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Simple, efficient and reliable method for the preparation of β-tricalcium phosphate

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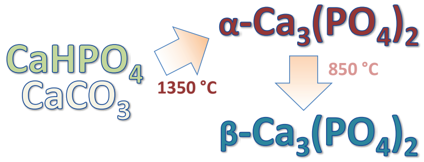
The solid-state reaction of $CaHPO_4$ with $CaCO_3$ in a ratio > 2 : 1 at 1350 °C led to the formation of α-tricalcium phosphate, the subsequent sintering of which at 850 °C gave a homogeneous phase of β-tricalcium phosphate, which does not contain crystalline impurities.



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β-Tricalcium phosphate $Ca_3(PO_4)_2$ (β-TCP) is one the most effective synthetic bone graft substitutes, demonstrating osteoconductive and osteoinductive properties.[1–4] Due to the higher solubility and resorption capacity of β-TCP[5–7] compared to hydroxyapatite,[8] which is the mineral core of bone,[9] β-TCP-based bone substitute materials attract special attention from researchers.[1–3,10,11] However, the presence of crystalline impurities can significantly complicate the prospects for the biomedical use of synthesized β-TCP. For example, calcium pyrophosphate $Ca_2P_2O_7$ (CPP)[12] is an unwanted impurity in TCP materials because it is the deposition of CPP that leads to one of the most painful and intractable types of arthritis.[13–15] Besides, the morphology of β-TCP is highly variable due to minimal amounts of CPP or hydroxyapatite impurities.

Common methods for the synthesis of β-TCP can be divided into two groups, namely: precipitation of amorphous calcium phosphates or calcium-deficient hydroxyapatite from aqueous solutions followed by calcination[5,11,16–20] and solid-state sintering of Ca^{2+} and phosphate-containing components at a temperature of ~1000 °C.[9,17,21,22] The first approach is more labor-intensive, but in some cases, β-TCP synthesis has been successfully performed with little or no impurities.[11,17–20] The second approach, solid-state, usually leads to the formation of complex crystalline phases containing α-TCP, β-TCP, CPP, $Ca_8P_2O_7(PO_4)_4$ and other calcium phosphates.[10,23,24] This work aimed to develop an efficient solid-state method to synthesize β-TCP without crystalline impurities of other calcium phosphates.

We hypothesized that stoichiometric β-TCP could be efficiently obtained by a solid-phase acid–base reaction of calcium hydrogen phosphate as the acid component and calcium carbonate as the base component, accompanied by the formation of volatile by-products. The choice of these starting materials was most suitable for obtaining β-TCP from the following reaction:

$$CaCO_3 + 2\ CaHPO_4{\cdot}2H_2O = Ca_3(PO_4)_2 + CO_2 + 5\ H_2O.$$

However, at conventional temperatures (~1000 °C), the solid-state method does not provide a successful reaction result in strict accordance with the above equation since the incomplete conversion of $CaCO_3$ inevitably leads to CPP formation. Also, the thermolysis of $CaCO_3$ with a local acid deficiency should lead to CaO and then to basic calcium phosphates.[4] Careful homogenization of the reaction components should be ensured to avoid side reactions.

We assumed that CPP (mp 1230 °C) could act as an intermediate homogenizer during TCP synthesis. This synthesis at 1200 °C and higher temperatures should lead to the formation of α-TCP,[25] which is more stable at these temperatures than β-TCP, according to the phase diagram of the $CaO–P_2O_5$ system[26] (Figure S1, see Online Supplementary Materials). However, α-TCP can be transformed to β-TCP at lower temperatures, as previously demonstrated in β-TCP hydrothermal synthesis.[27,28] Thus, the idea was to react $CaHPO_4$ with $CaCO_3$ at high temperatures (>> 1230 °C) followed by annealing at lower temperatures to ensure phase transition from α-TCP into β-TCP. It is possible because α-TCP (high-temperature form) and β-TCP (low-temperature form) are enantiotropically related.

To ensure that our assumption was correct, we conducted the solid-state synthesis of β-TCP by sintering either at 1000 °C for 10 h at a time, or sequentially at 1350 and 850 °C for 5 h each time, using different Ca/P ratios (Table 1, Figures S3 and S4).[†]

[†] $CaCO_3$ (1.00 g, 10 mmol) and $CaHPO_4{\cdot}2H_2O$ (3.44 g, 20 mmol) (for a Ca/P ratio of 1.5 : 1, for other ratios, the mass of $CaHPO_4{\cdot}2H_2O$ was increased proportionally) were finely ground using porcelane mortar, heated at 200 °C for 1 h and ground again. Then the mixture was placed in an alundum pot, heated to a predetermined temperature (1000 or 1350 °C)

Table 1 Solid-state β-TCP synthesis conditions, phase composition and crystallite size of products.

Run	Ca/P ratio [excess of $CaHPO_4$ (mol%)]	Temperature/°C		XRD detected phases		IR detected CPP after second sintering	Size of crystallites/ ±10 nm	
		First sintering	Second sintering	First sintering	Second sintering		First sintering	Second sintering
1	1.50 [0]	1000	1000	β-TCP, CPP	β-TCP, CPP	+	60	150
2	1.36 [10]	1000	1000	β-TCP, CPP	β-TCP, CPP	+	70	150
3	1.30 [15]	1000	1000	β-TCP, CPP	β-TCP, CPP	+	100	150
4	1.25 [20]	1000	1000	β-TCP, CPP	β-TCP, CPP	+	150	130
5	1.50 [0]	1350	850	α-TCP	β-TCP, α-TCP	–	35	60
6	1.36 [10]	1350	850	α-TCP, CPP	β-TCP	–	60	60
7	1.30 [15]	1350	850	α-TCP, CPP	β-TCP	–	30	70
8	1.25 [20]	1350	850	α-TCP, CPP	β-TCP, CPP	+	20	75

At 1000 °C, even at a Ca/P ratio of 1.50, the crystalline phase contained trace CPP amounts (Table 1, run 1), increasing with an increase in the Ca/P ratio (Table 1, runs 2–4). CPP was explicitly detected in all phases by a characteristic peak at 720 cm^{-1} in the IR spectrum [Figure 1(*a*)].[29,30] After sintering at 1350 °C and fast cooling in the second series (Table 1, runs 5–8), the products mainly contained α-TCP, while CPP was detected by XRD at a Ca/P ratio of 1.25–1.36 (Figure 2).

As previously demonstrated by Evdokimov *et al.*, [31] the highest rate of the transformation of α-TCP to β-TCP is observed in the temperature range from 800 to 900 °C. Accordingly, we continued our experiments on high-temperature sintering by annealing at 850 °C for 5 h and obtained unexpected results. In runs 5–7, CPP was not detected in the reaction products by either XRD (Figure S6) or IR spectroscopy [Figure 1(*b*)]. Even at a Ca/P ratio of 1.25, CPP was found only in trace amounts. The presence of a significant amount of α-TCP after the second sintering of the sample with a Ca/P ratio of 1.50 (Table 1, run 5) was the second notable result of our experiments.

We assume that at 1350 °C, the initially formed submelting CPP provides complete conversion of the reactants without the formation of basic calcium phosphates. During slow cooling to 850 °C and sintering for five hours at this temperature, glassy

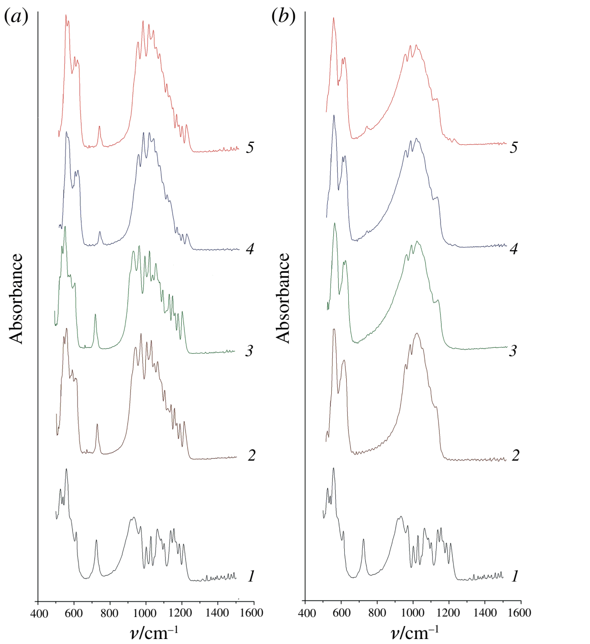

Figure 1 IR spectra of β-TCP samples obtained at (*a*) 1000 and (*b*) 1350 °C using (*2*) stoichiometric $CaHPO_4/CaCO_3$ ratio and (*3*) 10, (*4*) 15 and (*5*) 20% excess of $CaHPO_4$. IR spectra of (*1*) CPP are shown for comparison.

at a rate of 6 °C/min, held at this temperature for 5 h, and then held at 1000 or 850 °C, respectively, for additional 5 h. After cooling, the product was analyzed by X-ray diffraction (XRD) and IR spectroscopy.

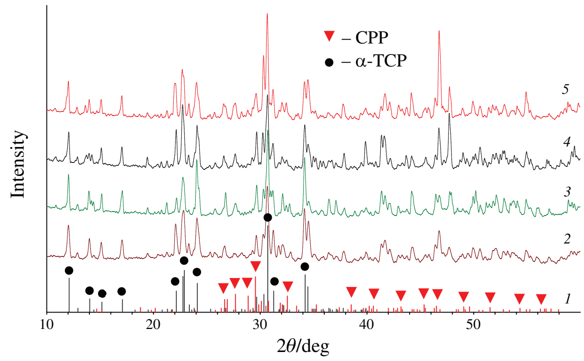

Figure 2 XRD patterns of TCP samples obtained after sintering at 1350 °C using (*2*) the stoichiometric $CaHPO_4/CaCO_3$ ratio and (*3*) 10, (*4*) 15 and (*5*) 20% excess of $CaHPO_4$, along with (*1*) reference standards for CPP (JCPDS 09-0346) and α-TCP (JCPDS 29-0359).

CPP promotes the complete conversion of α-TCP into β-TCP, without forming its own crystalline phase up to a Ca/P ratio of 1.30. Note that Hong *et al.*[32] previously discovered the positive impact of CPP on α-TCP to β-TCP transformation. Also, other synthetically available sources of Ca phosphate are possible to use in the synthesis of β-TCP. For example, the intermediate formation of β-TCP was observed during heat treatment of $Ca(NH_4)_2P_2O_7{\cdot}H_2O$, but the subsequent reactions led to β-calcium polyphosphate β-$Ca(PO_3)_2$ and tromelite $Ca_4P_6O_{19}$.[33]

Thus, we have developed a simple and efficient method for the synthesis of β-TCP, which does not contain crystalline impurities of other calcium phosphates. The high quality of β-TCP allows using it in composites for orthopedic surgery, and these studies are now on the way in our laboratory.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.05.032.

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