites, which allows calcium orthophosphates to be dissolved, transported from one place to another and precipitated when necessary. Crystallization, dissolution and phase transformation processes of different calcium orthophosphates under various experimental conditions have been reviewed recently in reference 115.

Due to the triprotic equilibrium that exists within orthophosphate-containing solutions, variations in pH alter the relative concentrations of the four polymorphs of orthophosphoric acid (**Fig. 4**)[116] and, thus, both the chemical composition (**Fig. 5**)[117] and the amount of the calcium orthophosphates that are formed

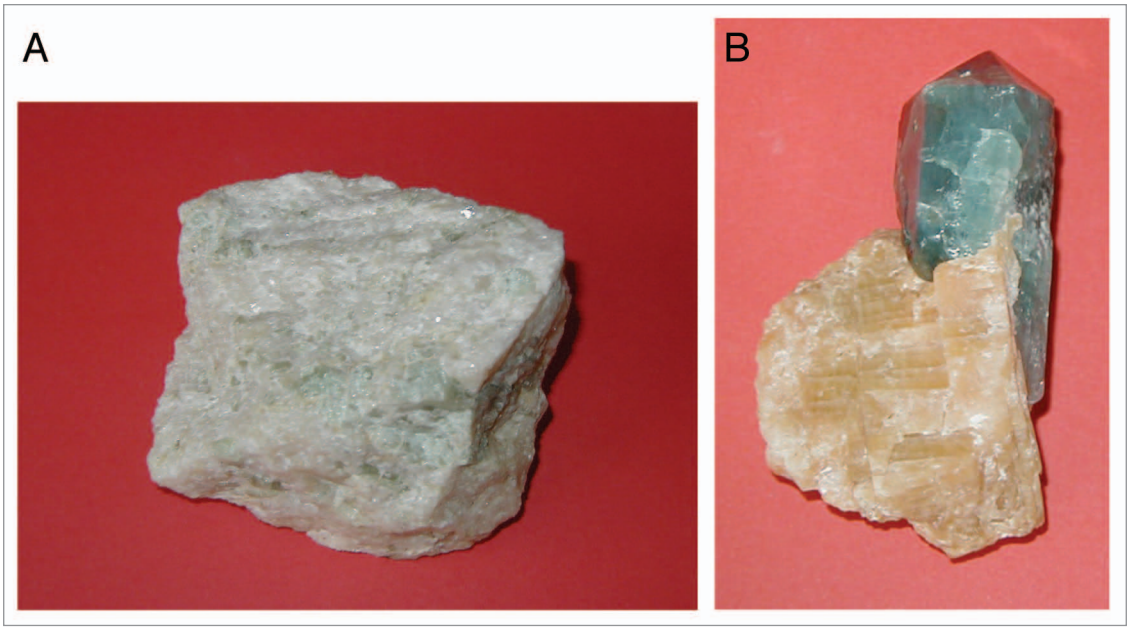

Figure 2. Polycrystalline (A) and single-crystalline (B) FA of a geological origin. The single crystal has a gray-green color due to incorporated ions of transition metals.

Table 2. Comparative composition and structural parameters of inorganic phases of adult human calcified tissues

Composition, wt%	Enamel	Dentine	Cementum	Bone	HA
Calcium[a]	36.5	35.1	~35	34.8	39.6
Phosphorus (as P)[a]	17.7	16.9	~16	15.2	18.5
Ca/P (molar ratio)[a]	1.63	1.61	~1.65	1.71	1.67
Sodium[a]	0.5	0.6	[c]	0.9	-
Magnesium[a]	0.44	1.23	0.5–0.9	0.72	-
Potassium[a]	0.08	0.05	[c]	0.03	-
Carbonate (as CO_3^{2-})[b]	3.5	5.6	[c]	7.4	-
Fluoride[a]	0.01	0.06	up to 0.9	0.03	-
Chloride[a]	0.30	0.01	[c]	0.13	-
Pyrophosphate (as $P_2O_7^{4-}$)[b]	0.022	0.10	[c]	0.07	-
Total inorganic[b]	97	70	60	65	100
Total organic[b]	1.5	20	25	25	-
Water[b]	1.5	10	15	10	-
Crystallographic properties: Lattice parameters (±0.003 Å)					
a-axis, Å	9.441	9.421	[c]	9.41	9.430
c-axis, Å	6.880	6.887	[c]	6.89	6.891
Crystallinity index (HA = 100)	70–75	33–37	~30	33–37	100
Typical crystal sizes (nm) [454, 544, 546]	100 μm x 50 x 50	35 x 25 x 4	[c]	50 x 25 x 4	200–600
Ignition products (800°C)	β-TCP + HA	β-TCP + HA	β-TCP + HA	HA + CaO	HA
Elastic modulus (GPa)	80	23.8 ± 3.7	15.0 ± 3.6	0.34–13.8	10
Tensile strength (MPa)	10	100	[c]	150	100

Due to the considerable variation found in biological samples, typical values are given in these cases.[27,107] [a]Ashed samples. [b]Unashed samples.
[c]Numerical values were not found in the literature but they should be similar to those for dentine.

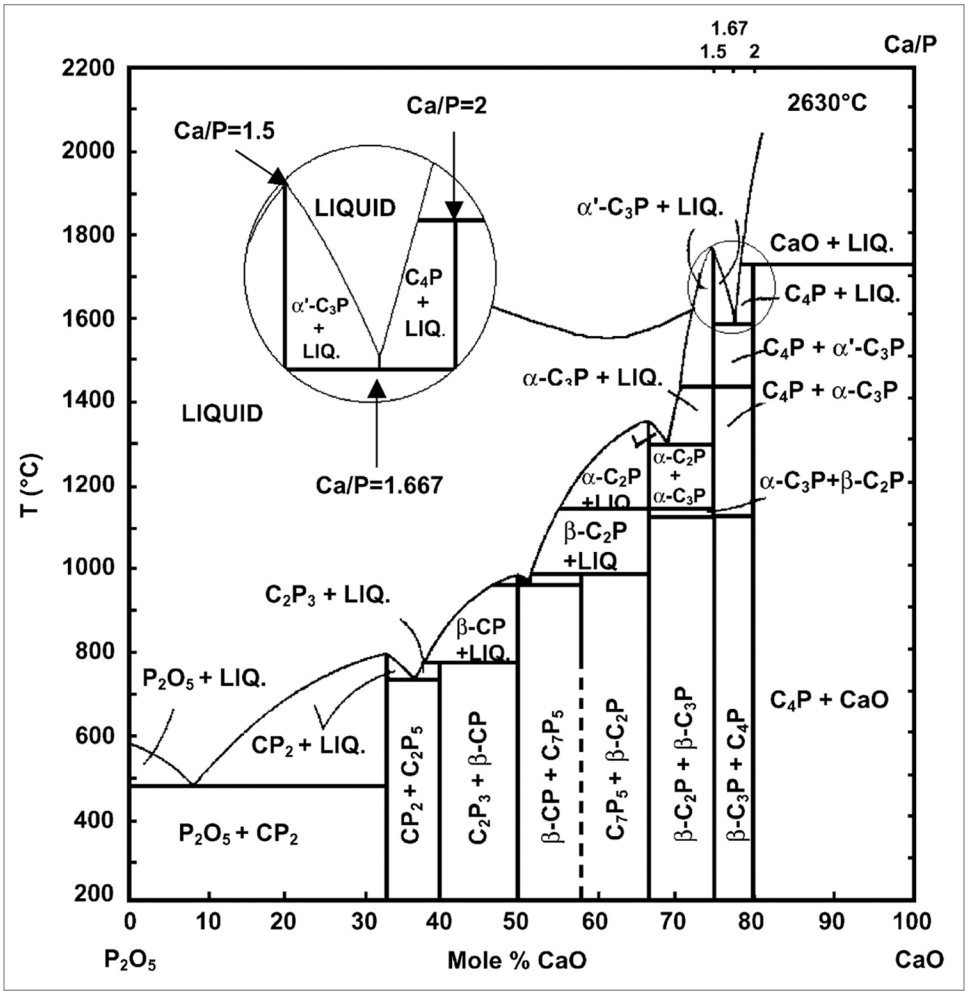

Figure 3. Phase diagram of the system CaO-P_2O_5 (C = CaO, p = P_2O_5) at elevated temperatures. Here: C_7P_5 means $7CaO{\cdot}5P_2O_5$; other abbreviations should be written out in the same manner. Reprinted from references 110 and 111 with permission.

by a direct precipitation. The solubility isotherms of different calcium orthophosphates are shown in **Figure 6**.[27,28,108,109,118-121] However, recently, the classic solubility data of calcium orthophosphates[27,28,108,109,118-121] were mentioned to be inappropriate.[122] According to the authors of the latter study, all previous solubility calculations were based on simplifications that are only crudely approximate. The problem lies in incongruent dissolution, leading to phase transformations and lack of the detailed solution equilibria. Using an absolute solid-titration approach, the true solubility isotherm of HA was found to lie substantially lower than previously reported. In addition, contrary to wide belief, DCPD appeared not to be the most stable phase below pH ~4.2, where CDHA is less soluble.[122]

A brief description of all known calcium orthophosphates (**Table 1**) is given below.

MCPM. Monocalcium phosphate monohydrate [$Ca(H_2PO_4)_2{\cdot}H_2O$; the IUPAC name is calcium dihydrogen orthophosphate monohydrate] is both the most acidic and the most water-soluble compound. It precipitates from highly acidic solutions that are normally used in the industry of phosphorus-containing fertilizer production ("triple superphosphate").[37] Besides, MCPM might be fabricated by a simple precipitation method using $CaCO_3$ and H_3PO_4 in aqueous and acetone media at ambient temperature.[123] At temperatures above ~100°C it releases a molecule of water and transforms into MCPA. Due to high acidity and solubility, MCPM is never found in biological calcifications. Moreover, pure MCPM is not biocompatible[d] with bones.[124] However, in medicine, MCPM is used as a component of several self-hardening calcium orthophosphate cements.[125-128] In addition, MCPM is used as a nutrient, acidulant and mineral supplement for dry baking powders, food, feed and some beverages.[129,130] Coupled with $NaHCO_3$, MCPM is used as a leavening agent for both dry baking powders and bakery dough. MCPM might be added to salt-curing preserves, pickled and marinated foods. According to the European classification of food additives, MCPM is marked as E341 additive. Occasionally, MCPM is added to toothpastes. MCPM might also be added to ceramics and glasses, while agriculture is the main consumer of a technical-grade MCPM, where it is used as a fertilizer.[37,129]

MCPA (or MCP). Monocalcium phosphate anhydrous [$Ca(H_2PO_4)_2$; the IUPAC name is calcium dihydrogen orthophosphate anhydrous] is the anhydrous form of MCPM. It

Table 3. Crystallographic data of calcium orthophosphates[27,112,113]

Compound	Space group	Unit cell parameters	Z[a]	Density, g cm^{-3}
MCPM	triclinic $P\bar{1}$	a = 5.6261(5), b = 11.889(2), c = 6.4731(8) Å, α = 98.633(6)°, β = 118.262(6)°, γ = 83.344(6)°	2	2.23
MCPA	triclinic $P\bar{1}$	a = 7.5577(5), b = 8.2531(6), c = 5.5504(3) Å, α = 109.87(1)°, β = 93.68(1)°, γ = 109.15(1)°	2	2.58
DCPD	monoclinic/a	a = 5.812(2), b = 15.180(3), c = 6.239(2) Å, β = 116.42(3)°	4	2.32
DCPA	triclinic $P\bar{1}$	a = 6.910(1), b = 6.627(2), c = 6.998(2) Å, α = 96.34(2)°, β = 103.82(2)°, γ = 88.33(2)°	4	2.89
OCP	triclinic $P\bar{1}$	a = 19.692(4), b = 9.523(2), c = 6.835(2) Å, α = 90.15(2)°, β = 92.54(2)°, γ = 108.65(1)°	1	2.61
α-TCP	monoclinic $P2_1/a$	a = 12.887(2), b = 27.280(4), c = 15.219(2) Å, β = 126.20(1)°	24	2.86
β-TCP	rhombohedral $R3cH$	$a = b$ = 10.4183(5), c = 37.3464(23) Å, γ = 120°	21[b]	3.08
HA	monoclinic $P2_1/b$ or hexagonal $P6_3/m$	a = 9.84214(8), b = 2a, c = 6.8814(7) Å, γ = 120° (monoclinic) $a = b$ = 9.4302(5), c = 6.8911(2) Å, γ = 120° (hexagonal)	4 2	3.16
FA	hexagonal $P6_3/m$	$a = b$ = 9.367, c = 6.884 Å, γ = 120°	2	3.20
OA	hexagonal $P\bar{6}$	$a = b$ = 9.432, c = 6.881 Å, α = 90.3°, β = 90.0°, γ = 119.9°	1	~3.2
TTCP	monoclinic $P2_1$	a = 7.023(1), b = 11.986(4), c = 9.473(2) Å, β = 90.90(1)°	4	3.05

[a]Number of formula units per unit cell. [b]Per the hexagonal unit cell.

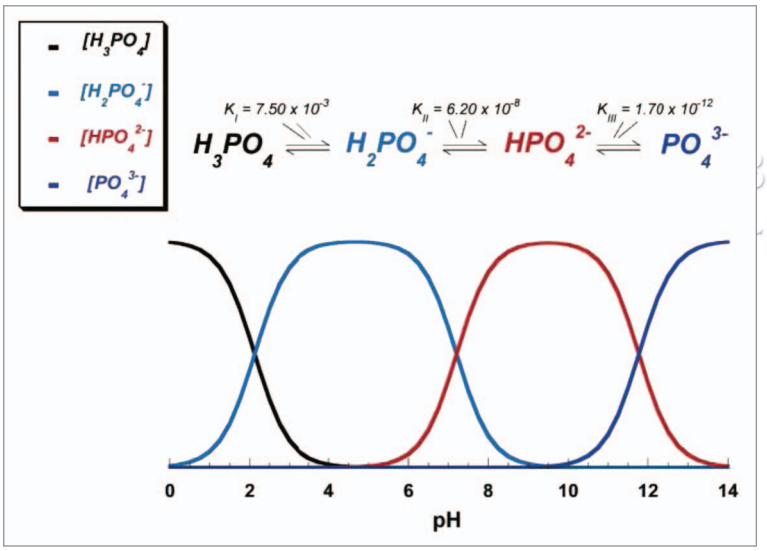

Figure 4. pH variation of ionic concentrations in triprotic equilibrium for phosphoric acid solutions. Reprinted from reference 116 with permission.

crystallizes under the same conditions as MCPM but at temperatures above ~100°C (e.g., from highly concentrated mother liquors during fertilizer production). Like MCPM, MCPA never appears in calcified tissues, and it is not biocompatible due to its acidity. There is no current application of MCPA in medicine. Due to its similarity with MCPM, in many cases, MCPA might be used instead of MCPM;[37,129] however, highly hydroscopic properties of MCPA reduce its commercial application.

DCPD. Dicalcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$; the IUPAC name is calcium hydrogen orthophosphate dihydrate; the mineral brushite[131]) can be easily crystallized from aqueous solutions at ~2.0 < pH < ~6.5. Interestingly, precipitation of DCPD by mixing a $Ca(OH)_2$ suspension and a H_3PO_4 solution in the equimolar quantities was found to occur in five stages; HA being the first precipitated phase.[132,133] Alternatively, DCPD might be prepared in gels.[134,135] DCPD transforms into DCPA at temperatures above ~80°C, and this transformation is accompanied by ~11% decrease in volume[136] and structural changes.[137] The value for $\Delta_r G^0$ for DCPD → DCPA transformation is -1.032 kJ/mol.[137] Briefly, DCPD crystals consist of $CaPO_4$ chains arranged parallel to each other, while lattice water molecules are interlayered between them. Using surface X-ray diffraction, Arsic et al. determined the atomic structure of the {010} interface of DCPD with water.[138,139] Since DCPD contains water layers as part of its crystal structure, special ordering properties at the interface are expected. This interface consists of two water bilayers with different ordering properties. The first is highly ordered and can be considered as part of the DCPD crystal structure. Surprisingly, the second water bilayer exhibits no in-plane order, but shows only layering in the perpendicular direction. It has been proposed that the low level of water ordering at the interface is correlated with the low solubility of DCPD in water.[139] Recently, data on DCPD solubility have been updated by solid titration technique.[140] The optical properties of DCPD are well described in reference 141, while many additional data on DCPD as well as a good picture of DCPD atomic structure are available in the literature.[142]

DCPD is of biological importance, because it is often found in pathological calcifications (dental calculi, crystalluria, chondrocalcinosis and urinary stones) and some carious lesions.[26,84-86] It has been proposed as an intermediate in both bone mineralization and dissolution of enamel in acids (dental erosion).[26,84,85] In medicine, DCPD is used in calcium orthophosphate cements[126,143-146] and as an intermediate for tooth remineralization. DCPD is added to toothpaste both for caries protection (in this case, it is coupled with F-containing compounds such as NaF and/or Na_2PO_3F) and as a gentle polishing agent.[147-151] Other

applications include a flame retardant,[152] a slow-release fertilizer, use in glass production as well as a calcium supplement in food, feed and cereals.[129] The importance of DCPD as a constituent of infant's food was discovered as early as in 1917.[153] In the food industry, it serves as a texturizer, bakery improver and water retention additive. In the dairy industry, DCPD is used as a mineral supplement. If added to food products, DCPD should be marked as E341 according to the European classification of food additives. In addition, plate-like crystals of DCPD might be used as a non-toxic, anticorrosive and passivating pigment for some ground coat paints.

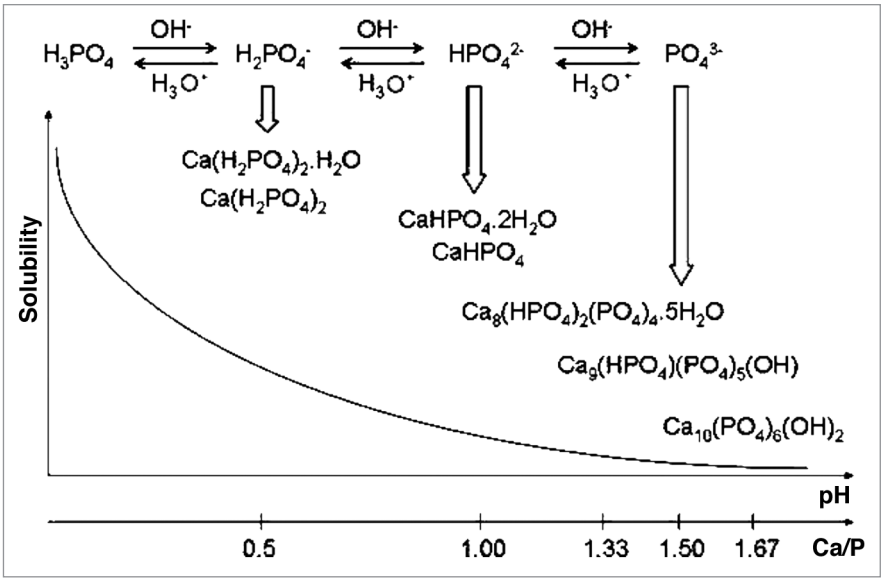

Figure 5. Various calcium orthophosphates obtained by neutralizing of orthophosphoric acid. Ca/P are reported in the figure. The solubility of calcium orthophosphates in water decreases drastically from left to right, HA being the most insoluble and stable phase. Reprinted from reference 117 with permission.

DCPA (or DCP). Dicalcium phosphate anhydrous ($CaHPO_4$; the IUPAC name is calcium hydrogen orthophosphate anhydrate, the mineral monetite[154]) is the anhydrous form of DCPD. It is less soluble than DCPD due to the absence of water inclusions. Like DCPD, DCPA can be crystallized from aqueous solutions but at temperatures ~100°C. Furthermore, it might be prepared at room temperature in gels,[134] ethanol[155] as well as in oil-in-water and water-in-oil systems.[156] DCPA is physically stable and resisted hydration even when dispersed in water for over 7 mo in the temperature range of 4–50°C.[157] A calcium-deficient DCPA was prepared recently. It might be sintered at ~300°C.[158] Unlike DCPD, DCPA occurs in neither normal nor pathological calcifications. It is used in calcium orthophosphate cements.[145,159-166] Besides, DCPA might be implanted.[167] Other applications include use as a polishing agent, a source of calcium and phosphate in nutritional supplements (e.g., in prepared breakfast cereals, enriched flour and noodle products), a tabletting aid[168] and a toothpaste component.[129] In addition, it is used as a dough conditioner in the food industry.

OCP. Octacalcium phosphate [$Ca_8(HPO_4)_2(PO_4)_4{\cdot}5H_2O$; the IUPAC name is tetracalcium hydrogen orthophosphate diorthophosphate pentahydrate; another name is octacalcium bis(hydrogenphosphate) tetrakis(phosphate) pentahydrate] is often found as an unstable transient intermediate during the precipitation of the thermodynamically more stable calcium orthophosphates (e.g., CDHA) in aqueous solutions. Its preparation technique might be found in references 169–174. A partially hydrolyzed form of OCP with Ca/P molar ratio of 1.37 might be prepared as well.[174,175] The full hydrolysis of OCP into CDHA occurs within ~6 h.[173] Furthermore, OCP might be non-stoichiometric and be either Ca-deficient (Ca/p = 1.26) or include excessive calcium (up to Ca/p = 1.48) in the structure.[174] Ion-substituted OCP might be prepared as well.[176] Crystals of OCP are typically small, extremely platy and almost invariably twinned.

The triclinic structure of OCP displays apatitic layers (with atomic arrangements of calcium and orthophosphate ions similar to those of HA) separated by hydrated layers (with atomic arrangements of calcium and orthophosphate ions similar to those in DCPD).[26-28,177,178] A similarity in crystal structure between OCP and HA[179,180] is one reason that the epitaxial growth of these phases is observed. Morphologically, OCP crystallizes as {100} blades of triclinic pinacoidal symmetry elongated along the *a*-axis and bordered by the forms {010}, {001} and {011}. It is generally assumed that in solutions, the hydrated layer of the (100) face is the layer most likely exposed to solution. The water content of OCP crystals is about 20% that of DCPD, and this is partly responsible for its lower solubility. New data on OCP solubility have been published recently in reference 181.

OCP is of a great biological importance, because it is one of the stable components of human dental and urinary calculi.[182-185] OCP was first proposed by W.E. Brown to participate as the initial phase in enamel mineral formation and bone formation through subsequent precipitation and stepwise hydrolysis of OCP.[179,180,186] It plays an important role in in vivo formation of apatitic biominerals. A "central OCP inclusion" (also known as "central dark line") is seen by transmission electron microscopy in many biological apatites and in some synthetically precipitated HA.[187-191] Although OCP has not been observed in vascular calcifications, it has been strongly suggested as a precursor phase to biological apatite found in natural and prosthetic heart valves.[192,193] In surgery, OCP is used for implantation into bone defects.[194-200] For comprehensive information on OCP, the readers are referred to other reviews in references 174 and 184.

β-TCP. β-tricalcium phosphate [β-$Ca_3(PO_4)_2$; the IUPAC name is tricalcium diorthophosphate β; other names are calcium orthophosphate tribasic β or tricalcium bis(orthophosphate) β] cannot be precipitated from aqueous solutions. It is a high temperature phase, which can be prepared at temperatures above

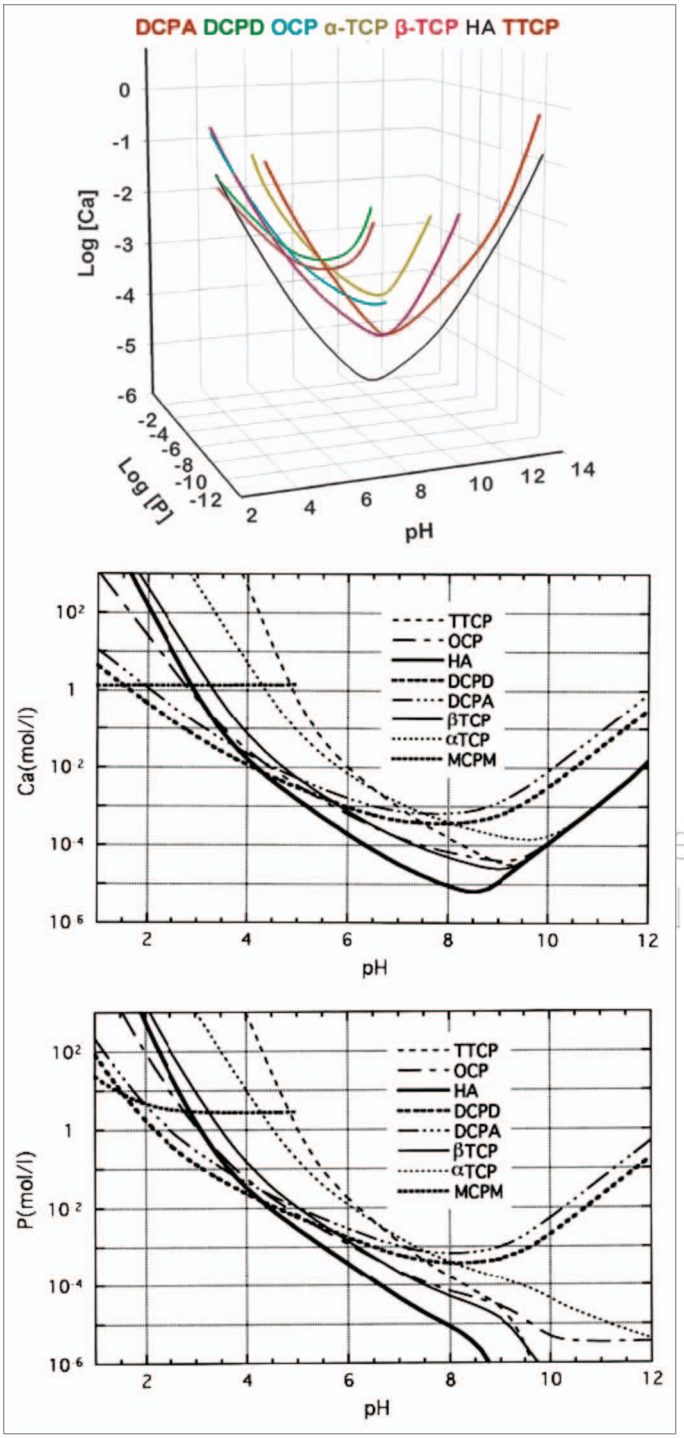

Figure 6. Top: a 3D version of the classical solubility phase diagrams for the ternary system $Ca(OH)_2$-H_3PO_4-H_2O. Reprinted from reference 118 with permission. Middle and bottom: solubility phase diagrams in two-dimensional graphs, showing two logarithms of the concentrations of (a) calcium and (b) orthophosphate ions as a function of the pH in solutions saturated with various salts. Reprinted from reference 119 with permission.

800°C by thermal decomposition of CDHA or by solid-state interaction of acidic calcium orthophosphates, e.g., DCPA, with a base, e.g., CaO. However, β-TCP can be obtained at a relatively low temperature (150°C) by precipitation in organic medium, such as ethylene glycol.[201,202] Apart from the chemical preparation routes, ion-substituted β-TCP can be prepared by calcining of bones;[203] such a type of β-TCP is occasionally called "bone ash." In β-TCP, there are three types of crystallographically non-equivalent PO_4^{3-} groups located at general points of the crystal, each type with different intratetrahedral bond lengths and angles. At temperatures above ~1,125°C, β-TCP is transformed into a high-temperature phase α-TCP. Being the stable phase at room temperature, β-TCP is less soluble in water than α-TCP (**Table 1**). Furthermore, the ideal β-TCP structure contains calcium ion vacancies that are too small to accommodate calcium ions but allow for the inclusion of magnesium ions, which thereby stabilize the structures.[204,205] Both ion-substituted[206-209] and organically modified[210-212] forms of β-TCP can be synthesized as well. The maximum substitution of Mg^{2+} in β-TCP was found to correspond to the $Ca_{2.61}[Mg(1)_{0.28},Mg(2)_{0.11}](PO_4)_2$ stoichiometric equation.[209] The modern structural data on β-TCP are available in references 213–215; those on Vicker's and Knoop microhardness studies might be found if reference 216, while solubility data can be found in reference 217. Furthermore, the ability of β-TCP to store an electrical charge by electrical polarization was studied, and this material was found to have a suitable composition and structure for both ion conduction and charge storage.[218]

Pure β-TCP never occurs in biological calcifications. Only the Mg-substituted form, called whitlockite[c] [β-TCMP-β-tricalcium magnesium phosphate, β-$(Ca,Mg)_3(PO_4)_2$], is found in dental calculi and urinary stones, dentineal caries, salivary stones, arthritic cartilage as well as in some soft tissue deposits.[26,84-86,219-222] However, it has not been observed in enamel, dentine or bone. In biomedicine, β-TCP is used in calcium orthophosphate bone cements[31,223-227] and other types of bone substitution bioceramics.[203,228-235] Dental applications of β-TCP are also known.[236] Pure β-TCP is added to some brands of toothpaste as a gentle polishing agent. Multivitamin complexes with calcium orthophosphate are widely available in the market, and β-TCP is used as the calcium phosphate there. In addition, β-TCP serves as a texturizer, bakery improver and anti-clumping agent for dry powdered food (flour, milk powder, dried cream, cocoa powder). Besides, β-TCP is added as a dietary or mineral supplement to food and feed, where it is marked as E341 according to the European classification of food additives. A prenatal development of rats during gestation was found to be sensitive to E341 (TCP) exposure.[237] There is a good review on the toxicological properties of inorganic phosphates, where the interested readers are referred.[238] Occasionally, β-TCP might be used as inert filler in pelleted drugs. Other applications comprise porcelains, pottery, enamel, use as a component for mordants and ackey as well as a polymer stabilizer.[129] β-TCP of a technical grade (as either calcined natural phosphorites or bone dust) is used as a slow-release fertilizer for acidic soils.[37]

α-TCP. α-tricalcium phosphate [α-$Ca_3(PO_4)_2$; the IUPAC name is tricalcium diorthophosphate α; other names are calcium

orthophosphate tribasic α or tricalcium bis(orthophosphate) α] is usually prepared from β-TCP at heating above ~1,125°C,[239] and it might be considered a high temperature phase of β-TCP. However, at the turn of the millennium, the previously forgotten data indicating that the presence of silicates stabilized α-TCP at lower temperatures of 800–1,000°C[240] has been rediscovered again. Such type of α-TCP is called "silicon-stabilized α-TCP".[241-246]

Although α-TCP and β-TCP have exactly the same chemical composition, they differ in their crystal structure (**Table 3**) and solubility (**Table 1**). In the absence of humidity, both polymorphs of TCP are stable at room temperatures; however, according to a density functional study, stability of β-TCP crystal lattice exceeds that of α-TCP.[214] Therefore, of the two, α-TCP is more reactive in aqueous systems, has a higher specific energy, and in aqueous solutions, it can be hydrolyzed to CDHA.[247-249] Milling was found to increase the α-TCP reactivity even more.[250] Although, α-TCP never occurs in biological calcifications, in medicine, it is used as a component of calcium orthophosphate cements.[126,143-146,161-163,251-254] On the other hand, the chemically pure α-TCP has received not much interest in the biomedical field.[233] The disadvantage for using α-TCP is its quick resorption rate (faster than formation of a new bone), which limits its application in this area. However, the silicon-stabilized α-TCP (more precisely, a biphasic composite with HA) has been commercialized as a starting material to produce bioresorbable porous ceramic scaffolds to be used as artificial bone grafts.[228,241-245] Upon implantation, α-TCP tends to convert to CDHA, which drastically reduces further degradation rate. Theoretical insights into bone grafting properties of the silicon-stabilized α-TCP might be found in reference 255. The structure of α-TCP is well-described in the literature,[214,215,256] while the surface and adsorption properties are available in reference 257. Similar to β-TCP, α-TCP of a technical grade might be used in slow-release fertilizer for acidic soils.[129]

To conclude, one should briefly mention the existence of α'-TCP phase. However, it lacks a practical interest, because it only exists at temperatures above ~1,465 ± 5°C and reverts to α-TCP by cooling below the transition temperature.

ACP. Amorphous calcium phosphates (ACPs) represent a special class of calcium orthophosphate salts, having variable chemical but more or less identical glass-like physical properties, in which there are neither translational nor orientational long-range orders (LRO) of the atomic positions. Until recently,[258] ACP has been considered as an individual chemical compound; however, this is just an amorphous state of other calcium orthophosphates. Therefore, in principle, all compounds mentioned in **Table 1** might be somehow fabricated in an amorphous state, but, currently, only a few of them (e.g., an amorphous TCP) are known.[258] Thus, strictly speaking, ACP should be excluded from **Table 1**.

Depending on the production temperatures, ACPs are divided into two major groups: low-temperature ACPs (prepared in aqueous solutions) and high-temperature ACPs. Low-temperature ACPs [described by the chemical formula $Ca_xH_y(PO_4)_z \cdot nH_2O$, n = 3–4.5; 15–20% H_2O] are often encountered as a transient precursor phase during precipitation of other calcium orthophosphates in aqueous systems. Usually, an ACP is the first phase precipitated from a supersaturated solution prepared by rapid mixing of solutions containing ions of calcium and orthophosphate;[27,259-264] however, other production techniques are known. ACPs are thought to be formed at the beginning of the precipitation due to a lower surface energy than that of OCP and apatites.[260] The amorphization degree of ACPs increases with the concentration increasing of Ca- and PO_4-containing solutions as well as at a high solution pH and a low crystallization temperature. A continuous gentle agitation of as precipitated ACPs in the mother solution, especially at elevated temperatures, results in a slow recrystallization and formation of better crystalline calcium orthophosphates, such as CDHA.[26,27] The lifetime of ACPs in aqueous solution was reported to be a function of the presence of additive molecules and ions, pH, ionic strength and temperature. Thus, ACPs may persist for appreciable periods and retain the amporphous state under some specific experimental conditions.[265] The chemical composition of ACPs strongly depends on the solution pH and the concentrations of mixing solutions. For example, ACPs with Ca/P ratios in the range of 1.18 (precipitated at solution pH = 6.6) to 1.53 (precipitated at solution pH = 11.7)[27,266] and even to 2.5[26,84,85] have been described. The presence of poly(ethylene glycol),[267] ions of pyrophosphate, carbonate and/or magnesium in solution during the crystallization promotes formation of ACPs and slows down their further transformation into more crystalline calcium orthophosphates, while the presence of fluoride has the opposite effect.[26-28,32,268] The solution-mediated transformation of an ACP to CDHA, which can be described by a "first-order" rate law, is a function only of the solution pH and depends upon the experimental conditions that regulate both the dissolution of ACP and the formation of early HA nuclei.[269]

High-temperature ACPs might be prepared using high-energy processing at elevated temperatures. This method is based on a rapid quenching of melted calcium orthophosphates occurring, e.g., during plasma spraying of HA.[270-272] A plasma jet, possessing very high temperatures (5,000–20,000°C), partly decomposes HA. That results in formation of a complicated mixture of products, some of which would be ACPs. Obviously, all types of high-temperature ACPs are definitively anhydrous contrary to the precipitated ACPs. Unfortunately, no adequate chemical formula is available to describe the high-temperature ACPs.

In general, as all amorphous compounds are characterized by a lack of LRO, it is problematic to discuss the structure of ACPs (they are X-ray amorphous). Concerning a short-range order (SRO) in ACPs, it exists, just due to the nature of chemical bonds. Unfortunately, in many cases, the SRO in ACPs is uncertain, because it depends on many variables, such as Ca/P ratio, preparation conditions, storage, admixtures, etc. It is well known that freshly precipitated ACPs contain 10–20% by weight of tightly bound water, which is removed by vacuum drying at elevated temperature.[273] Infrared spectra of ACPs show broad featureless phosphate absorption bands. Electron microscopy of freshly precipitated ACPs usually shows featureless nearly spherical particles with diameters in the range of 20 to 200 nm. However, there is a questionable opinion that ACPs might have an apatitic

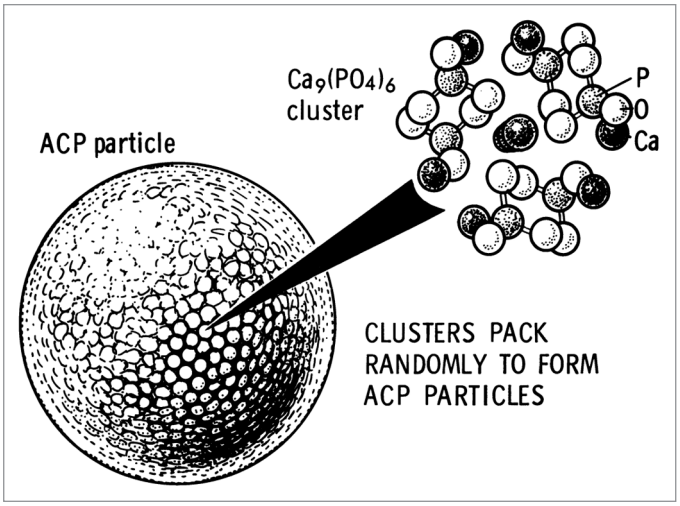

Figure 7. A model of ACP structure. Reprinted from reference 278 with permission.

structure but with a crystal size so small that they are X-ray amorphous. This is supported by X-ray absorption spectroscopic data (EXAFS) on biogenic and synthetic samples.[274-277] On the other hand, it was proposed that the basic structural unit of the precipitated ACPs is a 9.5 Å diameter, roughly spherical cluster of ions with the composition of $Ca_9(PO_4)_6$ (**Fig. 7**).[27,266,278,279] These clusters were found experimentally, first as nuclei during the crystallization of CDHA, and a model was developed to describe the crystallization of HA as a step-wise assembly of these units[280] [see section *3.10. HA (or HAp or OHAp)* below]. Biologically, ion-substituted ACPs (always containing ions of Na, Mg, carbonate and pyrophosphate) are found in soft-tissue pathological calcifications (e.g., heart valve calcifications of uremic patients).[26,84-86]

In medicine, pure ACPs are used in calcium orthophosphate cements[143-145] and as a filling material in dentistry.[258] Bioactive composites of ACPs with polymers have properties suitable for use in dentistry[281-284] and surgery.[285-288] Due to a reasonable solubility and physiological pH of aqueous solutions, ACP appeared to be consumable by some microorganisms, and for this reason, it might be added as a mineral supplement to culture media. Non-biomedical applications of ACPs comprise their use as a component for mordants and ackey. In the food industry, ACPs are used for syrup clearing. Occasionally, they might be used as inert filler in pelleted drugs. In addition, ACPs are used in glass and pottery production and as a raw material for production of some organic phosphates. To get further details on ACPs, the readers are referred to special reviews in references 258, 279, 289 and 290.

CDHA (or Ca-def HA). Calcium-deficient hydroxyapatite $[Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$ $(0 < x < 1)]$ can be easily prepared by simultaneous addition of calcium- and orthophosphate-containing solutions into boiling water followed by boiling the suspension for several hours (an aging stage). That is why, in literature, it might be called as "precipitated HA (PHA)".[291,292] Besides, it might be prepared by hydrolysis of α-TCP.[247-249] Other preparation techniques of CDHA are known as well.[293-295] During aging, initially precipitated ACPa are restructured and transformed into CDHA.[f] Therefore, there are many similarities in the structure, properties and application between the precipitated in alkaline solutions (pH > 8) ACPs and CDHA. Recent data indicated on presence of intermediate phases during further hydrolysis of CDHA to a more stable HA-like phase.[296] CDHA crystals are poorly crystalline and of submicron dimensions. They have a very large specific surface area, typically 25–100 m^2/g. On heating above ~700°C, dry CDHA with Ca/p = 1.5 will convert to β-TCP, and that with 1.5 < Ca/p < 1.67 will convert into a biphasic composite of HA and β-TCP (see the Biphasic, Triphasic and Multiphasic Calcium Orthophosphate Formulations section below).[297-308] A reasonable solid-state mechanism of a high-temperature transformation of CDHA into BCP has been proposed.[309,310]

The variability in Ca/P molar ratio of CDHA has been explained through different models: surface adsorption, lattice substitution and intercrystalline mixtures of HA and OCP.[311] Due to a lack of stoichiometry, CDHA usually contains other ions.[83] The extent depends on the counter-ions of the chemicals used for preparation (e.g., Na^+, Cl^-). Direct determinations of the CDHA structures are still missing, and the unit cell parameters remain uncertain. However, unlike that in ACPs (see section *3.8. ACP* above), a LRO exists in CDHA. The following lattice parameters were reported for formate (HCO_2^-) containing CDHA with Ca/p = 1.596 (ionic): a = 9.4729(20) and c = 6.8855(9) Å. A loss of Ca^{2+} ions happened exclusively from Ca(2) sites, while the PO_4 tetrahedron volume and P-O bonds were ~4.4% and ~1.4% smaller, respectively, than those in HA.[312]

A systematic study of defect constellations in CDHA is available in literature.[313] As a first approximation, CDHA may be considered as HA with some ions missing.[314] The more calcium is deficient, the more disorder and imperfections are in CDHA structure.[315] Furthermore, a direct correlation between Ca deficiency and the mechanical properties of the crystals was found: calcium deficiency lead to an 80% reduction in the hardness and elastic modulus and at least a 75% reduction in toughness in plate-shaped HA crystals.[316] According to the chemical formula of CDHA (**Table 1**), there are vacancies of Ca^{2+} [mainly on Ca(2) sites] and OH^- ions in crystal structure of this compound.[312,314-319] However, due to Ca^{2+} vacancies in CDHA, the resulting negative charge might be compensated by protonation of both an OH^- ion within the deficient calcium-triangle and a PO_4^{3-} ion in the nearest neighborhood of the vacant calcium site. This results in the presence of some water in the CDHA structure: $Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}(H_2O)_x$ $(0 < x < 1)$.[313] According to this approach, there are no hydroxide vacancies in CDHA, just a portion of OH^- ions are substituted by water molecules. Concerning possible vacancies of orthophosphate ions, nothing is known about their presence in CDHA. It is considered that a portion of PO_4^{3-} ions is either protonated (as HPO_4^{2-}) or substituted by other ions (e.g., CO_3^{2-}).[320] Theoretical investigations of the defect formation mechanism relevant to non-stoichiometry in CDHA are available in reference 321.

Unsubstituted CDHA (i.e., that containing ions of Ca^{2+}, PO_4^{3-}, HPO_4^{2-} and OH^- only) does not exist in biological systems. However, the ion substituted CDHA, Na^+, K^+, Mg^{2+}, Sr^{2+}

for Ca^{2+}; CO_3^{2-} for PO_4^{3-} or HPO_4^{2-}; F^-, Cl^-, CO_3^{2-} for OH^-, plus some water forms biological apatite, the main inorganic part of animal and human normal and pathological calcifications.[26,83,84] Therefore, CDHA is a very promising compound for industrial manufacturing of artificial bone substitutes,[322] including drug delivery applications.[323] Non-biomedical applications of CDHA are similar to those of ACP and HA. Interestingly, CDHA was found to possess a catalytic activity to produce biogasoline.[324]

HA (or HAp, or OHAp). Hydroxyapatite[g] [$Ca_5(PO_4)_3(OH)$, but is usually written as $Ca_{10}(PO_4)_6(OH)_2$ to denote that the crystal unit cell comprises two molecules; the IUPAC name is pentacalcium hydroxide tris(orthophosphate)] is the second most stable and least soluble calcium orthophosphate after FA. Chemically pure HA crystallizes in the monoclinic space group $P2_1/b$.[325] However, at temperatures above ~250°C, there is a monoclinic to hexagonal phase transition in HA (space group $P6_3/m$).[27,113,266,326,327] The detailed description of the HA structure was first reported in 1964,[328] and its interpretation in terms of aggregation of $Ca_9(PO_4)_6$ clusters, the so-called Posner's clusters, has been widely used since the publication of the article by Posner and Betts.[273] The $Ca_9(PO_4)_6$ clusters appeared to be energetically favored in comparison to alternative candidates, including $Ca_3(PO_4)_2$ and $Ca_6(PO_4)_4$ clusters.[329] In hexagonal HA, the hydroxide ions are more disordered within each row when compared with the monoclinic form, pointing either upward or downward in the structure. This induces strains that are compensated for by substitutions or ion vacancies. Some impurities, like partial substitution of hydroxide by fluoride or chloride, stabilize the hexagonal structure of HA at ambient temperature. For this reason, hexagonal HA is seldom the stoichiometric phase, and it is very rare that single crystals of natural HA exhibit the hexagonal space group. The crystal structure of HA is well-described in references 27 and 112–114 the detailed analysis of the electronic structure, bonding, charge transfer, optical and elastic properties are also available,[330-334] while the readers interested in Posner's clusters are referred to other papers.[329,335-337] A shell model was developed to study the lattice dynamics of HA,[338] while a cluster growth model was created to illustrate its growth.[280] Polarization characteristics[339,340] and pyroelectrical properties[341] of HA bioceramics have been investigated. First-principles calculations for the elastic properties of doped HA[342] and vacancy formation in HA[343] were performed. Computer simulations of the structures and properties of HA are well-described in recent feature articles.[344,345]

Several techniques might be utilized for HA preparation; they can be divided into solid-state reactions and wet methods,[346] which include precipitation, hydrothermal synthesis and hydrolysis of other calcium orthophosphates. Even under the ideal stoichiometric conditions, the precipitates are generally non-stoichiometric, suggesting intermediate formation of precursor phases, such as ACP and CDHA. HA can be prepared in aqueous solutions by mixing exactly stoichiometric quantities of Ca- and PO_4-containing solutions at pH > 9, followed by boiling for several days in CO_2-free atmosphere (the aging or maturation stage), filtration, drying and, usually, sintering at about 1,000°C.[347] As the first precipitates are rich in non-apatitic environments (see ACP and CDHA), the aging stage appears to be very important: the Ca/P molar ratio of 1.67 was attained in as little as 5 h after the completion of the reaction at 90°C.[348] The surface of freshly precipitated HA is composed of a structured hydrated layer containing easily exchangeable mobile ionic species.[349] Usually unsintered HA is poorly crystalline and often non-stoichiometric, resembling the aforementioned CDHA. However, well crystalline HA can be prepared from an aqueous solution.[350] Microcrystalline samples of HA can also be prepared by solid-state reaction of other calcium phosphates (e.g., MCPM, DCPA, DCPD, OCP) with CaO, $Ca(OH)_2$ or $CaCO_3$ at temperatures above ~1,200°C in an atmosphere of equal volumes of water and nitrogen. HA can be prepared by hydrothermal synthesis.[27,266,351,352] A water-free synthesis can be performed in ethanol from $Ca(OEt)_2$ (Et = ethyl) and H_3PO_4.[353,354] In addition, HA might be prepared by mechanochemical synthesis of a dry mixture of CaO and DCPD[346,355] or from coral skeletal carbonate by hydrothermal exchange.[356-358] Relatively large single crystals of HA might be prepared from those of chlorapatite[359] or by a recently developed controlled homogeneous precipitation method.[360] Smaller sized particles of HA might be prepared by a pyrosol technique, where an aerosol containing calcium and orthophosphate ions in the adequate ratio is transported to a furnace where the pyrolisis takes place.[361] Synthesis of nano-sized HA has also been described in references 362 and 363, while the chronological development of nano-sized HA synthesis might be found in another paper.[364] Two-dimensional nanocrystalline HA might be also synthesized.[365] Space-grown and terrestrial HA crystals were found to differ in size: the former appeared to be at least 1–1.5 orders of magnitude bigger in length.[366,367] Transparent HA ceramics is also known.[368-371] The detailed information on HA synthesis is available in references 372–380. In addition, there are good reviews on HA solubility, crystal growth and intermediate phases of HA crystallization[381] as well as on HA dissolution.[382]

Pure HA never occurs in biological systems. However, due to the chemical similarities to bone and teeth mineral (**Table 2**), HA is widely used as a coating on orthopedic (e.g., hip joint prosthesis) and dental implants.[383-390] HA particles might be implanted as well.[391] Due to a great similarity to biological apatite, HA has been used in liquid chromatography of nucleic acids, proteins and other biological compounds[392-401] and for drug delivery purposes[402-405] for a long time. Also, HA is added to some brands of toothpaste as a gentle polishing agent instead of calcium carbonate.[406,407] Non-biomedical applications of HA include its use as an environmentally friendly filler for elastomers,[408] a sorbent of poisonous chemical elements[409,410] and a carrier for various catalysts.[411-413] Furthermore, HA by itself might act as a catalyst for formaldehyde combustion at room temperature.[414] To conclude this topic, one should mention other reviews devoted to HA and its biomedical applications.[415-419]

FA (or FAp). Fluorapatite [$Ca_5(PO_4)_3F$, usually written as $Ca_{10}(PO_4)_6F_2$ to denote that the crystal unit cell comprises two molecules; the IUPAC name is pentacalcium fluoride tris(orthophosphate) is the only ion-substituted calcium

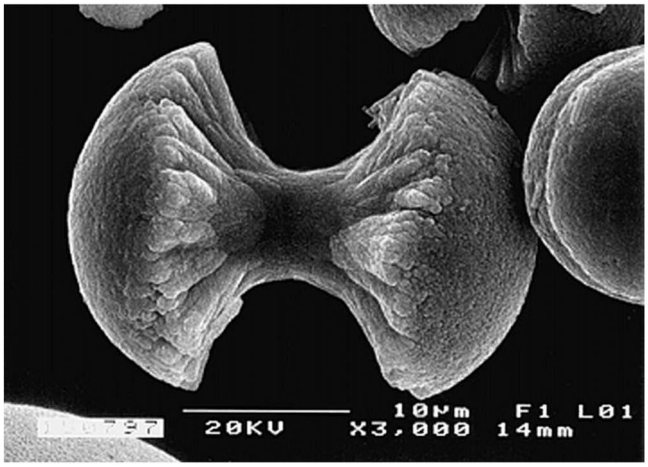

Figure 8. A biomimetically grown aggregate of FA that was crystallized in a gelatin matrix. Its shape can be explained and simulated by a fractal growth mechanism. Scale bar: 10 µm. Reprinted from reference 420 with permission.

orthophosphate considered in this review. It the hardest (5 according to the Mohs' scale of mineral hardness), most stable and least soluble compound among all calcium orthophosphates (**Table 1**). Perhaps, such "extreme" properties of FA are related to the specific position of F^- ions in the center of Ca(2) triangles of the crystal structure.[113] Due to its properties, FA is the only calcium orthophosphate that naturally forms large deposits suitable for the commercial use[36-39] (see also **Fig. 2**). Preparation techniques of the chemically pure FA are similar to the aforementioned ones for HA, but the synthesis must be performed in presence of the necessary amount of F^- ions (usually, NaF or NH_4F is added). Unlike that for HA (see CDHA), no data are available on existence of calcium-deficient FA. Under some special crystallization conditions (e.g., in presence of gelatin or citric acid), FA might form an unusual dumbbell-like fractal morphology that, finally, close into spheres (**Fig. 8**).[420-426] A hierarchical structure for FA was proposed.[427] The crystal structure of FA was studied for the first time in 1930[428,429] and is well-described in references 27, 112–114 and 430. The detailed analysis of the electronic structure, bonding, charge transfer and optical properties is available as well.[332] In addition, there are reviews on FA solubility[381] and the dissolution mechanism.[382]

FA easily forms solid solutions with HA with any desired F/OH molar ratio. Such compounds are called fluorhydroxyapatites (FHA) or hydroxyfluorapatites (HFA) and described with a chemical formula $Ca_{10}(PO_4)_6(OH)_{2-x}F_x$, where $0 < x < 2$. If the F/OH ratio is either uncertain or not important, the chemical formula of FHA and HFA is often written as $Ca_{10}(PO_4)_6(F,OH)_2$. The lattice parameters, crystal structure, solubility and other properties of FHA and HFA lay in between those for the chemically pure FA and HA.[431-435]

Similar to pure HA, pure FA never occurs in biological systems. Obviously, a lack of the necessary amount of toxic fluorides (the acute toxic dose of fluoride is ~5 mg/kg of body weight) in living organisms is the main reason of this fact (pure FA contains 3.7% mass F). Enameloid of shark teeth[32,103,436-440] and some exoskeletons of mollusks[441] seem to be the only exclusions, because they contain substantial amounts of FA. Among all normal calcified tissues of humans, the highest concentration of fluorides is found in bones and the lowest in dental enamel.[h] However, even in bones, the total amount of fluorides is not enough to form FA; it is generally considered that the inorganic part of bones consists of ion-substituted CDHA. Due to its low solubility, good chemical stability and the toxicity of high amounts of fluorides, chemically pure FA is rarely used as a bone substituting material.[442] However, various FA-containing composites,[443-445] FHA[446,447] and porous FA bioceramics[448] seem to be better candidates for biomedical applications. Furthermore, due to the ability to form FHA and/or HFA, minor amounts of fluorides might be intentionally added to calcium orthophosphate biomaterials.[449-455] The effect of fluoride contents in FHA on both osteoblast behavior[456,457] and leukemia cells proliferation[458] has been described. Non-biomedical applications of FA include its application as a catalyst.[459]

OA (or OAp, or OXA). Oxyapatite [$Ca_{10}(PO_4)_6O$; the IUPAC name is decacalcium oxide hexakis(phosphate)] is the least studied calcium orthophosphate. To the best of my knowledge, pure OA has never been prepared; therefore, its properties are not well-established. Furthermore, still there are doubts that pure OA exists. However, a mixture of OA and HA (oxy-HA) might be prepared by dehydration of HA at temperatures exceeding ~900°C (e.g., during plasma-spray of HA) only in the absence of water vapor.[27,28,460,461] It also might be crystallized in glass-ceramics.[462] Computer modeling techniques have been employed to qualitatively and quantitatively investigate the dehydration of HA to OA.[463] OA has the hexagonal space group symmetry $P\bar{6}$ (174) of cesanite type,[112] while the space group symmetry for partially dehydrated HA was found to change from hexagonal P63/m to triclinic $P\bar{1}$ when more than ca. 35% of the structurally bound water had been removed.[461] OA has no stability field in aqueous conditions;[464] it is very reactive and transforms to HA in contact with water vapor.[460] Due to the aforementioned problems with OA preparation, no information on biomedical applications of pure OA is available. Plasma-sprayed coatings of HA, in which OA might be present as an admixture phase, seem to be the only application.

TTCP (or TetCP). Tetracalcium phosphate or tetracalcium orthophosphate monoxide [$Ca_4(PO_4)_2O$; the IUPAC name is tetracalcium oxide bis(orthophosphate); the mineral hilgenstockite[465]] is the most basic calcium orthophosphate. However, its solubility in water is higher than that of HA (**Table 1**). TTCP cannot be precipitated from aqueous solutions. It can be prepared only by a solid-state reaction at temperatures above 1300°C, e.g., by heating homogenized equimolar quantities of DCPA and $CaCO_3$ in dry air or in a flow of dry nitrogen.[27,266,466,467] These reactions should be performed in a dry atmosphere in a vacuum or with rapid cooling (to prevent uptake of water and formation of HA). DCPA might easily be replaced by ammonium orthophosphates,[468,469] while calcium carbonate might be replaced by calcium acetate.[469] Furthermore, TTCP often appears as an unwanted byproduct in plasma-sprayed HA coatings, where it is

formed as a result of the thermal decomposition of HA to a mixture of high-temperature phases of α-TCP, TTCP and CaO.[470] TTCP is metastable: in both wet environment and aqueous solutions, it slowly hydrolyzes to HA and calcium hydroxide.[27,266,471] Consequently, TTCP is never found in biological calcifications. In medicine, TTCP is widely used for preparation of various self-setting calcium orthophosphate cements;[120,127,143,159,165,166,252,470,472] however, to the best of my knowledge, there is no commercial bone-substituting product consisting solely of TTCP. For the comprehensive information on TTCP, the readers are referred to a recent review in reference 470, while the structure,[473] spectra[474] and solubility[217] of TTCP are well-described elsewhere.

There is an opinion,[113,184] that all calcium orthophosphates listed in **Table 1** might be classified into three major structural types: (1) the apatite type, $Ca_{10}(PO_4)_6X_2$, which includes HA, FA, OA, CDHA, OCP and TTCP; (2) the glaserite type, named after the mineral glaserite, $K_3Na(SO_4)_2$, which includes all polymorphs of TCP and, perhaps, ACP and (3) the Ca-PO_4 sheet-containing compounds, which include DCPD, DCPA, MCPM and MCPA. According to the authors, a closer examination of the structures revealed that all available calcium orthophosphates could be included into distorted glaserite type structures, but with varying degrees of distortion.[113,184]

Biphasic, triphasic and multiphasic calcium orthophosphate formulations. Calcium orthophosphates might form biphasic, triphasic and multiphasic (polyphasic) compositions, in which the individual components cannot be separated from each other.[475] Presumably, the individual phases of such compositions are homogeneously "mixed" at well below submicron level (<0.1 μm) and strongly integrated with each other. Nevertheless, the presence of all individual phases is easily seen by X-ray diffraction technique.

The main idea of the multiphasic concept is determined by a balance of more stable calcium orthophosphate phases (e.g., HA) and more soluble calcium orthophosphate phases (e.g., any type of TCP). The usual way to prepare biphasic, triphasic and multiphasic calcium orthophosphates consists of sintering non-stoichiometric calcium orthophosphates, such as ACP and CDHA, at temperatures above ~700°C. Furthermore, a thermal decomposition of the stoichiometric calcium orthophosphates at temperatures above ~1300°C might be used as well;[476,477] however, this approach often results in the formation of complicated mixtures of various products including admixtures of CaO, calcium pyrophosphates, etc. Namely, transformation of HA into polyphasic calcium orthophosphates by annealing in a vacuum occurs as this: the outer part of HA is transformed into α-TCP and TTCP, while the α-TCP phase of the surface further transforms into CaO. Besides, in the boundary phase, HA is transformed into TTCP.[476]

Historically, Nery, Lynch and coworkers first used the term biphasic calcium phosphate (BCP) in 1986 to describe a bioceramic that consisted of a mixture of HA and β-TCP.[226] Based on the results of X-ray diffraction analysis, these authors found that the "tricalcium phosphate" preparation material used in their early publication[227] was in fact a mixture of ~20% HA and ~80% β-TCP. Currently, only biphasic and triphasic calcium orthophosphate formulations are known; perhaps more complicated formulations will be manufactured in the future. Furthermore, nowadays, only multiphasic and/or polyphasic compositions consisting of high-temperature phases of calcium orthophosphates, such as α-TCP, β-TCP, HA and, perhaps, high-temperature ACP, OA and TTCP, are known. No precise information on multiphasic compositions containing MCPM, MCPA, DCPD, DCPA, low-temperature ACP, OCP and CDHA has been found in the literature.[475] Perhaps, such formulations will be produced in future.

All BCP formulations might be subdivided into two major groups: those consisting of calcium orthophosphates having either the same (e.g., α-TCP and β-TCP) or different (e.g., β-TCP and HA) molar Ca/P ratios. Among all known BCP formulations, BCP consisting of HA and β-TCP is both the most known and the best investigated.[297-308] In 1986, LeGeros in the USA and Daculsi in France initiated the basic studies on preparation of this type of BCP and its in vitro properties. This material is soluble and gradually dissolves in the body, seeding new bone formation as it releases calcium and orthophosphate ions into the biological medium. Presently, commercial BCP products of different or similar HA/β-TCP ratios are manufactured in many parts of the world as bone-graft or bone substitute materials for orthopedic and dental applications under various trade marks and several manufacturers.[307] A similar combination of α-TCP with HA forms BCP as well.[241,242,244,478-481]

Recently the concept of BCP has been extended by preparation and characterization of biphasic TCP (BTCP), consisting of α-TCP and β-TCP phases.[482-486] The biphasic TCP is usually prepared by heating ACP precursors[484-486] in which the α-TCP/β-TCP ratio can be controlled by aging time and pH value during synthesis of the amorphous precursor.[485] Furthermore, triphasic formulations, consisting of HA, α-TCP and β-TCP[487] or HA, α-TCP and TTCP[476,477] have been prepared.

It is important to recognize that the major biomedical properties (such as bioactivity, bioresorbability, osteoconductivity and osteoinductivity) of the multiphasic and/or polyphasic compositions might be adjusted by changing the ratio among the calcium orthophosphate phases. When compared with both α- and β-TCP, HA is a more stable phase under the physiological conditions, as it has a lower solubility (**Table 1**) and, thus, slower resorption kinetics. Therefore, due to a higher biodegradability of the α- or β-TCP component, the reactivity of BCP increases with the TCP/HA ratio increasing. Thus, in vivo bioresorbability of BCP can be adjusted through the phase composition. Similar conclusions are also valid for both the biphasic TCP (in which α-TCP is a more soluble phase) and the triphasic (HA, α-TCP and β-TCP) formulation.

A phase transition from α-TCP into β-TCP in three types of BCPs (HA + TCP) was investigated, and the experimental results indicated that a sintering temperature for the complete phase transition from α-TCP into β-TCP increased with increasing HA content in BCP.[488] Further details on biphasic, triphasic and multiphasic calcium orthophosphate formulations might be found in a very recent review in reference 475.

Ion-substituted calcium orthophosphates. Finally, one should very briefly mention the existence of carbonated apatite,[489-495] chlorapatite[496-498] as well as a great number of various ion-substituted calcium orthophosphates.[83,499,500] Usually, they are of a non-stoichiometric nature, and there are too many of them to be mentioned in one review. Currently, this is a hot investigation topic; therefore, the readers are referred to other books and reviews in references 26–28, 32, 36, 38, 48, 266 and 416. In addition, there is a very good review, in which the structures of more than 75 chemically different apatites have been discussed in reference 112.

To conclude this topic, it is interesting to note that chemical elements not found in natural bones can be intentionally incorporated into calcium orthophosphate biomaterials to get special properties. For example, addition of Ag^{+},[501-503] Zn^{2+},[503,972] and Cu^{2+},[503,972,973] has been used for imparting antimicrobial effect, while radioactive isotopes of ^{90}Y,[504] ^{153}Sm[181,505-507] Re[505] have been incorporated into HA bioceramics and injected into knee joints to treat rheumatoid joint synovitis.[504,505,507] More to the point, apatites were found to incorporate individual molecules, such as water, oxygen and carbon dioxide.[83]

Biological Hard Tissues of Calcium Orthophosphates

Biological mineralization (or biomineralization) is the process of in vivo formation of inorganic minerals (so-called, biominerals). One should stress, that the term "biomineral" refers not only to a mineral produced by organisms, but also to the fact that almost all of these mineralized products are composite materials comprised of both inorganic and bioorganic components. Furthermore, having formed in vivo under well-controlled conditions, the biomineral phases often have properties, such as shape, size, crystallinity, isotopic and trace element compositions, quite unlike their inorganically formed counterparts (please, compare **Figs. 2, 8, 10 and 14**). Thus, the term "biomineral" reflects all this complexity.[103,438]

As shown in **Table 2** and discussed above, in the body of mammals, the vast majority of both normal and pathological calcifications consist of non-stoichiometric and ion-substituted calcium orthophosphates, mainly of apatitic structure.[88,509] At the atomic scale, nano-sized crystals bone apatite exhibit a variety of substitutions and vacancies that make the Ca/P molar ratio distinct from the stoichiometric HA ratio of 1.67. Their chemical composition is complicated and varies in relatively wide ranges. This depends on what the animal has ingested.[510] Occasionally, attempts are performed to compose chemical formulas of biological apatites. For example, the following formula $Ca_{8.856}Mg_{0.088}Na_{0.292}K_{0.010}(PO_4)_{5.312}(HPO_4)_{0.280}(CO_3)_{0.407}(OH)_{0.702}Cl_{0.078}(CO_3)_{0.050}$ was proposed to describe the chemical composition of the inorganic part of dental enamel.[511]

The impurities in biological apatite of bones and teeth introduce significant stresses into the crystal structure, which make it less stable and more reactive. Among all substituting ions, the presence of 4–8% of carbonates instead of orthophosphate anions (so called, B-type substitution[26-28,493]) and 0.5–1.5% of Mg is of special importance, because it leads to large lattice strain and significantly increases the solubility.[509,511,512] Higher concentrations of magnesium and carbonates in bone or dentine compared with those in enamel (**Table 2**) may explain a higher solubility and a lower crystallinity (smaller crystal size) of bone or dentine compared with enamel.

In addition, the crystals of biological apatite are always very small, which also increases its solubility when compared with that for the chemically pure HA and even CDHA.[83] However, biologic apatites of enamel have considerably larger crystal size (about 2,000 nm) compared with that of either bone or dentine apatite, as indicated by the well-defined diffraction peaks in the X-ray diffraction profile of enamel apatite and much broader diffraction peaks of either bone or dentine apatites (**Fig. 9**, center). Small dimensions and a low crystallinity are two distinct features of biological apatites, which, combined with their non-stoichiometric composition, inner crystalline disorder and presence of other ions in the crystal lattice, allow explaining their special behavior. For example, the small crystal size means that a large percentage of the atoms are on the surface of the crystals, providing a large specific surface area for sorption of ions, proteins and drugs.[508,512] The major physical properties of biological apatite are summarized in **Figure 9**. It is interesting to note, that the solubility and equilibrium phenomena of calcium orthophosphates related to the calcification process have been studied at least since 1925.[513,514]

Attempts to mimic the calcium orthophosphate nature of bones were first performed in 1913.[515] This discovery was clarified afterwards, suggesting that the bone mineral could be carbonated apatite.[516,517] Further optical and X-ray analysis of bones and other mineralized tissues matched analyses of two apatites: FA and dahllite.[518] Additional historical data on this point are available in literature.[42] Nowadays, according to Weiner and Wagner, "the term bone refers to a family of materials, all of which are built up of mineralized collagen fibrils."[104,519] For mammals, this family of materials includes dentine, the material that constitutes the inner layers of teeth, cementum, the thin layer that binds the roots of teeth to the jaw, deer antlers and some other materials.[104,105] It is worth noting, that bones and teeth contain almost 99% of the total body calcium and about 85% of the total body phosphorus, which amounts to a combined mass of approximately 2 kg in an average person.[520,521] In addition, it is important to recognize that calcium orthophosphates of bones are by no means inert; they play an important role in the metabolic functions of the body. The recent data on the physico-chemical and crystallographic study of biological apatite have been reviewed in reference 511. Besides, there is a comprehensive review on the application of surface science methods to study the properties of dental materials and related biomaterials.[522]

Bone. Bone, also called osseous tissue (Latin: *os*), is a type of hard endoskeletal connective tissue found in many vertebrate animals. All the bones of a single animal are, collectively, known as the skeleton. True bones are present in bony fish (osteichthyes) and all tetrapods. Bones support body structures, protect internal organs and, in conjunction with muscles, facilitate movement.[523] In addition, bones are also involved in blood cell

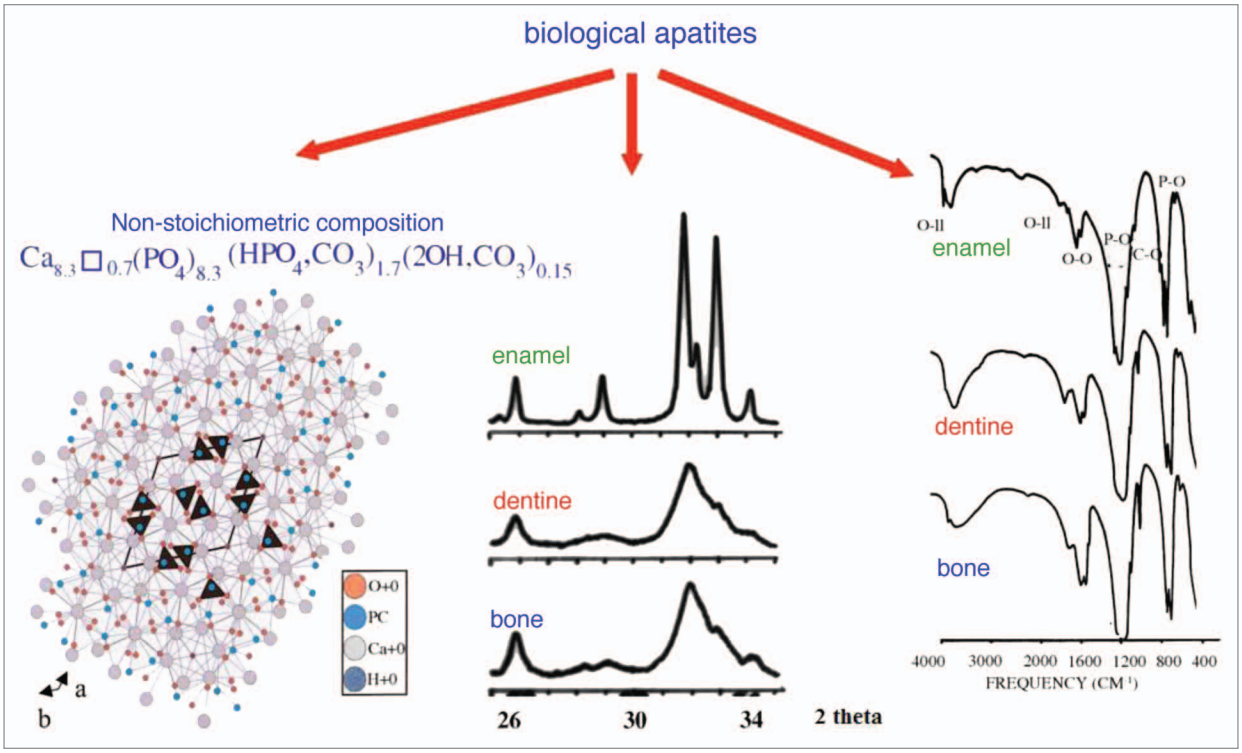

Figure 9. Left: crystal structure of a biological apatite. Powder X-ray diffraction patterns (center) and infrared spectra (right) of human enamel, dentine and bone. Reprinted from reference 508 with permission.

formation, calcium metabolism and act for mineral storage. From the material point of view, bone is a dynamic, highly vascularized tissue that is formed from a complicated biocomposite containing both inorganic (**Table 2**) and bioorganic (chiefly, collagen) compounds.[509,524-530] Furthermore, there is a cellular phase that consists of three different types of cells: osteoblasts, osteoclasts and osteocytes. The inorganic to bioorganic ratio is approximately 75% to 25% by dry weight and about 65% to 35% by volume. This ratio not only differs among animals, among bones in the same animal and over time in the same animal, but also it exerts a major control on the material properties of bone, such as its toughness, ultimate strength and stiffness. In general, load-bearing ability of bones depends on not only architectural properties, such as cortical thickness and bone diameter, but also intrinsic, size-independent material properties, such as porosity, level of mineralization, crystal size and properties derived from the organic phase of bone.[531] A higher mineral to collagen ratio typically yields stronger but more brittle, bones.[532-534] For example, bone from the leg of a cow has a relatively high concentration of calcium orthophosphates (for support), whereas bone from the antler of a deer has a relatively high concentration of collagen (for flexibility).[122] It is interesting to note, that bone exhibits several physical properties such as piezoelectricity[535] and pyroelectricity.[536]

Stability of the mineral composition of bones has a very long history: calcium orthophosphates were found in dinosaur fossils.[53,100,537-540] Therefore, organisms have had a great deal of time to exploit the feedback between composition and structure in apatite, on the one hand, and benefit from its biological functionality, on the other. Bone in modern animals is a relatively hard and lightweight porous composite material, formed mostly of biological apatite (i.e., poorly crystalline CDHA with ionic substitutions). It has relatively high compressive strength but poor tensile strength.[541] While bone is essentially brittle, it has a degree of significant plasticity contributed by its organic components.

The distribution of the inorganic and bioorganic phases depends on a highly complex process that takes place during bone formation. Each of these components may be assembled in different proportions, creating two different architectural structures depending on the bone type and function. They are characterized by different structural features that strongly correlate with the mechanical performance of the tissue. These two types of bones are (1) the cortical bone (or compact bone), which is a dense structure and (2) the cancellous bone (also known as trabecular or spongious bone), which is less dense and less stiff than compact bone. Usually, bone is composed of a relatively dense outer layer of cortical bone covering an internal mesh-like structure (average porosity of 75–95%) of cancellous bone, the density of which is about 0.2 g/cm^3, but it may vary at different points (**Fig. 10**). Cortical bone makes up a large portion of the skeletal mass; it has a high density (~1.80 g/cm^3) and a low surface area. Cancellous bone has an open meshwork or honeycomb-like structure. It has a relatively high surface area but forms a smaller portion of the skeleton. Bone is a porous material, with the pore sizes range from 1 to 100 μm in normal cortical bones and 200

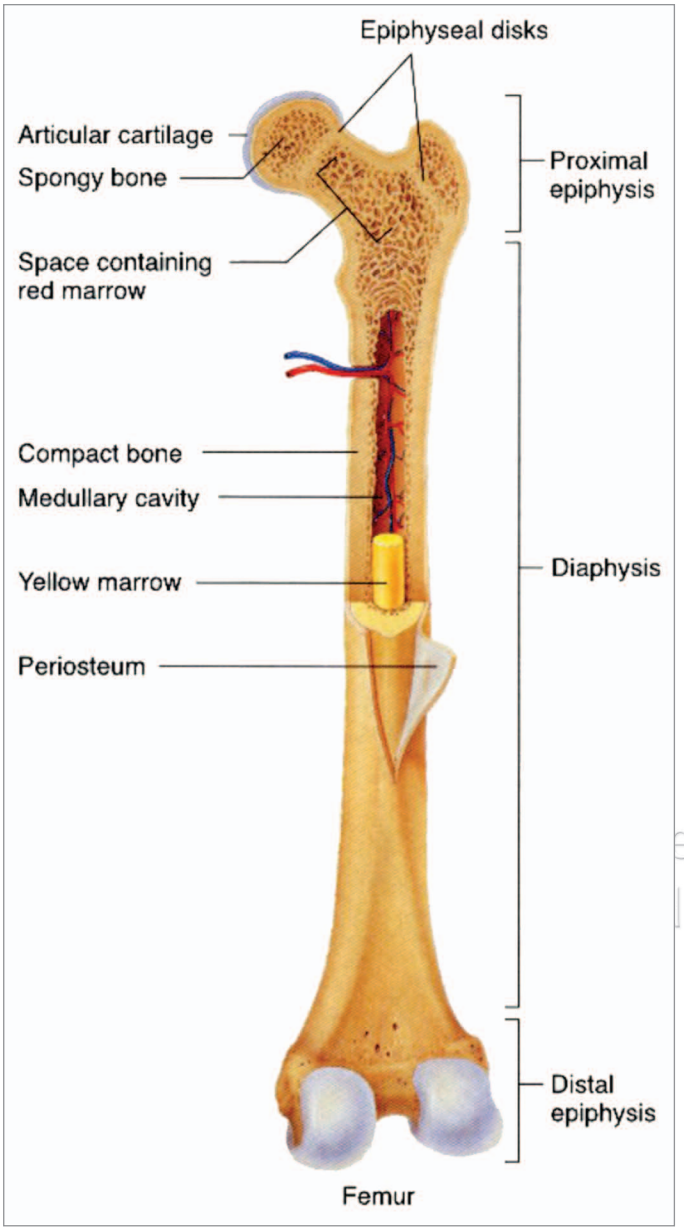

Figure 10. General structure of a mammalian bone. Other very good graphical sketches of the mammalian bone structure are available in references 88 and 508.

to 400 μm in trabecular bones. 55 to 70% of the pores in trabecular bones are interconnected. The porosity reduces the strength of bones but also reduces their weight.[26,32,84,85,101-104,525-529,542-546]

Bones can be either woven or lamellar. The fibers of woven bones are randomly aligned and, as a result, have a low strength. In contrast, lamellar bones have parallel fibers and are much stronger. Woven bones are put down rapidly during growth or repair,[547] but as growth continues, they are often replaced by lamellar bones. The replacement process is called "secondary bone formation" and described in details in reference 548. In addition, bones might be long, short, flat and irregular. The sizes and shapes of bones reflect their function. Namely, broad and flat bones, such as scapulae, anchor large muscle masses, flat skull bones protect the brain, ribs protect the lungs, pelvis protects other internal organs, short tubular bones in the digits of hands and feet provide specific grasping functions, hollow and thick-walled tubular bones, such as femur or radius, support weight and long bones enable locomotion.[549,550] Long bones are tubular in structure (e.g., the tibia). The central shaft of a long bone is called the diaphysis and has a medullar cavity filled with bone marrow (**Fig. 10**). Surrounding the medullar cavity is a thin layer of cancellous bone that also contains marrow. The extremities of the bone are called the epiphyses and are mostly cancellous bone covered by a relatively thin layer of compact bone. Short bones (e.g., finger bones) have a similar structure to long bones, except that they have no medullar cavity. Flat bones (e.g., the skull and ribs) consist of two layers of compact bone with a zone of cancellous bone sandwiched between them. Irregular bones (e.g., vertebrae) do not conform to any of the previous forms. Thus, bones are shaped in such a manner that strength is provided only where it is needed. All bones contain living cells embedded in a mineralized organic matrix that makes up the main bone material.[549-551] The structure of bones is most easily understood by differentiating between seven levels of organization, because bones exhibit a strongly hierarchical structure (**Fig. 11**).[103,104,416,509,524-529,535-540,542-545,553-558]

The mechanical properties of bones reconcile high stiffness and high elasticity in a manner that is not yet possible with synthetic materials.[554] Cortical bone specimens have been found to have tensile strength in the range of 79–151 MPa in longitudinal direction and 51–56 MPa in transversal direction. Bone's elasticity is also important for its function, giving the ability to the skeleton to withstand impact. Estimates of modulus of elasticity of bone samples are of the order of 17–20 GPa in the longitudinal direction and 6–13 GPa in the transversal direction.[559] The elastic properties of bone were successfully modeled at the level of mineralized collagen fibrils via step-by-step homogenization from the staggered arrangement of collagen molecules up to an array of parallel mineralized fibrils.[560] Recent investigations revealed that bone deformation was not homogeneous, but distributed between a tensile deformation of the fibrils and a shearing in the interfibrillar matrix between them.[561,562] Readers who are interested in further details are addressed to a good review on the effects of the microscopic and nano-scale structure on bone fragility.[563]

The smallest level of the bone hierarchy consists of the molecular components: water, biological apatite, collagen and other proteins.[509] The second smallest hierarchical level is formed by mineralization of collagen fibrils, which are of 80 to 100 nm thickness and a length of a few to tens of microns (**Fig. 11**). Thus, biocomposites of biological apatite and molecules of type I collagen are formed.[88,104,524,530,564] Some evidence for direct physical bonding between the collagen fibers and apatite crystals in bone has been found.[565] Eppell et al. used atomic force microscopy to measure the crystallites of mature cow bone.[566] They are always platelet-like (elongated along the crystallographic *c*-axis) and very thin,[87,567-569] with remarkably uniform thicknesses (determined in transmission electron microscopy) of 2–4 nm[i] (just a few unit cells thick, see **Table 2**). The nano-sized crystals of biological apatite exist in bones, not as discrete aggregates, but rather as a

continuous phase, which is indirectly evidenced by a very good strength of bones. This results in a very large surface area facing extracellular fluids, which is critically important for the rapid exchange of ions with these fluids. The nano-sized crystals of biological apatite are inserted in a nearly parallel way into the collagen fibrils, while the latter are formed by self-assembly[j] of collagen triple helices[104,524,552,570-572] using the self-organization mechanism.[573,574] Recent data from electron diffraction studies revealed that the mineral plates of biological apatite are not quite as ordered as previously assumed.[548] This imperfect arrangement of nearly parallel crystals has been supported by recent SAXS and transmission electron microscopy studies.[575]

The lowest level of hierarchical organization of bone has successfully been simulated by CDHA precipitation on peptide-amphiphile nanodimensional fibers.[574] However, apatite platelets nucleating on the surface of peptide tubules are not similar to the nanostructure of bone, and they are only an example of surface-induced nucleation (and not accurately characterized either), while the nanostructure of bone consists of intra-fibrillar platelets intercalated within the collagen fibrils. Olszta and Gower were the first to truly duplicate the bone nanostructure.[548] Unfortunately, the interface between collagen and crystals of biological apatite is still poorly understood; for the available details, the readers are referred to a review devoted to the structure and mechanical quality of the collagen/mineral nanodimensional biocomposite of bones.[564] There is still no clear idea why the crystals of biological apatite are platelet-shaped even though dahllite has hexagonal crystal symmetry.[103,104,525-529,535-540,542-546] One possible reason is that they grow via an OCP transition phase in which crystals are plate-shaped.[104] Another explanation involves the presence of citrates, which strongly bound to the (10$\bar{1}$0) surface of biological apatite because of space matching.[576,577] Therefore, the crystal growth in the (10$\bar{1}$0) direction becomes inhibited, while the citrate effect on other crystal surfaces of biological apatite appears to be very small, owing to poor space matching. Thus, after crystal growth, the (10$\bar{1}$0) crystal face becomes predominant, resulting in the plate-like morphology of biological apatite.[577]

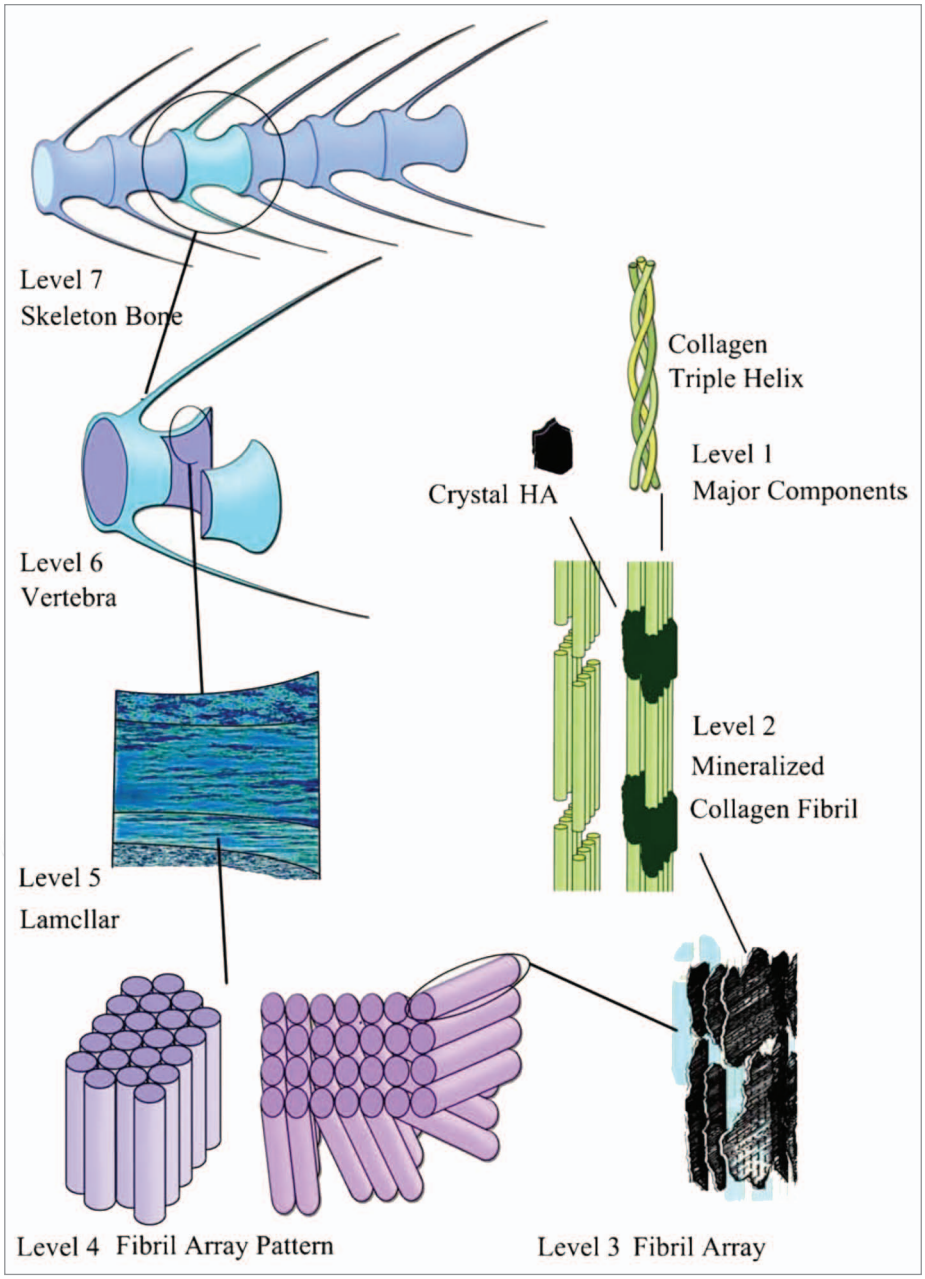

Figure 11. The seven hierarchical levels of organization of the zebrafish skeleton bone. Level 1: Isolated crystals and part of a collagen fibril with the triple helix structure. Level 2: Mineralized collagen fibrils. Level 3: The array of mineralized collagen fibrils with a cross-striation periodicity of nearly 60–70 nm. Level 4: Two fibril array patterns of organization as found in the zebrafish skeleton bone. Level 5: The lamellar structure in one vertebra. Level 6: A vertebra. Level 7: Skeleton bone. Reprinted from reference 552 with permission. Other good graphical sketches of the hierarchical structure of bones are available in references 104, 553 and 554.

The processes of bone formation (ossification) and growth are very complicated ones, and it is difficult to describe them without making a deep invasion into biology. It has been studied for decades,[547] but still there are missing points. Very briefly, ossification occurs through a direct or indirect process. In intramembranous (direct) ossification, direct transformation of mesenchymal cells from membranous tissue in osteoblasts occurs.[199,548,578] In endochondral (or indirect) ossification, bones appear and grow as

the result of calcification (or biomineralization) of connective tissues, mainly cartilage.[509,548] The ossified tissue is invaginated by blood vessels, which bring ions of calcium and orthophosphate to be deposited in the ossifying tissue. The biomineralization process is controlled to some extent by cells, and the organic matrices made by those cells facilitate the deposition of crystals.[551] There is an opinion, that, initially, the mineral crystals are formed in an environment rich in the so-called SIBLING (Small Integrin-Binding LIgand N-linked Glycoprotein) proteins. As bone crystals grow, there is greater association with proteins, such as osteocalcin, that regulate remodeling.[579] Thus, in vivo formation of hard tissues always occurs by mineral reinforcement of the previously formed network of soft tissues.[509,548-550,552]

Cartilage is composed of cells (chondrocytes and their precursor forms known as chondroblasts), fibers (collagen and elastic fibers) and extracellular matrix proteins (proteoglycans, which are a special class of heavily glycosylated glycoproteins).[580-582] The initial stage involves the synthesis and extracellular assembly of the collagen matrix framework of fibrils. At the second stage, the chondrocytes calcify the matrix before undergoing the programmed cell death (apoptosis). At this point, blood vessels penetrate this calcified matrix, bringing in osteoblasts (they are mononuclear cells primarily responsible for bone formation), which use the calcified cartilage matrix as a template to build bone, thus completing ossification.[580-582]

During ossification, the crystals of biological apatite grow with a specific crystalline orientation; the *c*-axes of the crystals are roughly parallel to the long axes of the collagen fibrils within which they are deposited.[104,105,509,510,520-522,525-527,530,548] Earlier, it was believed that this process occurred via epitaxial growth mechanism.[583] The same was suggested for dentine and enamel[584,585] (see Teeth section below) as well as for more primitive living organisms. For example, in the shell of the fossil marine animal *Lingula brachiopod unguis*, which consists of a biological apatite, the crystal *c*-axes are oriented parallel to the β-chitin fibrils.[441,586-589] Therefore, the orientation of biological apatite crystals parallel to the long axes of the organic framework could be a general feature of calcium orthophosphate biomineralization. However, the degree of biological apatite orientation appears to be a useful parameter to evaluate in vivo stress distribution, nano-scale microstructure and the related mechanical function, the regenerative process of the regenerated bone and to diagnose bone diseases such as osteoarthritis.[590,591] It is interesting to note that, contrary to what might be expected in accordance with possible processes of dissolution, formation and remineralization of hard tissues, no changes in phase composition of mineral part, crystal sizes (length, width and thickness) and arrangement of crystals on collagen fibers were detected in abnormal (osteoporotic) human bones compared with the normal ones.[592]

Some animals, such as newts, are able to regenerate amputated limbs. This is, of course, of high interest in regenerative medicine. Bone regeneration in the forelimbs of mature newts was studied by noninvasive X-ray microtomography to image regenerating limbs from 37 to 85 d. The missing limb skeletal elements were restored in a proximal-to-distal direction, which reiterated the developmental patterning program. However, in contrast to this proximal-distal sequence, the portion of the humerus distal to the amputation site was found to fail to ossify in synchrony with the regenerating radius and ulna. This finding suggests that the replacement of cartilage with mineralized bone close to the amputation site is delayed with respect to other regenerating skeletal elements.[593]

Unlike other mineralized tissues, bone continuously undergoes a remodeling process, as it is resorbed by specialized cells called osteoclasts and formed by another type of cells called osteoblasts (so called "bone lining cells") in a delicate equilibrium.[509,548,551,594,595] The purpose of remodeling is the release of calcium and the repair of micro-damaged bones from everyday stress. Osteoblasts are mononuclear cells primarily responsible for bone formation. They contain alkaline phosphatase, which enzymatically produce orthophosphate anions needed for the mineralization. In addition, there is one more type of cells, called osteocytes, that originate from osteoblasts, which have migrated into, become trapped and surrounded by bone matrix that they themselves produce.[509,525-528,548-551]

If osteoblasts are bone-forming cells, osteoclasts are multinuclear, macrophage-like cells that can be described as bone-destroying cells, because they mature and migrate to discrete bone surfaces.[551,594,595] Upon arrival, active enzymes, such as acid phosphatase, are secreted against the mineral substrate that causes dissolution. This process, called bone resorption, allows stored calcium to be released into systemic circulation and is an important process in regulating calcium balance.[594,595] The iteration of remodeling events at the cellular level is influential on shaping and sculpting the skeleton both during growth and afterwards. That is why mature bones always consist of a very complex mesh of bone patches, each of which has both a slightly different structure and a different age.[103-105,509-511,520-522,525-527,548] The interested readers are recommended a review on the interaction between biomaterials and osteoclasts.[596]

There is still no general agreement on the chemical mechanism of bone formation. It is clear that the inorganic part of bone consists of biological apatite, i.e., CDHA with ionic substitutions but without the detectable amounts of hydroxide.[597-601] However, the recent results of solid-state nuclear magnetic resonance on fresh-frozen and ground whole bones of several mammalian species revealed that the bone crystal OH^- was readily detectable; a rough estimate yielded an OH^- content of human cortical bone of about 20% of the amount expected in stoichiometric HA.[602] Various in vitro experiments on precipitation of CDHA and HA revealed that none of these compounds is directly precipitated from supersaturated aqueous solutions containing calcium and orthophosphate ions; some intermediate phases (precursors) are involved.[26,84,85,187-193,259-263] Depending on both the solution pH and crystallization conditions, three calcium orthophosphates (DCPD, ACP and OCP) have been discussed as possible precursors of CDHA precipitation in vitro. Due to this reason, the same calcium orthophosphates are suggested as possible precursors of biological apatite formation in vivo.

The transient nature of the precursor phase of bone, if it exists at all, makes it very difficult to detect, especially in vivo.[94]

However, in 1966 W.E. Brown proposed that OCP was the initial precipitate that then acted as a template upon which biological apatite nucleates.[186] This idea was extended in his further investigations.[603-606] The principal support for this concept derived from the following: (1) the close structural similarity of OCP and HA;[178,179] (2) formation of interlayered single crystals of OCP and HA (pseudomorphs of OCP); (3) the easier precipitation of OCP compared with HA; (4) the apparent plate- or lath-like habit of biological apatites that does not conform to hexagonal symmetry, but looks like a pseudomorph of triclinic OCP; (5) the presence of HPO_4^{2-} in bone mineral, particularly in newly formed bones.[511] Some evidences supporting this idea were found using high-resolution transmission electron microscopy: computer-simulated lattice images of the "central dark line" in mineralized tissues revealed that it consisted of OCP.[187-191] Recently, Raman spectroscopic indication for an OCP precursor phase was found during intra-membranous bone formation.[578] Other evidences of OCP to HA transformation, including a mechanistic model for the central dark line formation, might be found in literature.[607]

Simultaneously with Brown, the research group led by A.S. Posner proposed that ACP was the initially precipitated phase of bone and dentine mineral formation in vivo, thus explaining the non-stoichiometric Ca/P ratio in bones and teeth.[608-610] This conclusion was drawn from the following facts: (1) when calcium orthophosphates are prepared by rapid precipitation from aqueous solutions containing ions of calcium and orthophosphate at pH > 8.5, the initial solid phase is amorphous; (2) mature bone mineral is composed of a mixture of ion-substituted ACP and poorly crystallized ion-substituted CDHA and (3) early bone mineral has a lower crystallinity than mature bone, and the observed improvement in crystallinity with the age of the bone mineral is a result of a progressive reduction in the ACP content.[511,608-616] However, there are thermodynamic data proving that the transition of freshly precipitated ACP into CDHA involves intermediate formation of OCP.[617,618] Recently, the discovery of a stable amorphous calcium carbonate in sea urchin spines[619] reawakened the suggestion that a transient amorphous phase might also exist in bones.[548,620-624] Even more recently, evidence of an abundant ACP phase in the continuously forming fin bones of zebrafish was found.[625,626] The new bone mineral was found to be delivered and deposited as packages of nanodimensional spheres of ACP, which further transformed into platelets of crystalline apatite within the collagen matrix.[626]

Furthermore, to investigate how apatite crystals form inside collagen fibrils, researchers performed a time-resolved study starting from the earliest stages of mineral formation.[627] After 24 h of mineralization, calcium orthophosphate particles were found outside the fibril, associated with the overlap region, in close proximity to the gap zone. Cryogenic energy-dispersive X-ray spectroscopy confirmed that these precipitates were composed of calcium orthophosphate, while a low-dose selected-area electron diffraction technique showed a diffuse band characteristic of ACP. After 48 h, apatite crystals started to develop within a bed of ACP, and after 72 h, elongated electron-dense crystals were abundant within the fibril, in many cases, still embedded within a less dense matrix. A low-dose selected-area electron diffraction technique demonstrated that the mineral phase consisted of both ACP and oriented apatite, the latter identical to bone apatite.[627] This process is shown schematically in **Figure 12**.[628] The modern points of view on the bone formation mechanisms have been summarized in a recent excellent review in reference 548, where the interested readers are referred.

The maturation mechanism of bone minerals is not well-established, mainly because of the difficulty involved in the nanostructural analyses of bone minerals.[548,629] Only indirect evidence for the in vivo bone mineral maturation is available. For example, X-ray diffraction patterns of bones from animals of different ages show that the reflections become sharper with increasing age.[99,630] This effect is more pronounced in the crystallographic *a*-axis [(310) reflections] as compared with the *c*-axis [(002) reflections].[631,632] The most comprehensive report describing how normal human bone mineral changes in composition and crystal size as a function of age was based on X-ray diffraction analyses by Hanschin and Stern,[633] who examined 117 homogenized iliac crest biopsies from patients aged 0–95 y. They found that the bone mineral crystal size and perfection increased during the first 25–30 y and then decreased thereafter, slightly increasing in the oldest individuals. The same 117 homogenized biopsy samples were analyzed by wavelength-dispersive X-ray fluorescence to quantify the carbonate substitution in biological apatite as a function of age. Although the changes observed in carbonate substitution were relatively slight (at most 10%), there was a general increase from 0 to 90 y that is distinct from the absence of a change in crystallinity after age 30 in these samples.[553] In addition, other changes, like an increase of Ca^{2+} content and a decrease of HPO_4^{2-}, occur in bone mineral with age.[634-637] Both the crystal sizes and carbonate content were found to increase during aging in rats and cows.[635,636] The increase in carbonate content with age has also been reported in still other studies.[638-640] From a chemical point of view, these changes indicate to a slow transformation of poorly crystallized non-apatitic calcium orthophosphates into a better-crystallized ion-substituted carbonate-containing CDHA. While there are still many gaps in our knowledge, the researchers seem to be comfortable in stating that in all but the youngest bone and dentine, the only phase present is a highly disordered, highly substituted biological apatite.

In general, the biomineralization process (therefore, bone formation) can happen in two basic ways: either the mineral phase develops from the ambient environment, as it would from a supersaturated solution of the requisite ions, but requires the living system to nucleate and localize mineral deposition, or the mineral phase is developed under the direct regulatory control of the organism, so that the mineral deposits are not only localized but may be directed to form unique crystal habits not normally developed by a saturated solution of the requisite ions. In a very famous paper[641] and two extended elaborations,[103,642] the first type of biomineralization was called "biologically induced" mineralization and the second "(organic) matrix-mediated" biomineralization. In some papers, the former process is called "passive" and the latter one "active" biomineralization.[35] Briefly, an "active

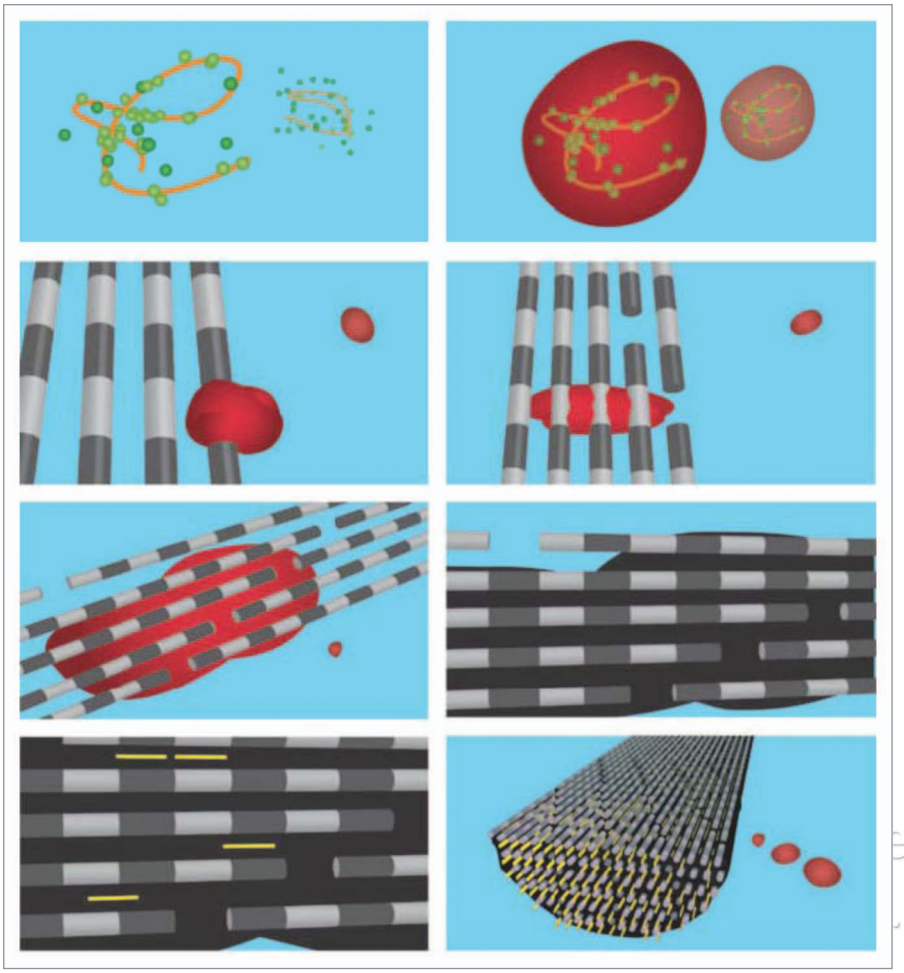

Figure 12. A schematic illustration of in vivo mineralization of a collagen fibril: top layer-calcium orthophosphate clusters (green) form complexes with biopolymers (orange line), forming stable mineral droplets; second top layer-mineral droplets bind to a distinct region on the collagen fibers and enter the fibril; second bottom layer-once inside the collagen, the mineral in a liquid state diffuses through the interior of the fibril and solidifies into a disordered phase of ACP (black); bottom layer-finally, directed by the collagen, ACP is transformed into oriented crystals of biological apatite (yellow). Reprinted from reference 628 with permission.

process" means the assembly of nano-sized crystals of calcium orthophosphate into bones due to an activity of the suitable cells (e.g., osteoblasts), i.e., within a matrix vesicle. Such structures have been discovered by transmission electron microscopy for bone and teeth formation.[643,644] A "passive" process does not require involvement of cells and means mineralization from supersaturated solutions with respect to the precipitation of biological apatite. In the latter case, thermodynamically, biomineralization might occur at any suitable nucleus. The collagen fibrils have a specific structure with a 67 nm periodicity and 35–40 nm gaps or holes between the ends of the collagen molecules, where bone mineral is incorporated in the mineralized fibril.[103,104,519,530,549,550] Such a nucleation within these holes would lead to discrete crystals with a size related to the nucleating cavity in the collagen fibril (**Fig. 11**). It was proposed that a temporary absence of the specific inhibitors might regulate the process of bone formation.[645-647]

To conclude the bone subject, let me briefly mention the practical application of bones. In the Stone Age, bones were used to manufacture art, weapons, needles, catchers, amulets, pendants, headdresses, etc. Nowadays, cut and polished bones from a variety of animals are sometimes used as a starting material for jewelry and other crafts. Ground cattle bone is occasionally used as a fertilizer. Furthermore, in medicine, bones are used for bone graft substitutes, e.g., allografts from cadavers.

Teeth. Teeth (singular, tooth) are dense structures found in the jaws of many vertebrates. They have various structures to allow them to fulfill their different purposes. The primary function of teeth is to tear and chew food. For carnivores, teeth are also a weapon. Therefore, teeth have to withstand a range of physical and chemical processes, including compressive forces (up to ~700 N), abrasion and chemical attack due to acidic foods or products of bacterial metabolism.[522] The roots of teeth are covered by gums. On the surface, teeth are covered by enamel up to ~2 mm thick at the cutting edges of the teeth, which helps to prevent cavities on the teeth. The biggest teeth of some gigantic animals (elephants, hippopotamuses, walruses, mammoths, narwhals, etc.) are known as tusks or ivory.

Similar to the various types of bones, there are various types of teeth. The shape of the teeth is related to the animal's food as well as its evolutionary descent. For example, plants are hard to digest, so herbivores have many molars for chewing. Carnivores need canines to kill and tear, and since meat is easy to digest, they can swallow without the need for molars to chew the food well. Thus, the following types of teeth are known: molars (used for grinding up food), carnassials (used for slicing food), premolars (small molars), canines (used for tearing apart food) and incisors (used for cutting food). While humans only have two sets of teeth, some animals have many more; for example, sharks grow a new set of teeth every two weeks. Some other animals grow just one set during the life, while teeth of rodents grow and wear away continually through the animal gnawing, maintaining constant length.[648,649]

Similar to bones, the inorganic part of teeth also consists of biological apatite.[650] The stability of the mineral composition of teeth also has a very long history; namely, calcium orthophosphates were found in fossil fish teeth.[651] Recent investigations of biological apatite from fossil human and animal teeth revealed its similarity to the modem biological apatite.[652]

The structure of teeth appears to be even more complicated than that of bones (see **Fig. 13**). Unlike bones, teeth consist of at

least two different materials: enamel, which is a hard outer layer consisting of calcium orthophosphates and dentine, which is a bone-like magnesium-rich tissue that forms the bulk of vertebrate teeth. In addition, there is a thin layer around the tooth roots called cementum. It is a thin layer of a bone-like calcified tissue that covers dentine at the roots of teeth and anchors them to the jaw.[653-656] Finally, there is the core, called pulp (commonly called "the nerve"); it is a remnant of the embryologic organ for tooth development and contains nerves and blood vessels necessary for tooth function (**Fig. 13**).[549,550,648,649] Both dentine and cementum are mineralized connective tissues with an organic matrix of collagenous proteins, while the inorganic component of them consists of biological apatite. As shown in **Table 2**, dentine, cementum and bone are quite similar, and for general purposes of material scientists, they can be regarded as being essentially the same material.[103-105,511,520-522,525-529,535-540,542-544,564,568-570,634,635] Thus, most statements made in the previous section for bones are also valid for dentine and cementum; however, unlike bones, both dentine and cementum lack vascularization.[k]

Dental enamel is the outermost layer of teeth. It is white and translucent, and its true color might be observed at the cutting edges of the teeth only. Enamel is highly mineralized and acellular, so it is not a living tissue. Nevertheless, it is sufficiently porous for diffusion and chemical reactions occur within its structure, particularly acidic dissolution (dental caries) and remineralization from saliva (possible healing of caries lesions). Enamel is the hardest substance in the body[541] and forms a solid, tough and wear-resistant surface for malaxation. In the mature state, it contains up to 98% inorganic phase (**Table 2**). The crystals of biological apatite of enamel are much larger, as evidenced by the higher crystallinity (reflecting greater crystal size and perfection) demonstrated in their X-ray diffraction patterns, than those of bone and dentine. Besides, enamel apatite has fewer ionic substitutions than bone or dentine mineral and more closely approximates the stoichiometric HA.[549] The organic phase of enamel does not contain collagen. Instead, enamel has two unique classes of proteins, called amelogenins and enamelins. While the role of these proteins is not yet fully understood, it is believed that both classes of proteins aid in enamel development by serving as a framework support.[648,649,657] The large amount of minerals in enamel accounts not only for its strength, but also for its brittleness. Dentine, which is less mineralized and less brittle, compensates for enamel and is necessary as a support.[648,649] Shark enameloid is an intermediate form bridging enamel and dentine. It has enamel-like crystals of fluoridated biological apatite associated with collagen fibrils.[83,103,436-440] Due to the presence of fluorides, biological apatite of shark enameloid shows both higher crystal sizes and a more regular hexagonal symmetry compared with non-fluoridated biological apatite of bones and teeth.[32] Similar correlation between the presence of fluorides and crystal dimensions was found for enamel.[658]

Like that for bones, seven levels of structural hierarchy have been also discovered in human enamel; moreover, the analysis of the enamel and bone hierarchical structure suggests similarities of the scale distribution at each level.[509,559,659] On the mesoscale level, there are three main structural components: a rod, an interrod and aprismatic enamel. Among them, the enamel rod

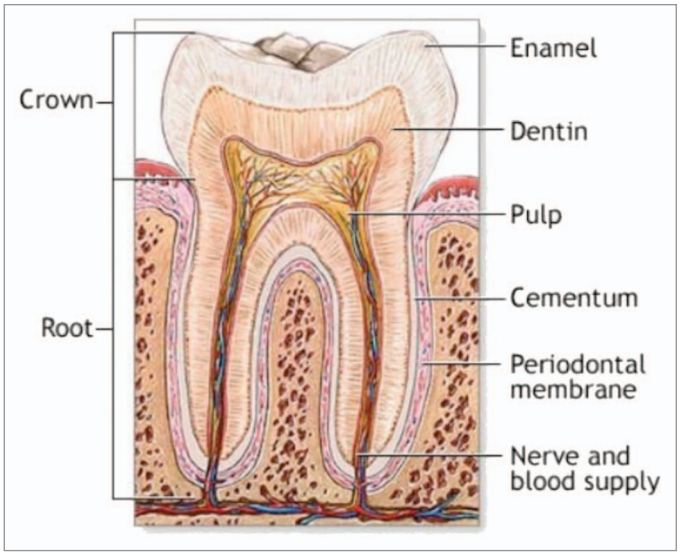

Figure 13. A schematic drawing of a tooth. Other very good graphical sketches of the mammalian tooth structure, including the hierarchical levels, are available in references 509 and 554.

(formerly called an enamel prism) is the basic unit of enamel. It is a tightly packed mass of biological apatite in an organized pattern. Each rod traverses uninterrupted through the thickness of enamel. They number 5 to 12 million rods per crown. The rods increase in diameter (4 up to 8 microns) as they flare outward from the dentine-enamel junction (DEJ). Needle-like enamel rods might be tens of microns long (up to 100 μm) but sometimes only 50 nm wide and 30 nm thick (**Fig. 14**).[648,649,660-667] They are quite different from the much smaller crystals of dentine and bone (**Table 2**), but all of them consist of biological apatite.[422,668,669] In cross-section, an enamel rod is best compared with a keyhole, with the top or head, oriented toward the crown of the tooth and the bottom or tail, oriented toward the root of the tooth.

The arrangement of the crystals of biological apatite within each enamel rod is highly complex. Enamel crystals in the head of the enamel rod are oriented parallel to the long axis of the rod. When found in the tail of the enamel rod, the crystals' orientation diverges slightly from the long axis.[648,649] The arrangement of the enamel rods is understood more clearly than their internal structure. Enamel rods are found in rows along the tooth (**Fig. 14**) and, within each row, the long axis of the enamel rod is generally perpendicular to the underlying dentine.[648,649,660-664] A recent AFM study indicated that CDHA crystals in enamel exhibited regular subdomains or subunits with distinct chemical properties related to topographical features and gave rise to patterned behavior in terms of the crystal surface itself and the manner in which it responded to low pH.[670]

The second structural component of the enamel matrix is the interrod (or interprismatic) enamel, which surrounds and packs between the rods. The difference between the rod and the interrod is the orientation of apatite crystals; the rod contains aligned crystallites, whereas the mineral in the interrod is less ordered. These structures coalesce to form the tough tissue of

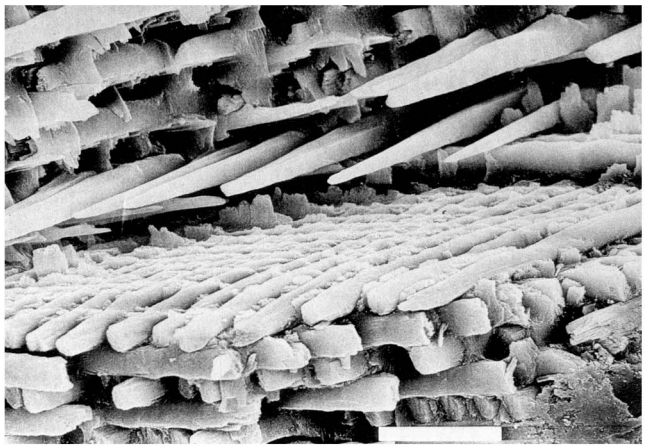

Figure 14. Scanning electron micrograph of the forming enamel of a continuously growing rat incisor showing ordered rods of calcium orthophosphates. Scale bar: 10 μm. Reprinted from reference 103 with permission.

enamel, which can withstand high forces and resist damage by crack deflection. The third structure, aprismatic enamel, refers to the structures containing apatite crystals that show no mesoscale or macroscale alignment.[509] Enamel is a selectively permeable membrane, allowing water and certain ions to pass via osmosis.[648,649]

The in vivo formation and development of teeth appears to be even more complicated when compared with the process described above for bone formation. The biological process by which teeth are formed from embryonic cells, grow and erupt into the mouth is very complex.[551] For human teeth enamel, dentine and cementum must all be developed during the appropriate stages of fetal development. Primary (baby) teeth start to form between the sixth and eighth weeks in utero, while the permanent teeth begin to form in the twentieth week in utero.[648,649] Recent data confirmed the necessity of calcium orthophosphates in the diet of pregnant and nursing mother to prevent early childhood dental caries.[671]

As teeth consist of at least two materials with different properties (enamel and dentine), the tooth bud (sometimes called "the tooth germ," which is an aggregation of cells that eventually forms a tooth) is organized into three parts: the enamel organ, the dental papilla and the dental follicle. The enamel organ is composed of at least four other groups of cells (for the biological details see refs. 648 and 649). Altogether, these groups of cells give rise to ameloblasts, which secrete enamel matrix proteins. The protein gel adjacent to ameloblasts is supersaturated with calcium orthophosphates, which leads to the precipitation of biological apatite. Similarly, the dental papilla contains cells that develop into odontoblasts, which are dentine-forming cells. The dental follicle gives rise to three important entities: cementoblasts, osteoblasts and fibroblasts. Cementoblasts form the cementum of a tooth.[654] Osteoblasts give rise to the alveolar bone around the roots of teeth (see bone formation above). Fibroblasts develop the periodontal ligaments that connect teeth to the alveolar bone through cementum.[549-551,648,649]

The first detectable crystals in enamel formation are flat thin ribbons[662-664] that were reported to be OCP,[542,672-674] β-$(Ca,Mg)_3(PO_4)_2$,[673] DCPD,[597,600] or ACP.[675] The formation process of enamel is different from that for bone or dentine: amelogenin being hydrophobic self-assembles into nano-sized spheres that guide the growth of the ribbon-like dental enamel crystals. During maturation of enamel, the mineral content increases from ~45 wt% initially up to ~98–99 wt%.[597,648,649] The enamel crystal rods widen and thicken by additional growth[597,600,676] with a simultaneous increase of the Ca/P molar ratio[676] and a decrease in carbonate content,[677-679] finally resulting in the most highly mineralized and hardest substance produced by vertebrates. It is interesting to note that in the radular teeth of chitons, ACP was found to be the first-formed calcium orthophosphate mineral, which, over a period of weeks, was transformed to dahllite.[680]

The crystal faces expressed in enamel are always (100) face and at the ends presumably (001),[681,682] which are the ones usually found in HA. The centers of enamel crystals contain a linear structure known as the "central dark line" (this line was also observed in bone and dentine), which consists of OCP.[187-191,607] As described above for bones, X-ray diffraction shows that the crystals of younger dentine are less crystalline than those of more mature dentine.[634] Therefore, maturation of dentine also means a slow transformation (re-crystallization?) of biological calcium orthophosphates from ion-substituted ACP to a better-crystallized ion-substituted CDHA.

The development of individual enamel and dentine crystals was studied by high-resolution transmission electron microscopy.[683-685] Both processes appear to be roughly comparable and were described in a four-step process. The first two steps include the initial nucleation and formation of nano-sized particles of biological apatite. They are followed by ribbon-like crystal formation, which, until recently, was considered the first step of biological crystal formation.[683-685] These complicated processes, starting with the heterogeneous nucleation of inorganic calcium orthophosphates on an organic extracellular matrix, are controlled in both tissues by the organic matrix and are under cellular control.[686] To complicate the process even further, regular and discrete domains of various charges or charge densities on the surface of apatite crystals derived from the maturation stage of enamel development were recently discovered by a combination of atomic and chemical force microscopy.[687] Binding of organic molecules (e.g., amelogenin[687]) at physiological solution pH appears to occur on the charged surface domains of apatite. The modern visions on dental tissue research have been reviewed recently in reference 688.

As teeth consist of several materials, there are mutual junctions among them. For example, a dentine-enamel junction (DEJ) is the interface between dentine and enamel. It is a remnant of the onset of enamel formation, because enamel grows outwards from this junction.[649,689,690] DEJ plays an important role in preventing crack propagation from enamel into dentine.[691] The major steps of enamel crystal growth at the junction have been described above, but the mechanism of the junction formation is still debatable. Some authors claim that enamel crystals grow epitaxially on the preexisting dentine crystals because of a high continuity between enamel and dentine crystals.[692-694] Others have shown

that enamel crystals are formed at a given distance from the dentine surface[672-674,695] and could either reach dentine crystals by a subsequent growth[696] or remain distant.[695,697] In addition, there are a cementum-enamel junction (CEJ),[698] which is quite similar to DEJ, and a cementum-dentine junction (CDJ).[653-655,699]

Enamel formation or amelogenesis, is a highly regulated process involving precise genetic control as well as protein-protein interactions, protein-mineral interactions and interactions involving the cell membrane. Much is still unknown about the interactions among proteins present in enamel matrix and the final crystalline phase of biological apatite.[509,700] At some point before a tooth erupts into the mouth, the ameloblasts are broken down. Consequently, enamel, unlike bones, has no way to regenerate itself using the process of "active mineralization" (see bone formation), because there is no biological process that repairs degraded or damaged enamel.[648,649] In addition, certain bacteria in the mouth feed on the remains of foods, especially sugars. They produce lactic acid, which dissolves the biological apatite of enamel in a process known as enamel demineralization that takes place below the critical pH of about 5.5. A similar process, called enamel erosion, occurs when a person consumes acid-containing (citric, lactic, phosphoric, etc.) soft drinks.[660,701-704] Evidence exist that there is a preferential loss of carbonates and Mg during acidic dissolution of mineral in dental caries. Luckily, saliva gradually neutralizes the acids that cause pH on teeth surface to rise above the critical pH. This might cause partial enamel remineralization, i.e., a return of the dissolved calcium orthophosphates to the enamel surface. Until recently, it was generally agreed, that if there was sufficient time between the intake of foods (generally, two to three hours) and if damage was very limited, teeth could repair themselves by the "passive mineralization" process.[705] Data on increased remineralization of tooth enamel by milk containing added casein phosphopeptide-ACP nanodimensional complexes[706] are in support of this hypothesis.

However, studies performed by using atomic force microscopy nano-indentation technique revealed that previously demineralized samples of dental enamel further exposed to remineralizing solutions did show a crystalline layer of calcium orthophosphates formed on their surface. Unfortunately, the re-precipitated deposits of calcium orthophosphates always consisted of loosely packed crystals and did not protect the underlying enamel from a subsequent acid attack. Furthermore, these surface deposits were completely removed by either a toothbrush or a short exposure to an erosive acidic solution.[660,707-709] In this context, it should be emphasized that the term "remineralization," which is often misused in the literature, should imply the process of mineral growth that goes hand in hand with a strengthening effect of the weakened enamel surface. Since no strengthening of an exposure to remineralizing solutions was observed, it might be considered that no "passive mineralization" was found (in spite of the real evidence of the re-precipitated surface deposits of calcium orthophosphates).[660,708,709]

An interesting hypothesis that nano-sized apatite crystallites occur in the oral cavity during extensive physiological wear of the hierarchical structured enamel surface due to dental abrasion and attrition has been published recently in reference 710. These nano-scaled apatite enamel crystallites might promote remineralization at the tooth surface. However, this idea should be verified experimentally. Thus, according to the current knowledge, the enamel self-repairing ability by a passive remineralization appears to be doubtful, while an active remineralization is impossible. Nevertheless, investigations in this field keep going.[210-212,711-722] For example, ACP-containing orthodontic biocomposite resins might reduce the enamel decalcification found in patients with poor oral hygiene.[722]

A content of fluoride added to either toothpaste or mouthwash lowers the solubility of calcium orthophosphates (by formation of FHA on the surface) and therefore improves the acid-resistance of dental enamel.[422,723-729] Furthermore, fluorides also reduce production of acids by bacteria in the mouth by reducing their ability to metabolize sugars. However, dental treatment by fluorides must be used with care, because an improper treatment results in formation of CaF_2 globules deposited on the enamel surface.[730]

To conclude the subject of teeth, let me briefly mention the practical application of teeth. Due to relatively small dimensions of normal teeth, only tusks and ivory of giant animals are used. For example, both the Greek and Roman civilizations used large quantities of ivory to make high value works of art, precious religious objects and decorative boxes for costly objects. Ivory was often used to form the whites of the eyes of statues. Prior to introduction of plastics, it was used for billiard balls, piano keys, buttons and ornamental items. The examples of modern carved ivory objects are small statuary, netsukes, jewelry, flatware handles and furniture inlays.

Antlers. Deer antlers (**Fig. 15**) are unique biological structures, since their growth rate is without parallel in vertebrates, and because they are the only bony appendages in mammals capable of complete regeneration. This allows for basic research in bone biology without the interference of surgical procedures and their adverse effects in animals where samples are obtained. In addition, antlers also allow for the gathering of a large amount of samples from different populations to assess nutritional and ecological effects on bone composition and structure.[732-735] They are costly sexual secondary characters of male deer and constitute 1 to 5% of their body weight.[736] Recent studies suggest that antler regeneration is a stem cell-based process, and that these stem cells are located in the pedicle periosteum.[731,737]

Antlers are not true horns; they are a simple extension of bone, so they have a matrix of biological apatite similar to that of mammalian bones.[738] Antlers are large and complex horn-like appendages of deer consisting of bony outgrowths from the head with no covering of keratin as found in true horns. Usually, they begin growing in March and reach maturity in August. In winter, antlers fall off; this is known as shedding. Similar to bones, antlers contain pores and can withstand applied stresses of over 300 MPa,[739-743] which is even higher than that of bones (**Table 2**). Therefore, antlers are occasionally considered an almost unbreakable bone.[534] Each antler grows from an attachment point on the skull called a pedicle. While an antler is growing, it is covered with highly vascular skin called velvet, which supplies oxygen and nutrients to the growing bone. Once the antler has achieved its proper size, the velvet starts to dry out,

Figure 15. Red deer stag at velvet shedding. The bare bone of the hard antlers is exposed. Reprinted from reference 731 with permission. A good cross-sectional image of a deer antler is available in reference 554.

cracks and breaks off, while the antler's bone dies. Fully developed antlers consist of dead bone only.[744-753] It was found that food processing cannot supply the mineral needs required for antler growth and, thus, male deer must temporary resorb calcium orthophosphate minerals from their own skeleton for antler growth.[754-756] Detailed studies revealed that daily food intake provided between 25 and 40% of calcium needed for antler mineralization, which resulted in a temporary skeleton demineralization.[755,756] Interestingly, though, antlers may act as large hearing aids; moose with antlers have far more sensitive hearing than moose without.[757]

Antlers are a good model to study bone biology, because they are accessible, shed after mating season and cast every year.[758] However, people seldom come across the antlers in the woods. Rabbits and rodents, such as mice and chipmunks, eat antlers (and bones of wild animals after they die) for calcium. Rodents and rabbits also gnaw bones and antlers to sharpen their incisors. Due to an extremely high growth rate, which can achieve 2–4 cm per day[744] combined with a very fast biomineralization, these unique appendages might be a well-suited animal model for studying the disturbances of bone formation induced by additives (e.g., by excess of fluoride).[746] Antler size and external characteristics were found to be influenced by nutrition, climatic variability and other factors. Thus, since antlers are periodically replaced, the analysis of naturally cast antlers offers the opportunity for a continuous and a noninvasive monitoring of the environmental pollution by these additives.[746] Recently, the first attempt to evaluate a potential use of deer antlers as a bone regeneration biomaterial was performed.[759]

To conclude this part, let me briefly mention the practical application of antlers. Associated with aristocracy, antlers have adorned European castles and hunting lodges for centuries. Today, furnishings and accessories made from antlers are featured in fine homes throughout the world and are a reflection of grace and elegance.

Pathological Calcification of Calcium Orthophosphates

In the body of mammals, osteoblasts and odontoblasts fix ions of calcium and orthophosphate and then precipitate biological apatite onto an organic matrix. This is the process of physiological biomineralization, which is restricted to specific sites in skeletal tissues, including growth plate cartilage, bones, teeth and antlers.[32,103] Normally, mammals are supposed to die with calcium orthophosphates located in bones and teeth (and antlers for male deer) only and nowhere else, because under normal conditions, soft tissues are not mineralized. Unfortunately, owing to aging, various diseases and certain pathological conditions, blood vessels, muscles, extracellular matrix of articular cartilaginous tissues of the joints and some internal organs are calcified as well. This process is called pathological calcification or ectopic (bio) mineralization and leads to morbidity and mortality.[32,103,760] In general, any type of abnormal accumulation of calcium orthophosphates in the wrong place are accounted for by a disruption of systemic defense mechanism against calcification.[761]

To the best of my knowledge, the first paper on a negative influence of unwanted depositions of calcium orthophosphates in the body was published as early as in 1911.[762] This finding was confirmed in later studies.[763,764] Unwanted depositions always lead to various diseases, for instance, soft tissue calcification (in damaged joints, blood vessels, dysfunctional areas in the brain, diseased organs, scleroderma, prostate stones),[220-222,765-770] kidney and urinary stones,[26,771-774] dental pulp stones and dental calculus,[182,183,185,219,775-778] salivary stones,[779] gall stones, pineal gland calcification, atherosclerotic arteries and veins,[86,780-783] coronary calcification,[784] cardiac skeleton, damaged cardiac valves,[785] calcification on artificial heart valves,[786-790] carpal tunnel,[791] cataracts,[792] malacoplakia, calcified menisci,[793,794] dermatomyositis[795,796] and still other diseases.[32] In addition, there is a metastatic calcification of nonosseous viable tissue occurring throughout the body,[797,798] but it primarily affects the interstitial tissue of the blood vessels, kidney, lungs and gastric mucosa. A metastatic calcification is defined as a deposition of calcium orthophosphates in previously normal tissue due to an abnormal biochemistry with disturbances in the calcium or phosphorus metabolism.[799] Common causes of the metastatic calcification include hyperparathyroidism, chronic renal disease, massive bone destruction in widespread bone metastases and increased intestinal calcium absorption. One author has mentioned "apatite diseases," which are characterized by the appearance of needle-like crystals comparable to those of bone apatite in the fibrous connective tissue.[800] All these cases are examples of calcinosis,[801-803] which might be described as a formation of calcium orthophosphate deposits in any soft tissue. In dentistry, a calculus or a tartar refers to a hardened plaque on the teeth formed by the presence of saliva, debris and minerals.[804] Its rough surface provides an ideal medium for bacterial growth, threatening the health of the gums and absorbing unaesthetic stains far more easily than natural teeth.[26]

Calcifying nanodimensional particles are the first calcium orthophosphate mineral containing particles isolated from

human blood, and they were detected in numerous pathologic calcification related diseases.[805] Interestingly, but contrary to the mineral phases of normal calcifications (bone, dentine, enamel, cementum, antlers), which consist of only one type of calcium orthophosphate (namely, biological apatite), the mineral phases of abnormal and/or pathological calcifications are found to occur as single or mixed phases of other types of calcium orthophosphates [ACP, DCPD, OCP, β-$(Ca,Mg)_3(PO_4)_2$] and/or other phosphate and non-phosphate compounds (e.g., magnesium orthophosphates, calcium pyrophosphates, calcium oxalates, etc.) in addition to or in place of biological apatite (**Table 4**).[26,28,32,85,142,219-222,298,775,806-810] However, precipitation of biological apatite in wrong places is also possible; this is so-called "HA deposition disease".[811-814]

Occurrence of non-apatite phases in the pathological calcifications may indicate that they were crystallized under the conditions different from homeostasis or crystallization of the apatite structures was inhibited and less stable phases crystallized instead, without further change to the more stable one. Furthermore, at the sites of pathological calcifications, the solution pH is often relatively low. Given that nucleation and crystal growth is not a highly regulated process in any pathological deposit, there is not likely just one fundamental formation mechanism for all possible calcification types. Furthermore, various bioorganic impurities in the local environment undoubtedly influence the crystallization process, resulting in a great variety of pathological deposits. Thus, it is a highly complex problem. In some cases, the chemical composition of an unwanted inorganic phase might depend on the age of the pathological calcification and its location. For example, DCPD is more frequently found in young (3 mo or younger) calculus; biological apatite is present in all ages of calculus, while β-$(Ca,Mg)_3(PO_4)_2$ occurs more frequently in sub-gingival calculus. In mature calculus, the relative abundance of OCP, β-$(Ca,Mg)_3(PO_4)_2$ and biological apatite also differ between the inner and outer layers.[85] It is interesting to note that the mineral phases of animal calculus (e.g., from dog) was found to consist of calcium carbonate and biological apatite, while human calculi do not contain calcium carbonate.[85,815]

The nucleation process is the main step in both normal and pathological calcifications. In vitro experiments conducted by Grases and Llobera[816] to simulate the formation of sedimentary urinary stones demonstrated that in the absence of organic matter, no calcium orthophosphates crystallized in cavities with scarce liquid renovation, but regular CDHA layers appeared on the wall around the cavity. Visible deposits of calcified organic materials (mixtures of organic matter and spherulites of CDHA) were formed when a glycoprotein (mucin) was present. In this case, the walls of the cavity as well as the glycoproteins had the capacity to act as heterogeneous nucleators of calcium orthophosphates. CDHA microcrystal nucleation on the surface of epithelial cells can be a critical step in the formation of kidney stones,[817] and identical mechanisms can be thought for unwanted calcifications in other soft tissues of the body, such as cardiac valves or vascular ducts. Monolayers of CDHA crystals can bind to epithelial cells. A large amount of kidney stones contains CDHA as the crystallization nuclei.

Table 4. Occurrence of calcium phosphates in biological systems (human)[85]

Calcium phosphate	Occurrence
biological apatite	enamel, dentine, bone, dental calculi, stones, urinary stones, soft-tissue deposits
OCP	dental calculi and urinary stones
DCPD	dental calculi, crystalluria, chrondrocalcinosis, in some carious lesions
β-$(Ca,Mg)_3(PO_4)_2$	dental calculi, salivary stones, arthritic cartilage, soft-tissue deposits
$Ca_2P_2O_7{\cdot}2H_2O$	pseudo-gout deposits in synovium fluids
ACP	heart calcifications in uremic patients, kidney stones

In general, formation of crystals in pathological mineralizations follows the same principles as normal calcifications.[818-820] Namely, local conditions for nucleation require a certain degree of local supersaturation induced by biochemical processes, which can be promoted by deficiency of inhibitors (like diphosphate, Mg^{2+} or even citrate ions) and/or the presence of matrix of a bioorganic material (such as cholesterol) or other crystals of different solids; those might act as heterogeneous nuclei. In addition, other regulators (activators and inhibitors) of physiological biomineralization have been identified and characterized.[818-825] What's more, the biological fluids (e.g., serum, saliva, synovial fluids) are normally supersaturated with respect to biological apatite precipitation;[26,85,103] therefore, in principle, calcification is thermodynamically feasible in any part of the body. However, normally this is not the case. Therefore, in the healthy body, the appropriate inhibitory mechanisms must be at work to prevent a superfluous calcification of soft tissues. These inhibition mechanisms are a hot research topic in molecular medicine, but this subject is beyond the scope of current review. The interested readers are referred, for example, to a very interesting review on molecular recognition at the protein/HA interface.[826] More to the point, molecular, endocrine and genetic mechanisms of arterial calcification have been reviewed in another paper.[827]

Very recently, an arachidic acid Langmuir monolayer system has been reported as a model for pathological mineralization of ion-substituted carbonated apatites from simulated body fluid.[828] The authors have demonstrated that the surface-induced formation of carbonated apatites starts with aggregation of pre-nucleation clusters of yet-unknown calcium orthophosphates, leading to nucleation of ACP before further development of oriented apatite crystals. This process is schematically shown in **Figure 16**.[628,828]

To conclude this part, it is worth remembering that calcium orthophosphates of biological origin are sparingly soluble in aqueous solutions. Removing them from the places of unwanted deposition would be the equivalent of bone demineralization; that is a challenge. Therefore, the majority of therapeutic approaches are directed at preventing the progression of pathological calcifications. Among them, a chelation therapy might be of some interest to chemists and materials researchers because

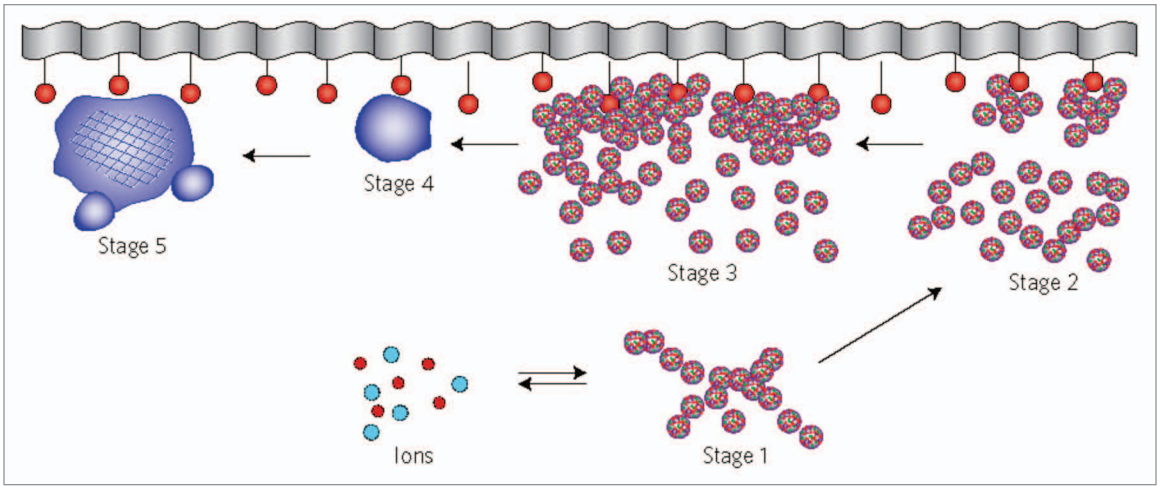

Figure 16. A schematic representation of the different stages of a surface-directed mineralization of calcium orthophosphates. In stage 1, aggregates of pre-nucleation clusters are in equilibrium with ions in solution. The clusters approach a surface with chemical functionality. In stage 2, pre-nucleation clusters aggregate near the surface, with loose aggregates still in solution. In stage 3, further aggregation causes densification near the surface. In stage 4, nucleation of spherical particles of ACP occurs at the surface only. In stage 5, crystallization occurs in the region of the ACP particles directed by the surface. Reprinted from references 628 and 828 with permission.

it deals with chemical processes.[829,830] The general principles of demineralization and decalcification [i.e., removing the mineral Ca-containing compounds (phosphates and carbonates) from the bioorganic matrix] have been extensively reviewed in references 831 and 832, where the interested readers are referred.

Biomimetic Crystallization of Calcium Orthophosphates

The term "biomimetics" ("the mimicry of life") was coined by an American inventor, engineer and biophysicist Otto Herbert Schmitt (1913–1998) in the 1950s. Biomimetics (also known as bionics, biognosis and/or biomimicry) might be defined as application of the methods and systems found in nature to the study, design and construction of new engineering systems, materials, chemical compounds and modern technology. Another definition describes biomimetics as a micro-structural process that mimics or inspires the biological mechanism, in part or as a whole.[833] This biological process generates highly ordered materials with a hybrid composition, a complex texture and ultrafine crystallites through a hierarchical self-assembly and begins by designing and synthesizing molecules that have an ability to self-assemble or self-organize spontaneously to higher order structures.

Historically, the biomimetic concept is very old (e.g., the Chinese wanted to make artificial silk ~3,000 y ago; Daedalus' wings were one early design failure), but the implementation is gathering momentum only recently. The first papers with the term "biomimetics" in the title were published in 1972.[834,835] In spite of the tremendous achievements of modern science and technology, nature's ability to assemble inorganic compounds into hard tissues (shells, spicules, teeth, bones, antlers, skeletons, etc.) is still not achievable by the synthetic procedures. This is not surprising; designs found in nature are the result of millions of years of evolution and competition for survival. The models that failed are fossils; those that survived are the success.[836] In the context of this review, biomimetics is considered the mimicking of natural manufacturing methods to generate artificial calcified tissues (grafts, implants, prostheses) that might be used as temporary or permanent replacements of the missing, lost, injured or damaged bones and teeth. It is important to notice that precipitation of calcium orthophosphates and calcium carbonates have been considered to correlate with bone formation at least since 1923.[837]

A key step in the biomimetic bone graft production is attributed to the crystal growth of apatite phase onto a collagen matrix. Therefore, the matter of choosing the correct experimental conditions and good mimicking solutions is of primary importance. The easiest way to perform the crystallization would be mixing of aqueous solutions containing the ions of calcium and orthophosphate.[26-28] Unfortunately, such a type of crystallization provides precipitates with properties (chemical composition, Ca/P ratio, crystallinity level, particle size distribution, etc.) far different from those of biological apatite. This can be explained by the following paramount differences between the in vivo biological and in vitro chemical crystallization conditions:[838] (1) In vitro crystallization normally occurs at permanently depleting concentrations of calcium and orthophosphate ions, while the concentrations of all ions and molecules are kept strictly constant during biological mineralization (the same is valid for the solution pH); (2) Chemical crystallization is a fast process (time scale of minutes to days), while the biological process is a slow one (time scale of weeks to years) and (3) Many inorganic, bioorganic, biological and polymeric compounds are present in biological liquids (blood plasma, serum, saliva). Each of these compounds might act as an inhibitor, promoter, nucleator or even as a template for the growth of biological apatite.[508] In addition, each of them somehow influences the crystallization kinetics and might be either incorporated into the solid structure or co-precipitated

with calcium orthophosphates. (4) Chemical crystallization is, by all means, a "passive" process, while the biological mineralization is strongly influenced by cells and occurs by the self-organization mechanisms.[551,573,574] Still there are no good ways to overcome this difference.

The first and the second differences might be overcome by using the appropriate crystallization techniques. The details are available in reference 838, but, briefly, the first problem might be overcome by either a continuous flow of a supersaturated solution[839,840] or using a constant-composition (CC) technique.[193,841,842] The second difference might be surpassed by a restrained diffusion of calcium and orthophosphate ions from the opposite directions in, for example, a double-diffusion (DD) crystallization device or in viscous gels.[420-422,424,425,843-846] The CC and DD techniques have been combined into a single constant-composition double-diffusion (CCDD) device, which currently seems to be the most advanced experimental tool to perform biomimetic crystallization.[838,847-851] However, in no case should the CCDD device be considered the final construction; it still has much room for further improvement, e.g., by upgrading the design of the crystallization chamber.[852] Other constructions, e.g., to study calcification of biological heart valve prostheses,[853] are also possible. In addition, one should keep in mind that the potential of the standard CC technique has not reached its limit yet; for example, recently a good mimicking of the self-organized microstructure of tooth enamel has been achieved.[854]

The third major difference between the in vivo and in vitro crystallization conditions might be overcome by using the appropriate crystallization solutions.[838] The presence of calcium and orthophosphate ions in some biological fluids has been known, at least, since 1921.[855,856] Therefore, the best way would be to perform experiments using natural liquids (blood serum, saliva, lymph, etc.), but this is not easy due to great variability of the chemical and biochemical compositions of natural liquids and problems with their collection and storage. As stated before, using supersaturated aqueous solutions containing only the ions of calcium and orthophosphate appears to be unable to mimic the crystallization of biological apatite; therefore, more advanced solutions have been elaborated. To the best of my knowledge, Hanks' balanced salt solution (HBSS) [857] was the first successful simulating medium containing the ions of calcium and orthophosphate together with other inorganic ions and glucose. HBSS is commercially available and still used in biomimetic experiments;[858-860] its chemical composition might be taken, e.g., from references 861 and 862. Other popular physiological solutions include α-modified Eagle's[l] medium (α-MEM) and its variation, Dulbecco's[m] modified Eagle's medium (DMEM), which contain numerous bioorganic (alanine, aspartic acid, glycine, biotin, vitamin C, folic acid, riboflavin) and inorganic ($CaCl_2$, KCl, NaCl, NaH_2PO_4) components,[863-867] phosphate buffered saline (PBS) that contains only inorganic ($CaCl_2$, $MgCl_2$, KCl, KH_2PO_4, NaCl, NaH_2PO_4) components.[868,869] Furthermore, artificial saliva,[870-872] synthetic urine[816,873] and simulated milk ultrafiltrate (SMUF) [874-877] solutions are available. They contain both bioorganic (e.g., xantan gum or sodium carboxymethylcellulose, sorbitol, etc.) and inorganic (e.g., $CaCl_2$, $MgCl_2$, KCl, KH_2PO_4, NaCl, KH_2PO_4) compounds. Additional media used for mineralization studies are listed in Table 3 of reference 551. All these simulating solutions are commercially available.

However, the most popular biomimetic solution is a protein-free acellular simulated body fluid (SBF). It was introduced by Kokubo et al.[878] and is occasionally called Kokubo's SBF. It is a metastable aqueous solution with pH ~7.40, supersaturated with respect to the precipitation of OCP, β-TCP, CDHA and HA,[879] containing only inorganic ions in concentrations nearly equal to those in human blood plasma. However, the standard SBF formulation, first, contains the tris/HCl buffer, and second, the concentration of hydrogencarbonate (4.2 mM) is only a fraction of that in blood plasma (27 mM).[878] The problem of a low concentration of hydrogencarbonate ions has been overcome by first introducing a "synthetic body fluid"[880-882] and later a revised SBF (rSBF).[883,884] Due to the chemical similarity with human blood plasma, rSBF currently seems to be the best simulating solution. However, it contains Hepes buffer, loses CO_2 in open vessels and does not contain any organic and/or biological molecules.[883,884] Other types of SBF are also available,[885-888] and the interested readers are referred to a leading opinion co-authored by the SBF inventor,[889] where the entire history and the preparation techniques of various SBF formulations are well-described. Recently, another leading opinion on the suitability of SBF for the in vitro bioactivity tests was published.[890] The authors demonstrated that (1) there is presently no enough scientific data to support the SBF suitability and (2) even though bioactivity tests with SBFs are valid, the way the tests are generally conducted leaves room for further improvements. Furthermore, the preparation protocol of SBF solutions was reconsidered, and a new procedure was suggested to improve the reproducibility of bioactivity tests.[890] The application of SBF for the surface mineralization of various materials in vitro has been reviewed in reference 891, while the theoretical analysis of calcium orthophosphate precipitation (the driving force and the nucleation rate based on the classical crystallization theory) in SBF is also available.[879] It is important to note that nanometer-sized prenucleation clusters in SBF solutions have been discovered;[828] those clusters are believed to be the initial building blocks of crystallized calcium orthophosphates (e.g., CDHA[280]), while the crystallization process itself occurs via intermediate formation of ACP (**Fig. 16**).

Further attempts to improve the biomimetic properties of SBF and rSBF have been performed.[889,890] Efforts were made to replace artificial buffers (tris/HCl, Hepes) while simultaneous;y increasing the concentration of hydrogencarbonates for SBF[892-894] or avoiding losses of CO_2 from open vessels for rSBF[838,847-851] by means of permanent bubbling of gaseous CO_2 through the solutions. Addition of the most important organic and biological compounds, like glucose,[849] albumin,[847,894] lactates[895] and collagen[896] is another direction for improving biomimetic properties of various types of SBF. Once a cow milk-based rSBF was prepared.[897] Further improvements of all biomimetic solutions are to be made in future. Occasionally, condensed solutions of SBF (e.g., 1.5-fold, 2-fold,[896,898,899] 5-fold[900,901] and even 10-fold[902]) are used to accelerate precipitation and increase the amount of precipitates. However, whenever possible this should

be avoided, because the application of condensed solutions of SBF leads to changes in the chemical composition of the precipitates; namely, the concentration of carbonates increases, while the concentration of orthophosphates decreases.[903]

To conclude this part, one should note on difficulties in mimicking the calcification process that occurs in bones and teeth. A reasonable mechanism of the induction of CDHA nucleation and crystallization by carboxylate groups on the bioorganic matrices looks as this. At first, calcium and orthophosphate ions are combined with carboxylate groups. By using these as seeds, CDHA crystals then grow to generate interfaces that contain the most stable structure of the {100} faces. Such a crystallization mechanism explains why the *c*-axes of biological apatite are parallel to the organic matrices. Collagen fibers can be regarded as axis-like organic matrices: when CDHA is formed on the surface of collagen fibers parallel to the *c*-axes, the *c*-axes are oriented parallel to the fiber orientation.[904] A step further would be to perform the precipitation from the simulating solutions on templates of biomineralization proteins for the control of crystal organization and properties. For example, there are successful attempts to crystallize calcium orthophosphates on collagen in order to obtain bone-like composites.[545,905-914] Such collagen/calcium orthophosphate biocomposites are currently under investigation for clinical use. Other popular biomimetic matrixes to perform calcium orthophosphate crystallization comprise gelatin,[420-425,915-917] chitosan,[915,918,919] organic polyelectrolytes,[920-923] metals and alloys,[924-930] polymers,[931] cellulose,[932] self-assembled monolayers[933] and many other materials. Such biomimetically prepared calcium orthophosphate precipitates are occasionally called "organoapatites."[509,934]

Conclusions and Outlook

By the end of the 20th century, it became clear that calcium orthophosphate biomaterials and bioceramics by themselves could not give a complete response to the clinical needs for artificial implants. Biomaterials with more demanding properties were required. Namely, in 1998, Prof. Larry L. Hench published a forecast for the future of biomaterials development,[935] where he noted that available that time bioactive materials (calcium orthophosphates, bioactive glasses and glass ceramics) had already improved prostheses lifetime, but, unfortunately, any type of prosthesis had mechanical limitations. As a solution, he proposed that biomaterial researchers would need to focus on tissue regeneration instead of tissue replacement. A working hypothesis was announced: "Long-term survivability of prosthesis will be increased by the use of biomaterials that enhance the regeneration of natural tissues."[935] One path to follow is the regeneration of bone using calcium orthophosphate scaffolds that mimic the structure of biological apatite, bond to bone, and in some cases, activate the genes within bone cells to stimulate new bone growth.[936-938] Thus, more than 10 y ago Prof. Hench predicted a rapid development of tissue engineering field, where calcium orthophosphates play an auxiliary role. The history has shown that tissue engineering, indeed, is a very rapidly developed field of science and research.[939]

However, what can be said about calcium orthophosphates themselves? The major questions on chemistry, crystallization, ion-substitution, crystallography, thermodynamics and phase relationships for the chemically pure calcium orthophosphates were answered in the 20th century. Some important topics for DCPD and CDHA have been additionally investigated in the field of self-setting calcium orthophosphate formulations. Conversely, calcium orthophosphates of biological origin, including the control of their morphology and interaction of calcium orthophosphate bioceramics with various bioorganic compounds, are not well-investigated yet. The same is valid for the nanocrystalline and amorphous samples of calcium orthophosphates. Small amounts of bone-like apatite might be easily prepared by crystallization from SBF and rSBF, but what can be said about larger quantities? A standard method of increasing the concentration causes chemical changes in the precipitates.[903] After a necessary technology is developed, one will have to think of scaffold preparation from this material, keeping in mind that any thermal treatment would destroy this material. A spark plasma sintering approach based on the use of pulsed current and enabling very fast heating and cooling rates seemed to be the first hint of achieving this goal.[940] However, a rapid development of the self-setting calcium orthophosphate formulations, which can be easily doped by the necessary chemical elements, seems to be a better solution to this problem. Furthermore, the existence of OA remains to be questionable, and the bioactivity mechanism of calcium orthophosphates requires better understanding.

To date, although calcium orthophosphate biomaterials and bioceramics have been extensively studied for over 50 y, their ability to trigger bone formation is still incomparable with other biomaterials. Naturally, the biomaterials field is shifting toward biologically active systems in order to improve their performance and to expand their use.[941] Because of this, tissue engineering is the strongest direction of current research, which, in the case of calcium orthophosphates, means fabrication of proper substrates and/or scaffolds to carry cells, hormones and biochemical factors to be further used in surgery and medicine. Presumably, a synthesis of various types of calcium orthophosphate-based biocomposites and hybrid biomaterials occupies the second important place. For example, even composites with carbon nanotubes already exist![942-944] The third important place is occupied by investigations devoted to the synthesis and characterization of various nano-sized particles and nanodimensional crystals of calcium orthophosphates as well as by synthesis of calcium orthophosphates with controlled particle geometry.[508] In general, the geometry of crystal phases can be varied by controlling the precipitation conditions, such as temperature, solution pH, concentration of the reagents, hydrodynamics, presence of various admixtures, inhibitors or promoters, ultrasonication, etc. All these approaches might be useful in preparation of calcium orthophosphate fibers, whiskers, hollow microspheres, etc. In addition, a great attention is paid to manufacturing of the self-setting calcium orthophosphate formulations and multiphase[n] mixtures mimicking as closely as possible the mineral component of biological apatite. Work

looking into ecological methods of synthesis of calcium orthophosphates might be of great importance as well.[945] A deeper study of the fascinating growth rate of deer antlers and the ability of some animals, such as newts, to regenerate amputated limbs might provide new and unexpected approaches to the bone-healing concept, and this too will be important for further development of both biomimetics and biomineralization fields. Unfortunately, no currently available grafting biomaterials can substitute the bones' mechanical function, illustrating the yet-unmet medical need that would entirely substitute and regenerate a damaged tissue or organ. In a close future, the foreseeable application of calcium orthophosphates will be as a component of the third generation biomaterials,[935,938] where they will support cells and/or other biologically active substances (peptides, growth factors, hormones, drugs, etc.) to guide regeneration of hard tissues.[946-956]

To finalize this review, one should note that, in spite of a long history of calcium orthophosphate research and many important discoveries, many gaps still remain in our knowledge to be investigated in future.

Notes

[a] As a mineral species, apatite was first recognized by the father of German geology Abraham Gottlob Werner (1750–1817) in 1786 and named by him from the ancient Greek απατάω (apatao)—"to mislead" or "to deceive," because it had previously been mistaken for other minerals, such as beryl, tourmaline, chrysolite, amethyst, fluorite, etc. Currently, apatite is the name for a group of minerals with the same crystallographic structure and does not indicate one chemical composition. That is why, the term "calcium apatite" is used in this review.

[b] There are reports that dahllite belongs to the francolite group. Natural dahllite might be a rock-forming mineral.[969] For example, it was found in some phosphorite concretions of Podolia.[970,971] In addition, it was found in both massive and accretionary crustal phosphorites.[49]

[c] Collagens are fibrous, insoluble proteins found in the connective tissues, including skin, bone, ligaments and cartilage.

[d] Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application.[957] For further details on this topic, the interested readers are referred to reference 958.

[e] In 1941, to honor Mr. Herbert Percy Whitlock (1868–1948), an American mineralogist, the curator of the American Museum of Natural History, New York City, New York, USA, the term whitlockite was coined as a synonym for β-TCP identified by its X-ray diffraction pattern in phosphate rocks.[775,959,960] Therefore, strictly speaking, β-TCMP should be called as a "magnesium whitlokite". Its solubility is less than that of β-TCP.[961] An iron-containing whitlockite with chemical formula $Ca_9(Mg,Fe^{2+})(PO_4)_6(PO_3,OH)$ exists in nature: is a relatively rare natural mineral but is found in granitic pegmatite and has also been found in meteorites. It can form small, but distinct and well-formed crystals.[962,963]

[f] In some research papers, CDHA is defined as "precipitated HA."[964-966]

[g] It is worth noting that hydroxylapatite would be a more accurate description (perhaps, hydroxideapatite would be even better because it relates to calcium hydroxide) while by both the medical and material communities it is usually called as hydroxyapatite.

[h] The amount of fluorides on the very surface of dental enamel might be increased by using fluoride-containing toothpastes and mouthwashes.[723-726] Fluoride-containing toothpastes and mouthwashes are widely used in practice due to the well-known anti-cariogenic effect of fluorides that is related to the solubility decreasing.[727,728]

[i] Due to the nanoscopic dimensions, biological apatite is occasionally called "nano-apatite."[104]

[j] Self-assembling is the autonomous organization of components into patterns or structures without human intervention. It is considered that self-assembling processes are common throughout nature and technology.[967]

[k] Strictly speaking, there are some differences among these biological materials. For example, the hardness of live dentine is less than that of enamel but is greater than that of bone or cementum.[653] When pulp of the tooth dies or is removed by a dentist, the properties of dentine change: it becomes brittle, liable to fracture and looses a reparative capability.

[l] Named after Harry Eagle (1905–1992), an American physician and pathologist.

[m] Named after Renato Dulbecco (born February 22, 1914), an Italian-born US virologist, who shared the 1975 Nobel Prize in Physiology or Medicine for his work on reverse transcriptase.

[n] For multiphase compositions of various calcium orthophosphates, the problem of accurate phase quantification often arises. The problem is usually solved by the Rietveld refinement and the readers are referred to a recent paper on this subject.[968]

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