Synthesis of octacalcium phosphate intercalated with dicarboxylate ions from calcium carbonate and phosphoric acid

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We have investigated the effect of the Ca/P molar ratio in the starting composition on the synthesis of octacalcium phosphate intercalated with dicarboxylate ions (OCPC), starting from calcium carbonate and phosphoric acid in the presence of a dicarboxylic acid, such as succinic acid, adipic acid, or suberic acid. For a Ca/P molar ratio in the starting composition of 1.6, which is the stoichiometric value for OCPC, the highest yield of OCPC with a high degree of crystallinity was obtained for the OCPC samples synthesized with starting Ca/P molar ratios of 1.5, 1.6, and 1.7. The Ca/P molar ratio of the starting composition is an important factor in the synthesis of OCPC. This synthesis route provides for the effective production of OCPC samples.

1. Introduction

Octacalcium phosphate (OCP, $Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$) is one of the calcium phosphates. It is known that OCP is the precursor of hydroxyapatite in teeth and bones.[1] OCP has a layered structure composed of an "apatite layer", whose structure is similar to hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$) and a "hydrated layer", which contains water.[2] The layered structure of OCP confers interesting characteristics to OCP. Since the HPO_4^{2-} ions in OCP can be substituted for dicarboxylate ions, various organic modifications are expected to be applied to OCP. Monma et al. reported the first OCP intercalated with dicarboxylate ions (OCPC).[3] They synthesized OCPC using the hydrolysis of alpha-tricalcium phosphate (α-TCP, $Ca_3(PO_4)_2$) in the presence of succinic acid. After this report, various OCPC samples with various dicarboxylate ions were reported using the same process, i.e. the hydrolysis of α-TCP in the presence of dicarboxylic acids.[4]-[7] Aoki et al.[8] synthesized aspartate-OCP and revealed that it showed a high ability to adsorb formaldehyde due to the incorporation of aspartate. This indicates the potential to obtain OCP samples with various functionalities by incorporating dicarboxylate ions.

The "hydrated layer" contains two types of HPO_4^- ions": one that links to the "apatite layer", and another that is located between the "apatite layers" like a pillar. The pillar-like HPO_4^- ions can be replaced by various dicarboxylate ions ($^-OOC-R-COO^-$, where R = organic groups) to form OCPC samples.[9],[10] From this knowledge, the stoichiometric composition of OCPC samples is given by

$$Ca_8(HPO_4)(OOC-R-COO)(PO_4)_4 \cdot mH_2O.$$
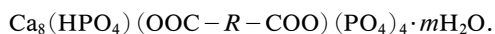
The Ca/P molar ratio of stoichiometric OCPC samples is 1.6. However, the starting material for the synthesis of OCPC samples in the conventional method is α-TCP, whose Ca/P molar ratio is 1.5. This suggests that this reaction is not stoichiometric. If the Ca/P molar ratio of the starting

material is adjusted at 1.6, then the formation of the OCPC samples is expected to be promoted. However, there has been no such a trial conducted because α-TCP was used as a starting material. We have previously reported that OCP can be synthesized from $CaCO_3$ and H_3PO_4.[11] This process would be also useful to prepare OCPC samples because it is easy to control the Ca/P molar ratio of the starting composition. In this study, we have synthesized OCPC samples from $CaCO_3$ and H_3PO_4 in the presence of dicarboxylic acids, with different Ca/P molar ratios in the starting composition, in order to investigate the effect of the Ca/P molar ratio in the starting composition.

2. Materials and methods

2.1 Synthesis of OCP samples intercalated with dicarboxylate ions

Phosphoric acid (H_3PO_4, 85%, Nacalai Tesque Inc.) 0.010 mol and 0.002 mol of a dicarboxylic acid were added to $100\,cm^3$ of ultra-pure water, and the mixture was stirred. Succinic acid, adipic acid, and suberic acid (Wako Pure Chemical Industries Inc.), which have been reported to be easily incorporated into OCP,[9] were used as the dicarboxylic acids, and their chemical formulae are shown in **Table 1**. The resultant homogeneous solutions were kept at 60°C, and then 0.015, 0.016, or 0.017 mol of calcium carbonate ($CaCO_3$, Nacalai Tesque Inc.) was added to the solutions under stirring. The samples were denoted as SucOCP(x), AdiOCP(x), and SubOCP(x), respectively, where x is the Ca/P molar ratio. The resulting suspension was stirred at 60°C for a period of 6 h. An OCP sample without any dicarboxylate ions (NoOCP(1.33)) was also prepared using 0.010 mol of phosphoric acid and 0.0133 mol of calcium carbonate using the same procedure as above. The product was obtained using suction filtration and dried at 60°C. The pH of the suspension and the phase of the product were monitored during synthesis.

Table 1. Chemical Formula of Dicarboxylic Acids Used in the Present Study

Name	Chemical formula
Succinic acid	$HOOC-(CH_2)_2-COOH$
Adipic acid	$HOOC-(CH_2)_4-COOH$
Suberic acid	$HOOC-(CH_2)_6-COOH$

Fig. 1. Powder XRD patterns of the dicarboxylic acids used in the present study.

As a reference, the OCP samples intercalated with dicarboxylate ions were also prepared by hydrolysis of α-TCP in the presence of dicarboxylic acids, after the method of Monma et al.[12] The dicarboxylic acid, 0.025 mol, was dissolved in 100 cm³ of ultra-pure water. The pH of this solution was adjusted to pH = 6.0 by addition of an ammonia solution. Two grams of α-TCP (0.00645 mol, Taihei Chemical Industrial Co., Ltd.) was added, and the solution stirred at 40°C for a period of 3 h. These samples were denoted as SucOCP(TCP), AdiOCP(TCP), and SubOCP(TCP), respectively. An OCP sample without any dicarboxylate ions (NoOCP(TCP)) was also prepared. Sodium acetate, 0.05 mol, was dissolved in 100 cm³ of ultra-pure water, and about 0.5 cm³ of acetic acid was used to adjust the pH to pH = 5.4. Two grams of α-TCP (0.00645 mol, Taihei Chemical Industrial Co., Ltd.) was added to the solution, which was then stirred at 50°C for a period of 3 h. The product was obtained using suction filtration, and dried at 60°C.

2.2 Characterization

The phase of the product was examined using powder X-ray diffraction (XRD, RINT2200V/PC-LR, Rigaku). In the XRD analysis, the product was mixed with silicon (Si, Nacalai Tesque Inc.) as a standard, in a mass ratio of product:silicon = 9:1.

A mass of 40 mg of the product was dissolved in 20 cm³ of a 2 mass% nitric acid solution (HNO₃, Nacalai Tesque Inc.). After dilution of this solution, the element concentration was examined using inductively coupled plasma atomic emission spectroscopy (ICP, Optima2000DV, Perkin Elmer, USA) to determine the composition of the product.

The morphology of the product was observed using field emission scanning electron microscopy (FE-SEM, S-4800, Hitachi). Before the SEM observations were carried out, a thin coating of gold was deposited on the surface of the product.

3. Results

Figure 1 shows the powder XRD patterns of the dicarboxylic acids. **Figure 2** shows the powder XRD patterns of the products synthesized from CaCO₃ and H₃PO₄ for a Ca/P molar ratio of 1.6, or from α-TCP with different dicarboxylic acids. Silicon was added as a standard. For both starting materials, only the peaks ascribed to OCP (PDF#26–1056) were detected, regardless of starting material used when no dicarboxylic acid was added. The 010 diffraction line occurring around $2\theta = 4.7°$ shifted to lower angles, and the shift increased with increasing the length of the $(CH_2)_n$ chain of
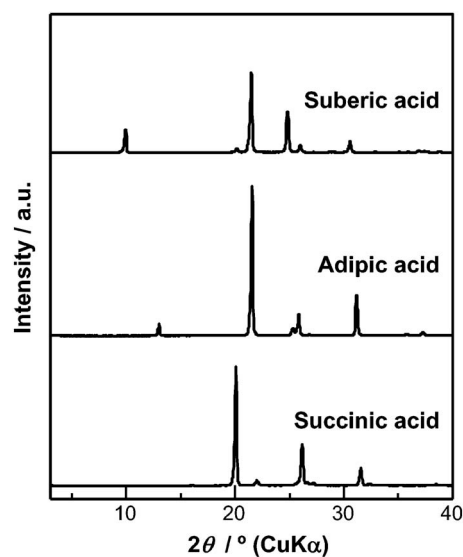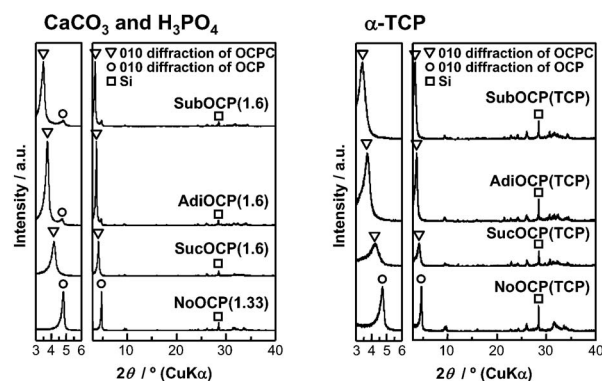

Fig. 2. Powder XRD patterns of the products.

the dicarboxylic acid, regardless of the starting materials when dicarboxylic acids were added. This is due to the intercalation of dicarboxylate ions and the formation of OCPCs, and this tendency is consistent with previous reports.[9] Although the 010 diffraction of OCP without intercalation was also detected for AdiOCP(1.6) and SubOCP(1.6), the peak intensity is much smaller than that of the corresponding OCPC and this indicates that the main products are OCPCs even for these samples. The peaks assigned to the free dicarboxylic acids were not detected in any samples. On comparing the intensity of the silicon peak, the intensities of the 010 diffraction lines of the OCPC samples synthesized from CaCO₃ and H₃PO₄ were higher than those from the α-TCP. **Table 2** shows the interplanar spacing d_{010} of the products determined from Fig. 2 and their Ca/P molar ratios determined using ICP. The d_{010} value increased with increasing $(CH_2)_n$ chain length in the dicarboxylate ions. The molar ratio of PureOCP(1.33) and PureOCP(TCP) was close to a value of 1.33, which is the stoichiometric value of OCP. When dicarboxylic acids were added, the molar ratio approached a value of 1.6, which is the value of $Ca_8(HPO_4)(OOC-R-COO)(PO_4)_4 \cdot mH_2O$, regardless of the starting

Table 2. Interplanar Spacing d_{010} and Ca/P Molar Ratio of the Products

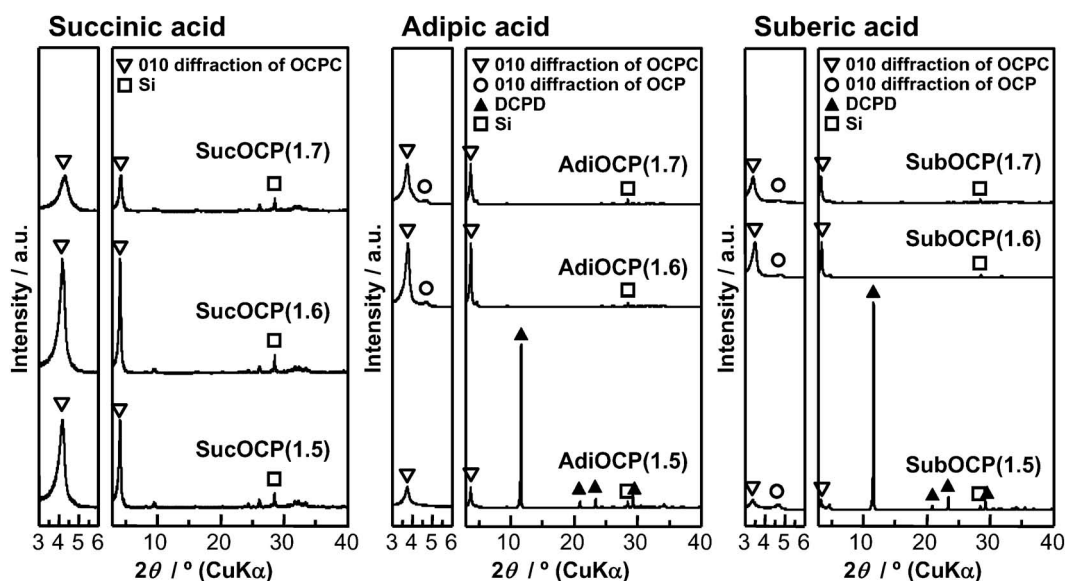| CaCO$_3$ and H$_3$PO$_4$			α-TCP		
Sample	d_{010} / nm	Ca/P (n=3)	Sample	d_{010} / nm	Ca/P (n=3)
NoOCP(1.33)	1.86	1.36 ± 0.05	NoOCP(TCP)	1.86	1.31 ± 0.03
SucOCP(1.6)	2.14	1.56 ± 0.02	SucOCP(TCP)	2.10	1.53 ± 0.01
AdiOCP(1.6)	2.36	1.55 ± 0.02	AdiOCP(TCP)	2.31	1.52 ± 0.02
SubOCP(1.6)	2.59	1.51 ± 0.01	SubOCP(TCP)	2.59	1.51 ± 0.04

Fig. 3. Powder XRD patterns of the products.

material used. The Ca/P molar ratio of SucOCP(1.6) and AdiOCP(1.6) prepared from CaCO$_3$ and H$_3$PO$_4$ was closer to a value of 1.6 than that of SucOCP(TCP) and AdiOCP(TCP) synthesized from α-TCP.

The XRD patterns of the products synthesized from CaCO$_3$ and H$_3$PO$_4$ with different Ca/P ratios in their starting compositions are shown in **Fig. 3**. When succinic acid was added, the 010 diffraction peak, due to OCP being intercalated with succinate ions, was observed for all the products synthesized from CaCO$_3$ and H$_3$PO$_4$. The peak intensity of the product prepared for a Ca/P molar ratio of 1.6 in the starting composition had the highest peak intensity among all the products. When adipic or suberic acid was added, a strong peak ascribed to dicalcium phosphate dihydrate (DCPD) was observed using a Ca/P molar ratio of 1.5 in the starting composition. When the Ca/P molar ratio was either 1.6 or 1.7, the 010 diffraction peak ascribed to OCP intercalated with adipate or suberate ions was observed. For all the dicarboxylic acids, the peak intensity of the OCPC samples prepared with a Ca/P molar ratio of 1.6 in the starting composition was the highest among the various Ca/P ratios studied.

Figure 4 shows the changes in pH of the suspension during the preparations. The stable phase of calcium phosphates is
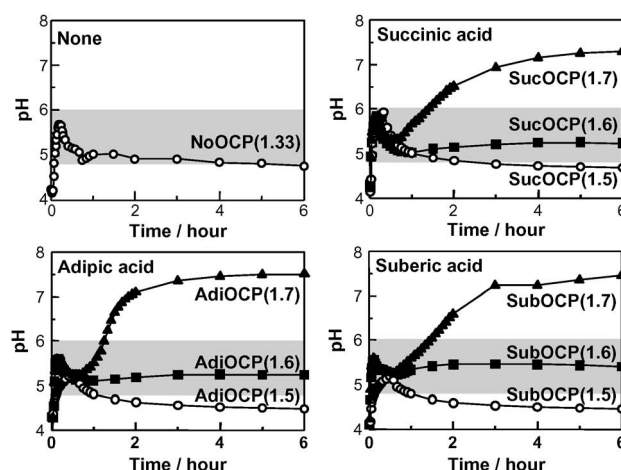

Fig. 4. pH-time curves of the suspension at 60°C. (The shaded area shows the pH range (pH = 4.8–6) in which OCP is stable.)

known to be strongly dependent on the pH and the temperature. The stable phases at 60°C are DCPD for pH ≤ 4.8, OCP for 4.8 ≤ pH ≤ 6.0, and Ca-deficient hydroxyapatite (DAp)

for pH$\geq$6.0.[9] For all the starting compositions, the pH increased rapidly to pH = 5–6 during the initial stage. When the Ca/P molar ratio in the starting composition was 1.6, the pH was stable in the region where OCP was stable. On the other hand, the pH increased to the region where DAp was stable for Ca/P = 1.7, and decreased to the region where DCPD was stable for Ca/P = 1.5. In the case of NoOCP (1.33), the pH was in the region where OCP was stable. To examine the reaction scheme of PureOCP(1.33), SucOCP (1.6), AdiOCP(1.6), and SubOCP(1.6), a part of the suspension was taken out while the reaction was in progress, dried, and examined using XRD. **Figure 5** shows the powder XRD patterns of the product produced during the preparation. The peaks due to DCPD were detected at an early stage and these disappeared after a period of 1–2 h, and the peak intensity of the OCPC samples increased. This indicates that the OCPC was formed after the formation of DCPD.

Figure 6 shows SEM photographs of the product synthesized from CaCO$_3$ and H$_3$PO$_4$ for a Ca/P molar ratio of 1.6, or from α-TCP with different dicarboxylic acids. Plate-like particles were observed in all the samples.

4. Discussion

The XRD patterns showed the peak shift of the 010 diffraction line when OCP was prepared with the dicarboxylic acids. As these peak sifts were consistent with the previous studies,[9] these results supported that we could prepare the OCP intercalated with dicarboxylate ions.

From the data in Fig. 5, the OCPC samples are assumed to be formed via the following mechanism: In the initial stage, the pH was low due to the presence of H$_3$PO$_4$ and dicarboxylic acid, and the reaction between CaCO$_3$ and H$_3$O$^+$ yielded Ca^{2+} ions. The Ca^{2+} ions then reacted with HPO$_4^{2-}$ ions

derived from H$_3$PO$_4$ to form DCPD. After proceeding these reactions and the pH increased, the formed DCPD began to react with Ca^{2+} and the dicarboxylic acids to form OCP intercalated with dicarboxylate ions. The proposed reaction
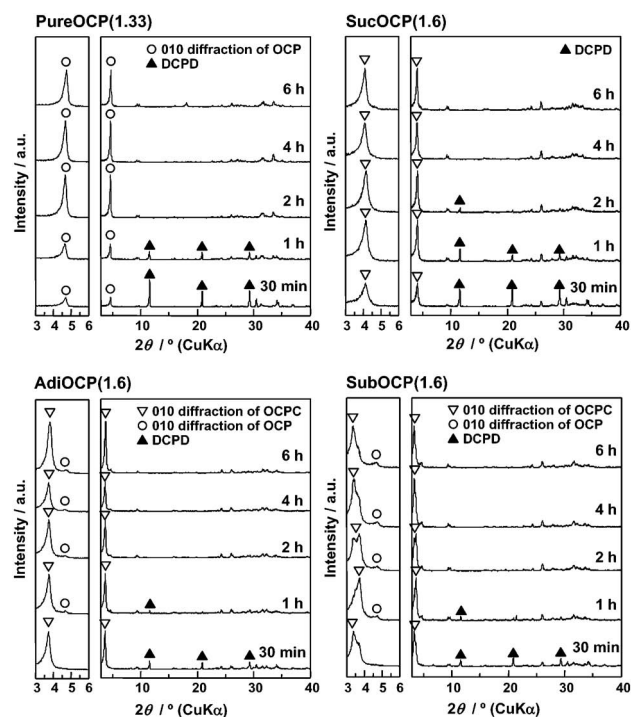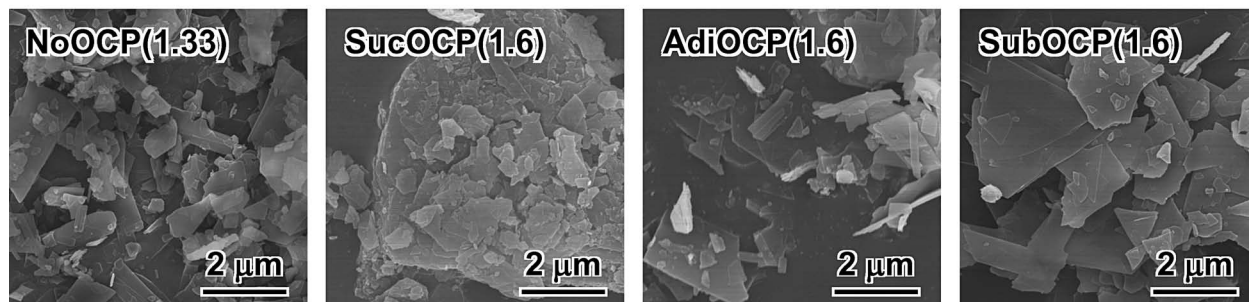

Fig. 5.   Powder XRD patterns of the products for various periods. In the left part, the 2θ scale between 3° and 6° was expanded.
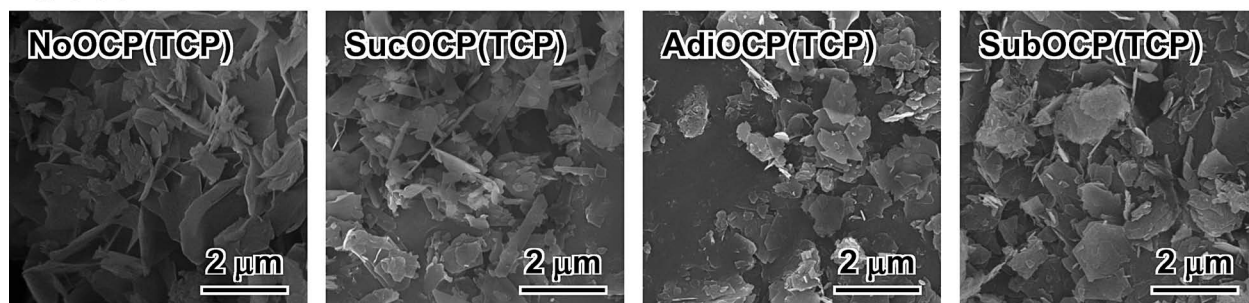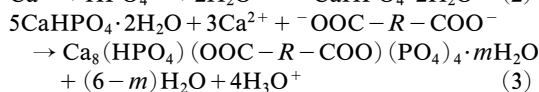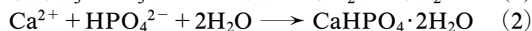

Fig. 6.   FE-SEM images of the products.

formulae are as follows:

$$CaCO_3 + 2H_3O^+ \longrightarrow Ca^{2+} + 3H_2O + CO_2 \qquad (1)$$
$$Ca^{2+} + HPO_4^{2-} + 2H_2O \longrightarrow CaHPO_4 \cdot 2H_2O \qquad (2)$$
$$5CaHPO_4 \cdot 2H_2O + 3Ca^{2+} + {}^-OOC - R - COO^-$$
$$\rightarrow Ca_8(HPO_4)(OOC - R - COO)(PO_4)_4 \cdot mH_2O$$
$$+ (6-m)H_2O + 4H_3O^+ \qquad (3)$$
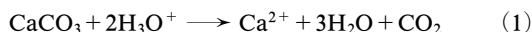
The generation of CO_2 was confirmed by the observation of gas generated from the suspension. When the Ca/P molar ratio in the starting composition was 1.6, the final value of the pH was in the region where OCP was stable, and OCP samples intercalated with carboxylate ions were formed effectively. On the other hand, DCPD remained for Sample AdiOCP(1.5) and Sample SubOCP(1.5) as the pH had decreased to the pH range where DCPD was stable. For a Ca/P molar ratio of 1.7, the pH increased to the region where DAp was stable. Therefore, both OCPC and DAp were able to form. However, detection of the formation of DAp was difficult because the XRD patterns of OCP and DAp overlap. The formation of OCPC through the formation of DCPD as an intermediate might confer a high degree of crystallinity to the OCPC samples. The results of the pH changes indicated that the starting composition of Ca/P molar ratio of 1.6 provided the optimum pH conditions.

In the data shown in Fig. 5, in Sample SubOCP(1.6), after a period of 2 h, the peak ascribed to OCPC occurring at $2\theta = 3$–$4°$ split into two peaks. This should have been due to the formation two types of OCP intercalated with suberate ions with different arrangements. Markovic et al.[13] suggested the existence of carboxylate ions with two different arrangements in OCPC. This suggests the possibility of different arrangements and resultant different interplanar spacing d_{010}. We speculated that OCPC with a metastable arrangement of carboxylate ions was formed at first, and then transformed into a more stable form of OCPC in Sample SubOCP(1.6).

From our results, a Ca/P molar ratio of 1.6 in the starting composition, which is the stoichiometric composition, is the best Ca/P molar ratio for the formation of OCPC because both the chemical equilibrium and the pH of the reaction system are optimum for the formation of OCPC.

5. Summary

When the Ca/P molar ratio in the starting composition was 1.6, which is the stoichiometric value of OCPC, the highest yield of OCPC samples with a high degree of crystallinity was obtained. The Ca/P molar ratio in the starting composition is an important factor in the synthesis of OCPC samples. This synthesis route provides for effective production of OCPC samples.

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