

Mechanism of the Solid-State Transformation of a Calcium-Deficient Hydroxyapatite (CDHA) into Biphasic Calcium Phosphate (BCP) at Elevated Temperatures

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Three types of poorly crystallized calcium-deficient hydroxyapatites (CDHA) with Ca/P molar ratios 1.50, 1.58, and 1.67 were prepared from $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ and KOH. These were sintered at 1050 °C for 4 h. Well-crystallized β -tricalcium phosphate (β -TCP), biphasic calcium phosphate (BCP), and stoichiometric hydroxyapatite (HA) were produced, respectively. The sintered and unsintered calcium phosphates were studied by X-ray diffraction (XRD) and Fourier transform infrared (FTIR) spectroscopy. In addition, Ca/P molar ratios were determined by a chemical analysis. Thermogravimetric analysis (TGA) revealed a loss of water for the period of sintering. On the basis of the experimental data, a structure of BCP was suggested. After applying the numerical values of ionic (OH^- , Ca^{2+} , and PO_4^{3-}) diffusion coefficients at 1000 °C, the solid-state transformation mechanism of CDHA into BCP was proposed.

1. Introduction

Due to the chemical similarity to human bones^{1,2} and good resorbability,^{3–8} biphasic calcium phosphate (BCP) consisting of hydroxyapatite (HA, chemical formula $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) and the β -form of tricalcium phosphate (β -TCP, chemical formula $\text{Ca}_3(\text{PO}_4)_2$) is widely used in medicine as a bone graft substitute. Normally, BCP is produced by sintering of a nonstoichiometric calcium-deficient hydroxyapatite (CDHA, chemical formula $\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}$, where $0 < x < 1$) at the temperatures 1000–1200 °C for the period 1–4 h.^{9,10} For the period of sintering, CDHA is transformed into BCP, but the mechanism of this process remains unclear.

At present, the structure of BCP also remains unclear. The X-ray diffraction (XRD) pattern of BCP is similar to the pattern of a mechanical mixture of HA and β -TCP

powders (Figure 1); BCP might be considered as a mixture of these compounds. However, two phases in BCP are completely undistinguishable: nothing has ever been reported on the success on their mechanical separation from each other. Surface investigations of BCP with a scanning electron microscope under the highest possible magnifications (up to $\times 300\,000$) were unable to detect anything that could be interpreted as two different phases. The latter means either that BCP is a solid solution of HA and β -TCP or that BCP really consists of two different phases but with very small dimensions of crystals. The first case contradicts the results of XRD. According to the literature on XRD,¹¹ the very small crystallite sizes (less than 20–30 nm) and solid solutions result in diffraction peaks broadening (the smaller the crystallites, the broader the diffraction peaks). A mosaic structure is also well-known: usually the solids consist of crystallites (other names: subgrains, blocks) 50–100 nm in size.¹²

All the above is valid for apatites. For example, crystallites of biological HA of 130 nm \times 30 nm in human enamel showed well-defined diffraction peaks, while those of 20 nm \times 4 nm in dentine and 25 nm \times 3 nm in bone showed very broad diffraction peaks (ref 1, pp 110 and 113). X-ray coherent scattering blocks of 50–60 nm size were discovered in natural fluorapatite, and the diffraction peaks were rather broad.¹³ XRD study of the chemically pure HA revealed that the crystallites of 40–60 nm size gave rise to diffraction peak broaden-

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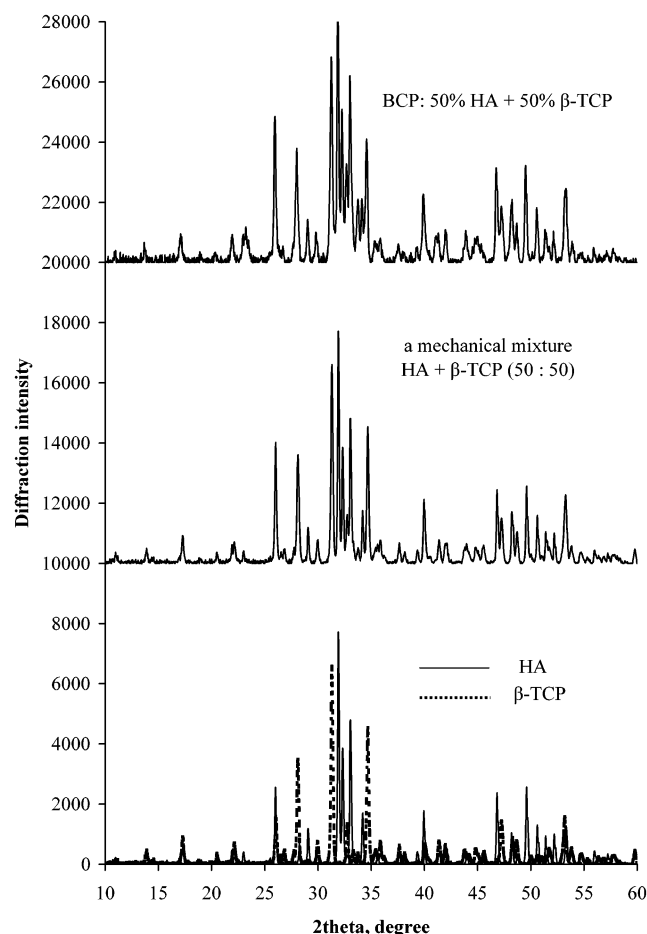


Figure 1. XRD patterns: bottom, the patterns of pure HA and β -TCP printed together; middle, mathematical summation of HA and β -TCP patterns; upper, BCP (50% HA + 50% β -TCP).

ing, but those of 75, 100, and, especially, 130 nm size had very sharp diffraction peaks.^{14,15} Even broader diffraction peaks were found for crystallites of HA having 20–50 nm sizes.¹⁶ On the other hand, the sizes of crystallites in chemically pure HA sintered at 1200 °C were determined to be 102 ± 2 nm and the diffraction peaks were sharp.¹⁷ The detailed measurements of crystallite dimensions in synthetic HA, three types of bone, and the commercial biomaterial Endobone (Merck Biomaterial, Darmstadt, Germany) were performed by synchrotron XRD.¹⁸ The authors found that the average crystallite sizes of bones were within 8–23 nm (depending on the sample and the diffraction line index), giving rise to the very broad diffraction peaks. Similar measurements for synthetic HA revealed the average crystallite size within 22–34 nm and broad diffraction peaks. Only Endobone (consisting of 100% HA) had dimensions of crystallites larger than 63–65 nm and sharp diffraction peaks as the result.¹⁸

Therefore, according to the available references, the well-defined sharp diffraction peaks of HA and β -TCP found in BCP (Figure 1, upper spectrum) point out that both phases consist of crystallites (blocks, subgrains) at least 60 nm in all dimensions. In the current paper, we verify this suggestion and postulate reasonable transformation mechanisms of poorly crystallized CDHA into BCP at elevated temperatures.

2. Materials and Methods

For BCP preparation, we used the experimental procedure described in refs 9, 10, 17, 19, and 20. Chemically pure (*pro analysi* quality) dicalcium phosphate dihydrate (DCPD, chemical formula $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$), KOH (both purchased from Merck), and distilled water were used as the initial reagents. Unlike the previous authors who used NaOH and found up to 1 wt % of Na in the final products (CDHA, HA, BCP, and β -TCP),^{9,10} we used KOH. In the absence of carbonates, ions of potassium were found to not incorporate into the crystal lattice of HA.^{21,22}

The preparation of CDHA involved formulation of an aqueous suspension of DCPD (100 g L^{-1}) followed by the addition of KOH (36 g of KOH solid per 1 L of suspension). The suspension was kept boiling and stirring for 4 h under the permanent flow of nitrogen followed by cooling, filtration, washing the precipitate by water, and drying (24 h at 80 °C). The quality of washing was controlled by phenolphthalein: washing was considered complete when the indicator did not change color. After drying, the powder of CDHA was sintered for 4 h at the temperature 1050 °C followed by cooling until ambient temperature. Further details on BCP preparation can be found in the original references.^{9,10,17,19,20}

Both stoichiometric HA and β -TCP were prepared in a similar way. The only difference was in the amounts of solid KOH. To prepare HA, hydrolysis of DCPD should be performed in excess KOH, while for preparation of β -TCP the amount of KOH should be less. Therefore, the following amounts of solid KOH per 1 L of aqueous suspension of DCPD (100 g/L) were used: 45 g of KOH to prepare HA and 31 g of KOH to prepare β -TCP. The powders were then filtrated, washed, dried, and sintered as described above.

The chemical and structural compositions of CDHA, BCP, HA, and β -TCP were studied by FTIR (1720X, Perkin-Elmer) in the range 400–4000 cm^{-1} (3–5 mg of the solid were mixed with 300 mg of spectral-grade KBr followed by pellets' pressing at 12 000 kg/cm^2); XRD (Diffract 5000, Kristalloflex, Siemens) within a 2θ value of 10–60° (Cu K α radiation was used); thermogravimetric analysis (TGA) (TGS 2, System 4, Perkin-Elmer) in the temperature range 25–1050 °C (heating rate 3°/min; in a permanent flow of pure argon), and chemical analysis. For the chemical analysis, 0.2 g of each calcium phosphate was dissolved in 10 mL of 0.5 M HCl followed by the quantitative determination of calcium (titration with sodium ethylenediaminetetraacetate; EDTA), potassium (inductively coupled plasma spectroscopy), and phosphate (photometric measurements with the molybdate yellow complex) ions.

3. Results

The results of XRD measurements of CDHA, HA, β -TCP, and BCP (50% HA + 50% β -TCP) before and after the sintering are shown in Figures 2 and 3, respectively. As seen in the figures, sintering results in

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Table 1. TGA Results on Heating of Three Types of CDHA from 25 to 1050 °C

calcium phosphate	total wt ost, %	temp of the TGA peaks ^a
CDHA giving rise to 100% HA	2.6	100(s), 390(s), 680(w)
CDHA giving rise to BCP	8.1	100(s), 370(s), 650(w), 780(s)
CDHA giving rise to 100% β -TCP	3.1	100(s), 380(s), 670(w), 850(w)

^a (s), strong TGA peaks; (w), weak TGA peaks.

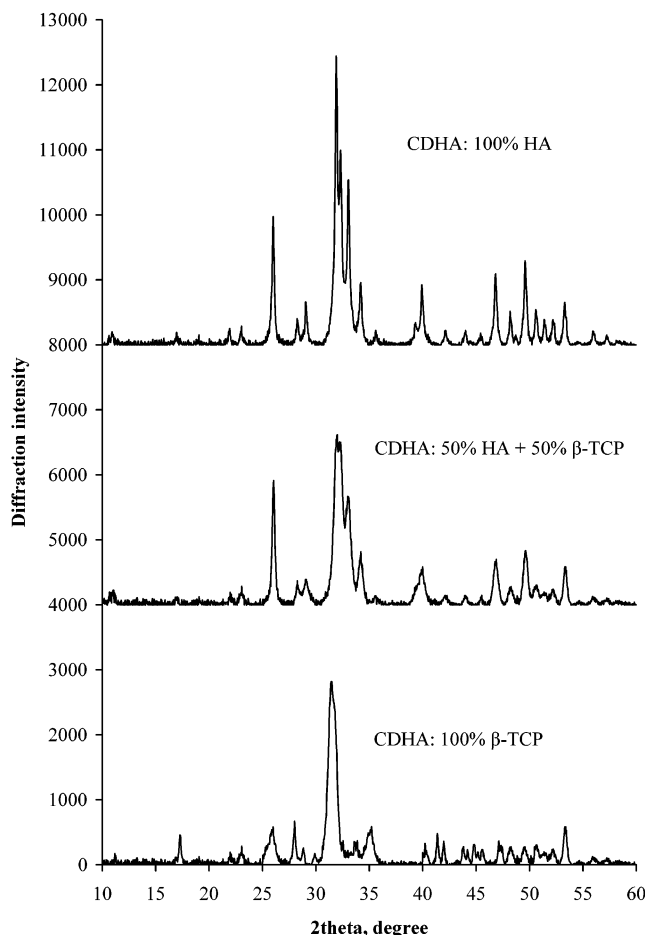


Figure 2. XRD patterns: bottom, the pattern of CDHA that after sintering gives rise to pure β -TCP; middle, the pattern of CDHA that after sintering gives rise to BCP (50% HA + 50% β -TCP); upper, the pattern of CDHA that after sintering gives rise to pure HA (all before sintering). Please, note that in the last case not CDHA but HA is formed. However, to stress the difference between the unsintered and sintered HA, the former is called CDHA.

transformation of relatively broad and poorly resolved diffraction peaks of CDHA into the sharp and well-resolved ones of HA, β -TCP, and BCP.

The results of FTIR are shown in Figures 4 and 5. Like in the above case of XRD, the IR absorption bands are better resolved in the spectra of sintered samples. Moreover, in the case of BCP, sintering resulted in the disappearance of the hydrophosphate absorption band at 870 cm^{-1} and a decrease in intensity of the hydroxide band at 3570 cm^{-1} . Bands of carbonates in the range 1400–1600 cm^{-1} are not seen in the FTIR spectra. Therefore, our samples did not contain detectable amounts of carbonates.

The results of TGA revealed that for the duration of sintering the total mass of samples decreased by 2.7–8.2%, depending on the type of CDHA. The mass decreasing happened mainly at temperatures below 400

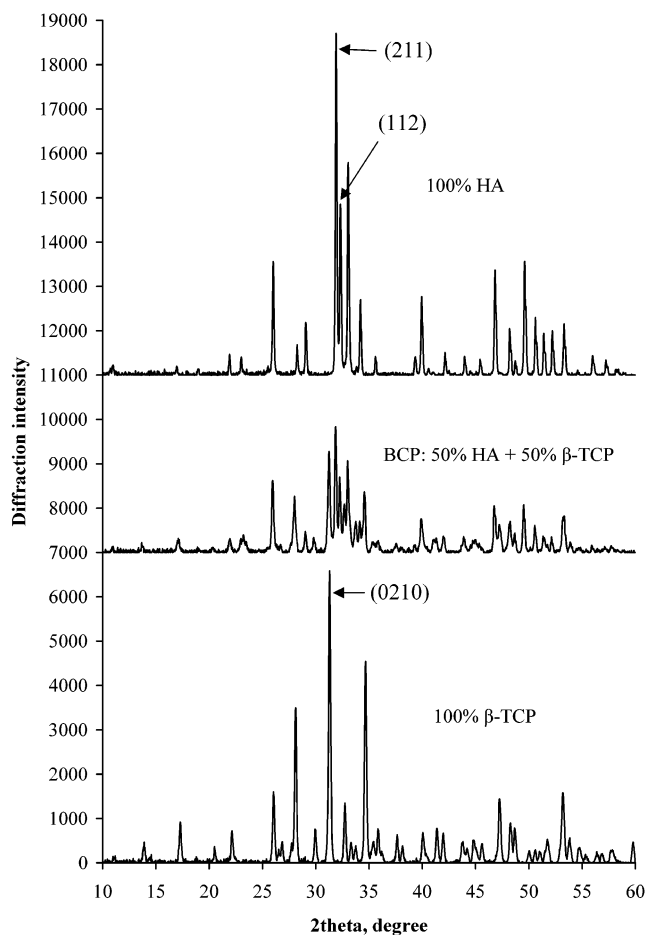


Figure 3. XRD patterns: bottom, the pattern of pure β -TCP; middle, the pattern of BCP (50% HA + 50% β -TCP); upper, the pattern of pure HA (all after sintering). The marked peaks correspond to the crystallographic directions: (211) and (112) for HA and (0210) for β -TCP.²

°C. However, decrease in mass was also observed at higher temperatures (Table 1). The former is due to elimination of adsorbed (100 °C) and lattice (270–400 °C) water, while the latter is due to either traces of carbonate^{23,24} or constitutional water formed by the chemical interaction between HPO_4^{2-} and OH^- (probably, via an intermediate formation of pyrophosphate (ref 1, p 36; ref 2, pp 141 and 188)). As the specific carbonate bands were not found in the FTIR spectra (Figures 4 and 5), we argue that the weight loss observed at the temperatures above 600 °C was due to the chemical interaction between HPO_4^{2-} and OH^- .

The results of chemical analysis (Ca/P molar ratios and amounts of incorporated potassium) are summarized in Table 2.

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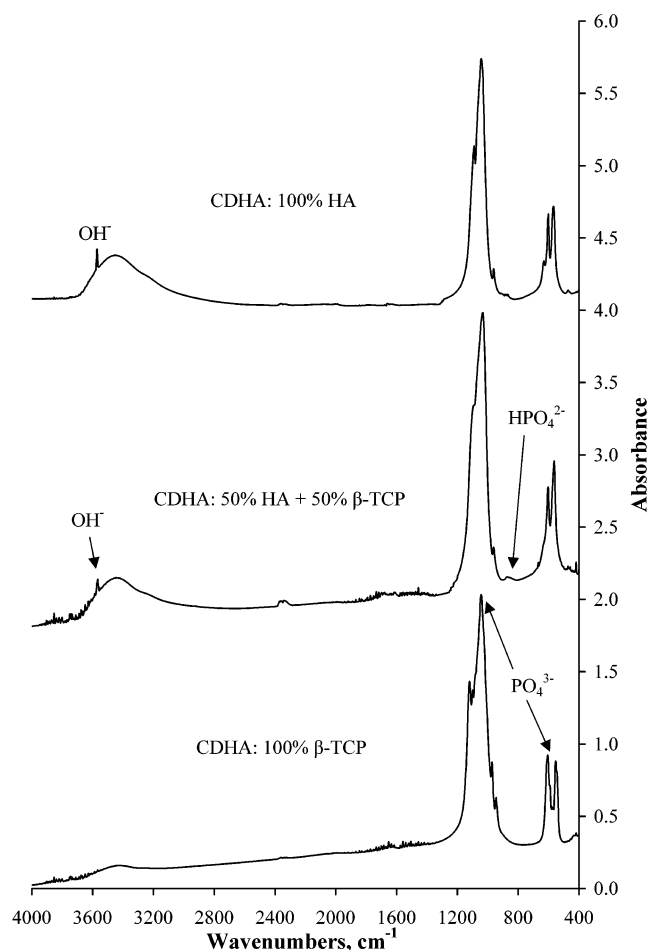
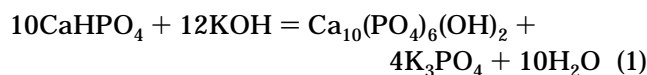


Figure 4. FTIR spectra: bottom, CDHA that after sintering gives rise to pure β -TCP; middle, CDHA that after sintering gives rise to BCP (50% HA + 50% β -TCP); upper, CDHA that after sintering gives rise to pure HA (all before sintering).

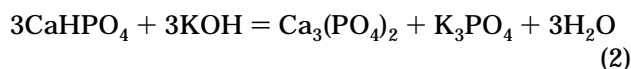
4. Discussion

Chemical equations of CDHA preparation can be written as follows (incorporation of the traces of potassium is omitted):

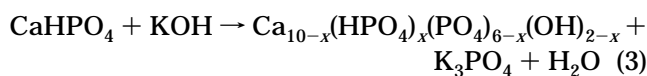
(a) CDHA after sintering giving rise to 100% HA



(b) CDHA after sintering giving rise to 100% β -TCP



(c) CDHA after sintering giving rise to BCP



where $0 < x < 1$. In the case $x = 0.5$ (CDHA after sintering giving rise to BCP/50% HA + 50% β -TCP), the following equation can be written:

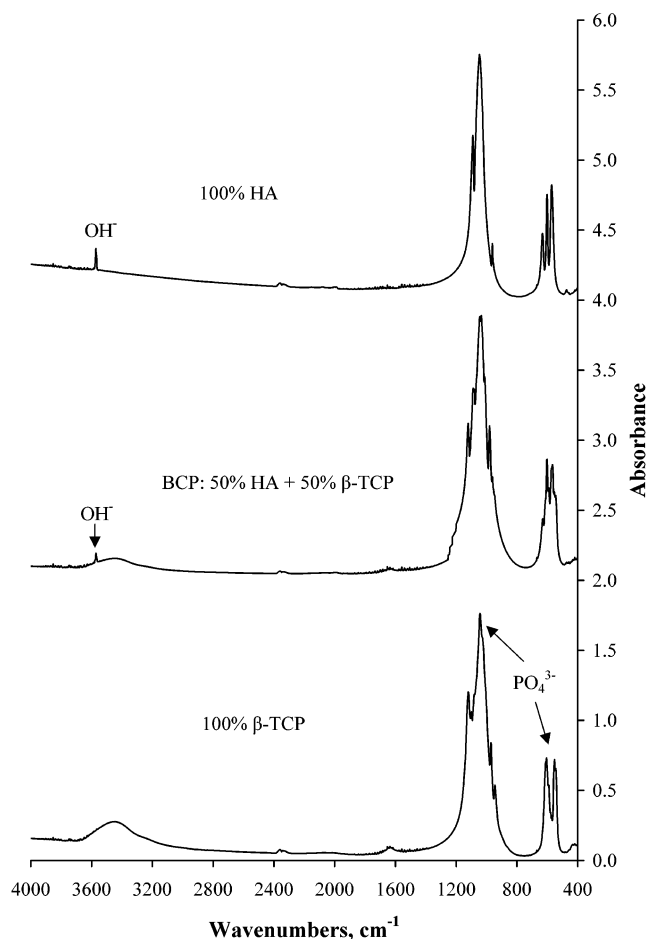
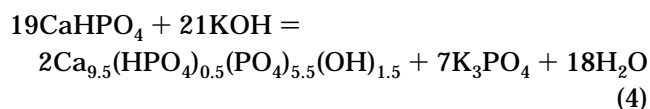


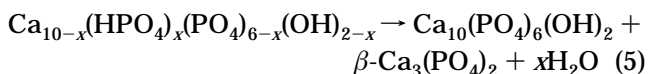
Figure 5. FTIR spectra: bottom, pure β -TCP; middle, BCP (50% HA + 50% β -TCP); upper, HA (all after sintering).

Table 2. Results of Chemical Analysis (Ca/P molar ratio and K , wt %)

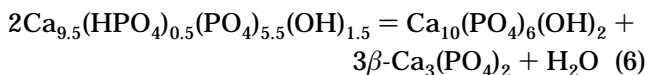
calcium phosphate	Ca/P ratio	K , wt %
CDHA giving rise to 100% HA	1.66 ± 0.03	0.03 ± 0.01
CDHA giving rise to BCP	1.58 ± 0.03	0.02 ± 0.01
CDHA giving rise to 100% β -TCP	1.49 ± 0.03	0.02 ± 0.01
100% HA	1.68 ± 0.02	0.03 ± 0.01
BCP/50% HA + 50% β -TCP	1.59 ± 0.02	0.02 ± 0.01
100% β -TCP	1.51 ± 0.02	0.02 ± 0.01

As seen from the equations, the chemical composition of CDHA strongly depends on the initial molar ratio DCPD/KOH.

No chemical transformations took place except loosening of adsorbed water (Table 1) for the period of sintering with as precipitated $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ and $\text{Ca}_3(\text{PO}_4)_2$. Therefore, the chemical reaction of sintering might be written only for CDHA after sintering giving rise to BCP:^{9,10,17,19,20}



where $0 < x < 1$. In the case $x = 0.5$ (CDHA giving rise to BCP/50% HA + 50% β -TCP), the above reaction might be rewritten as



BCP of 50% HA and 50% β -TCP (w/w) is formed as the result.

The direct determinations of CDHA structure are still lacking, but the chemical, spectroscopic, and lattice parameters indicate that the structure of CDHA resembles that of stoichiometric HA with some ions of calcium and hydroxide missing and incorporation of protons instead.^{2,25,26} Water also might be incorporated into the crystal structure of CDHA, where it occupies the vacant positions of hydroxide ions, while the second hydrogen of the each incorporated water molecule might occupy the closest vacant position from the calcium cation.^{25,26} The presence of protons in the CDHA looks like replacement of some PO_4^{3-} ions by HPO_4^{2-} , which is seen as a specific band at 870 cm^{-1} in FTIR spectra (Figure 4). At some stage of sintering, ions of H^+ and OH^- start to interact with each other (probably, via intermediate formation of pyrophosphate)^{1,2} according to the net reactions in eqs 5–7. Removal of water was followed by the TGA technique. Several weight-loss peaks were detected (Table 1). However, among the high-temperature peaks, only that at $780\text{ }^\circ\text{C}$ was attributed to reactions 5–7 (ref 1, p 36; ref 2, pp 141 and 188). Weak weight-loss peaks at $650\text{--}680$ and $850\text{ }^\circ\text{C}$ (Table 1) were due to some impurities.

The results of FTIR investigations of CHDA (which gives rise to BCP, when sintered) and BCP itself demonstrate decreasing intensity of the hydroxide band at 3570 cm^{-1} and disappearance of the HPO_4^{2-} band at 875 cm^{-1} (the middle spectra in Figures 4 and 5). These are indirect confirmation of chemical eqs 5–7. Minor differences between the sintered and unsintered compounds were found in the FTIR spectra of the other two calcium phosphates (the ground and upper spectra in Figures 4 and 5). Therefore, no chemical transformations happened with these compounds during the sintering.

The XRD results exhibited a transformation from the broad peaks of CHDA to the sharp peaks of HA, BCP, and β -TCP (Figures 2 and 3). Therefore, the crystallites became greater. On the basis of X-ray diffraction peak broadening, the mean crystallite dimension (τ) can be calculated via the Scherrer equation:²⁷

$$\tau = \frac{K\lambda}{\beta \cos \theta} \quad (7)$$

where β is the line broadening due to the effect of small crystallites (β must be given in radians); K is the so-called "shape factor", which usually takes a value of about 0.9 (ref 11, p 90); λ is the wavelength, equal to 1.54056 \AA (Cu $K\alpha$ radiation); and θ is the diffraction peak's angle. The diffraction peak broadening is measured at the half-intensity maximum of the main diffraction peaks.^{11,12} The calculated values of the mean crystallite dimensions are summarized in Table 3. The crystallite dimensions both for sintered and unsintered calcium phosphates decrease with Ca/P molar ratio decreasing.

As neither of the measurements revealed any differences between the sintered and unsintered HA and TCP

Table 3. Calculated Values of the Mean Crystallite Dimensions (τ) (Main Diffraction Peaks at $2\theta = 31\text{--}32^\circ$ Were Used)

calcium phosphate	β , ^a deg	τ , nm
CDHA giving rise to 100% HA	0.7/2 ^b	~27
CDHA giving rise to BCP	1.0/2 ^b	~19
CDHA giving rise to 100% β -TCP	0.9	~10
100% HA	0.12	~78
BCP/50% HA + 50% β -TCP	0.15	~62
100% β -TCP	0.19	~49

^a For the calculations, this value must be in radians. ^b Divided by 2, because after sintering these broad peaks give rise to two sharp peaks.

except absorbed water lose (TGA) and differences in the diffraction peaks' breadth (XRD), we may conclude that sintering of CDHA, giving rise to 100% HA, and of CDHA, giving rise to 100% β -TCP, just resulted in crystallite agglomeration. Considering the cubic shape for the crystallites (as a first approximation) with the dimensions taken from Table 3, it is possible to suggest that, in the case of the as-precipitated HA, approximately each 24 small crystallites were agglomerated into the bigger ones ($24\text{ times } 27 \times 27 \times 27\text{ nm}^3$ is close to $78 \times 78 \times 78\text{ nm}^3$). In the case of as-precipitated TCP, approximately each 117 small crystallites were agglomerated into the bigger ones ($117\text{ times } 10 \times 10 \times 10\text{ nm}^3$ is close to $49 \times 49 \times 49\text{ nm}^3$).

In the case of the real CDHA (CDHA giving rise to BCP/50% HA and 50% β -TCP), a further elucidation depends on the structure of CDHA. If CDHA consists of HA with some ions of calcium and hydroxide missing and proton incorporation together with some molecules of water in the vacant sites,^{2,26} formation of BCP may be described as shown in Figure 6. In this case, after the lose of the constitutional water, approximately 35 crystallites of CDHA were agglomerated into one crystallite of either HA or β -TCP ($35\text{ times } 19 \times 19 \times 19\text{ nm}^3$ is close to $62 \times 62 \times 62\text{ nm}^3$). However, another model of the structure of CDHA might also be suitable: CDHA giving rise to BCP might initially consist of very small (therefore, X-ray amorphous), randomly distributed crystallites of HA and TCP. In this case, BCP formation is shown in Figure 7.

From the chemical point of view, the following relation exists between HA and TCP:



Therefore, to provide the transformations shown in Figures 6 and 7, ions of hydroxide and calcium should diffuse over the distance of 1–2 crystallites (19–38 nm according to Table 3). Indeed, ionic diffusion was found in apatites: at $1000\text{ }^\circ\text{C}$ the diffusion coefficient of hydroxide (OD^- , where D is deuterium) was measured to be $2 \times 10^{-11}\text{ cm}^2\text{ s}^{-1}$, while similar values for Ca^{2+} and PO_4^{3-} were 10^{-15} and $<10^{-17}\text{ cm}^2\text{ s}^{-1}$, respectively (ref 2, p 106). On the basis of these numerical values, calculations of the ionic diffusion have been performed, and the results are summarized in Table 4. As seen from the calculations, 4 h of sintering at $1050\text{ }^\circ\text{C}$ is enough for the transformations, shown in Figures 6 and 7, to occur.

5. Conclusions

Thus, the chemical and structural transformations occurring with calcium phosphates during sintering

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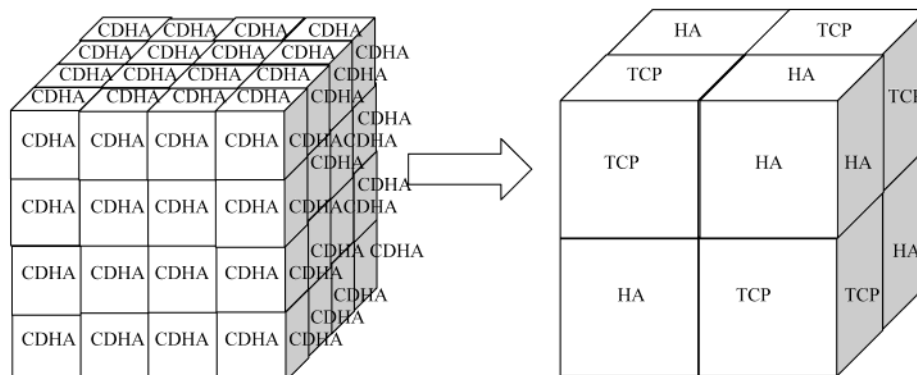


Figure 6. Schematic drawing of BCP formation from small crystallites of CDHA. The cubic structure is shown for simplicity. In reality: the crystal structure and the space group of CDHA are still unknown, while β -TCP crystallizes in the rhombohedral space group $R\bar{3}c$ with unit cell parameters $a = b = 10.439(1)$, $c = 37.375(6)$ Å, $\gamma = 120^\circ$, and $Z = 21$ (hexagonal setting) and HA crystallizes in either the hexagonal space group $P6_3/m$ (unit cell parameters $a = b = 9.4302(5)$, $c = 6.8911(2)$ Å, $\gamma = 120^\circ$ (hexagonal), $Z = 2$) or the monoclinic space group $P2_1/b$ (unit cell parameters $a = 9.84214(8)$, $b = 2a$, $c = 6.8814(7)$ Å, $\gamma = 120^\circ$, $Z = 4$).^{1,2}

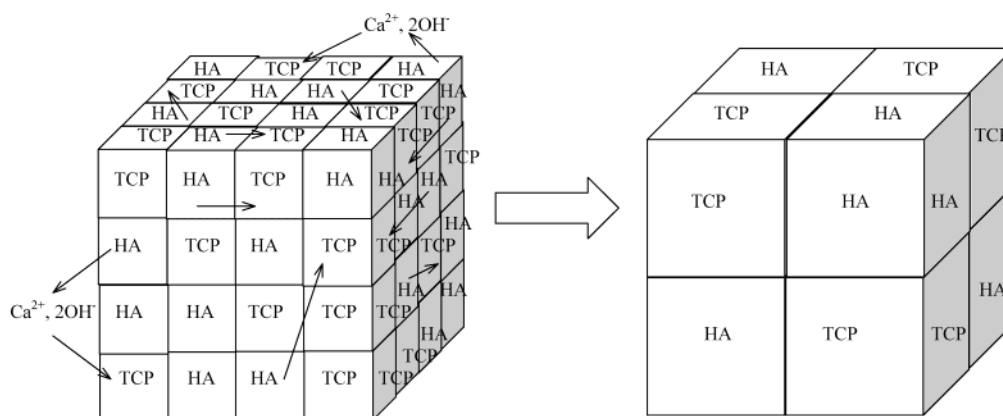


Figure 7. Schematic drawing of BCP formation from randomly distributed small crystallites of HA and TCP. Possible ways of ionic diffusion (ions of calcium and hydroxide, but *not* molecules of $\text{Ca}(\text{OH})_2$) are shown by arrows. The cubic structure is shown for simplicity. For the real situation, see caption of Figure 6.

Table 4. Times Necessary for the Ions to Diffuse over the Distance of One or Two Crystallite Dimensions

	1 crystallite (19 nm)	2 crystallites (38 nm)
hydroxide	0.18 s	0.72 s
calcium	3610 s (~1 h)	14 400 s (~4 h)
phosphate	>361 000 s (>4 days)	>1 440 000 s (>16 days)

have been studied. HA and TCP as-precipitated (often mentioned as “CDHA giving rise to 100% HA” and “CDHA giving rise to 100% β -TCP”, respectively) were found to undergo minor changes for the period of sintering at 1050 °C for 4 h. Lose of adsorbed water and diffraction peaks’ sharpening (therefore, the crystallite dimensions increasing) were the only changes happening with these compounds. The situation was more complicated for CDHA giving rise to BCP: this type of CDHA consisted of crystallites with the mean dimen-

sions 19 nm and had the structure presented in either Figure 6 or Figure 7.

BCP was found to consist of HA and β -TCP crystallites with the mean dimensions 62 nm. However, distinct microcrystals 200–600 nm in size of HA and β -TCP were found in BCP with high-resolution transmission electron microscopy.^{28–30} On the basis of these data, a reasonable choice between Figures 6 and 7 can be made. Only the transformation mechanism shown in Figure 6 correlates well with the calculations on ionic diffusion (Table 4). As seen in Table 4, 4 h of sintering at 1050 °C is not enough for calcium ions to diffuse over the distance 200–600 nm, as required by the mechanism in Figure 7. Thus, we argue that, at elevated temperatures, CDHA transforms to BCP according to the mechanism shown in Figure 6.

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