

Determination of the activation energies of phase transition for calcium orthophosphates based on powder X-ray diffraction data

Kateryna Vasylenko

Ukrainian State University of Chemical Technology

Yuriy Sakhno

University of Delaware

Deb Jaisi

University of Delaware

Mykola Nikolenko (✉ n_nikolenko@ukr.net)

Ukrainian State University of Chemical Technology

Research Article

Keywords: X-ray powder diffraction analysis, calcium orthophosphates, activation energies

Posted Date: May 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-506356/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Crystal Research and Technology on December 17th, 2021. See the published version at <https://doi.org/10.1002/crat.202100215>.

Determination of the activation energies of phase transition for calcium orthophosphates based on powder X-ray diffraction data

Kateryna Vasylenko¹, Yuriy Sakhno²; Deb Jaisi²; Mykola Nikolenko^{1,*}

¹Faculty of Chemical Technologies and Ecology, Ukrainian State University of Chemical Technology, Dnipro, 49005, Ukraine

²Department of Plant and Soil Sciences, University of Delaware, Newark, DE, 19716, USA

* *Corresponding author: Nikolenko N. Email: n_nikolenko@ukr.net*

Submitted to: Scientific Reports

May 08, 2021

ABSTRACT

Kinetic studies of the transformation of calcium orthophosphates metastable precipitates were performed under different synthesis conditions. Phase composition and degree of crystallinity were investigated by X-ray powder diffraction analysis. In acidic solution, precipitates of $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ (DCPD) and CaHPO_4 (DCPA) are formed at the early stage of precipitation, with the degree of crystallinity at the range of 17-35%. Specifically, DCPD precipitates at 30°C and anhydrous DCPA at 50°C. In alkaline solution (pH 8-10), only amorphous forms of calcium orthophosphate is precipitated, which is explained by the high degree of supersaturation (i.e., the high rate of precipitation compared to that in acidic media). The diffraction peaks of DCPD and DCPA are found to be 0.3-0.45 degrees lower relative to their reference data, which is caused by decrease of lattice strain during early stage of crystallization. Furthermore, the initial molar ratio of Ca/P in reagent mixture was found to play subsidiary role in determining the composition of final calcium phosphate precipitates. The effect of pH on the composition of precipitates is illustrated by the solubility isotherms of pure calcium orthophosphates. Given that the intensities of diffraction peaks are proportional to planar density of the material in the given plane, we propose, for the first time, to determine activation energy of phase transformation of calcium orthophosphate from X-ray powder diffraction patterns. Based on this relationship developed, the activation energy for the recrystallization DCPD and DCPA are 10.2 and 13.1 kJ/mol, respectively and for the phase transition of DCPD to DCPA – 36.7 kJ/mol. Further recrystallization to most thermodynamically stable $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ hydroxyapatite (HA) occurs at the activation energy of 5.2 kJ/mol. These findings are critical on phase transition and transformation of calcium phosphate minerals.

Introduction

Among inorganic compounds of calcium and phosphorus, calcium orthophosphates are of particular interest. They are the mineral basis of bone tissue and are therefore considered as promising biomaterials. They are actively used in modern plastic surgery and medical cosmetology.¹⁻³ For example, one of the most common procedures in cosmetology today is contouring, the filler of which includes calcium hydroxyapatite (HA).⁴⁻⁶ Calcium phosphates have various other applications including acidity regulator, emulsifier, leavening agent, anticoagulant and moisture retaining agent, plant tissue sealant, and fertilizer.

The changes in physical and chemical properties, including crystallography and thermodynamic parameters in calcium phosphates such as due to ion substitution and phase

transformations are well studied in the 20th century ¹. However, it is unclear so far why certain forms of calcium phosphates are precipitated under specific pH of the solution, Ca/P molar ratio, or precipitation method. Specifically, conditions of precipitation and ranges of phase transitions of metastable states of calcium phosphates are also not fully investigated. This gap in fundamental science has limited accurate behavior of calcium phosphates in various applications such as to medical and cosmetic applications and novel phosphate fertilizers for agricultural applications ⁴. Therefore a detailed understanding of the mechanism of phase transformation during synthesis as well as during dissolution is needed,

In the $\text{Ca}(\text{OH})_2\text{-H}_3\text{PO}_4\text{-H}_2\text{O}$ system, the formation of eight individual calcium orthophosphates with a molar ratio of Ca/P in the range from 0.5 to 1.67 are well known: $\text{Ca}(\text{H}_2\text{PO}_4)_2\cdot\text{H}_2\text{O}$, $\text{Ca}(\text{H}_2\text{PO}_4)_2$, $\text{CaHPO}_4\cdot 2\text{H}_2\text{O}$ (DCPD), CaHPO_4 (DCPA), $\alpha\text{-Ca}_3(\text{PO}_4)_2$, $\beta\text{-Ca}_3(\text{PO}_4)_2$, $\text{Ca}_8(\text{HPO}_4)_2(\text{PO}_4)_4\cdot 5\text{H}_2\text{O}$ and HA. Moreover, variable composition of phosphates generates other group: amorphous calcium phosphate $\text{Ca}_x\text{H}_y(\text{PO}_4)_z\cdot n\text{H}_2\text{O}$ (Ca/P = 1,2-2,2) and Ca-deficient hydroxyapatite $\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}$ (Ca/P = 1.50-1.67) ^{7,8}. A separate group of calcium orthophosphates are formed from ion-substitution: fluoroapatites $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$ and $\text{Ca}_{10}(\text{PO}_4)_6\text{F}(\text{OH})$, carbonate-containing apatites, apatites with the addition of cations of various metals ^{4,9,10}. Among these groups, two-, three- and even multi-phase calcium orthophosphates, in which the individual components cannot be separated from each other, are known ¹. Transformational or dry synthesis routes at high temperature generate another group: tetracalcium phosphate $\text{Ca}_4(\text{PO}_4)_2\text{O}$, oxyapatite $\text{Ca}_{10}(\text{PO}_4)_6\text{O}$, tricalcium phosphate $\text{Ca}_3(\text{PO}_4)_2$. For example, tricalcium phosphate is formed by heat treatment above 800°C from calcium and phosphorus precursors at a Ca/P ratio of 1.5. This phosphate is stable at room temperature but hydrolyzed in an aqueous solution, which indicates its metastable nature.

As outlined above, the possibility of the formation of metastable phases and additional phase transformations significantly complicates the choice of optimal conditions for the synthesis of calcium orthophosphates ^{8,11,12}. The complexity of the calcium orthophosphates precipitation is well illustrated by Ferreira et al ¹³ by highlighting the equimolar Ca/P ratio of $\text{Ca}(\text{OH})_2$ and phosphoric acid forms DCPD and five stages of intermediate stages before the formation of hydroxyapatite (HA). According to Briak-Ben ¹⁴, hydroxyapatite precipitation, when calcium salts and phosphate ions are mixed even at a strict stoichiometric Ca/P ratio of 1.67, occurs due to the formation of amorphous or Ca-deficient calcium phosphate. It should also be noted that the chemical composition of the hydroxyapatite surface does not

necessarily coincide with its unit cell composition ¹⁵. This discrepancy could be explained by the processes of hydrolysis and the metastable nature of the material. These lines of evidence from past studies allude that processes of chemical precipitation of calcium orthophosphates, specially metastable and intermediate phases, is by far from fully understood. In this communication, the phase transformations of metastable states calcium orthophosphates are studied. For the first time, we show that the kinetics of the reaction is controlled by distinct differences in activation energies, which form different metastable phases and limit phase transformations.

Materials and methods

Various calcium phosphate materials were synthesized at different conditions. In all cases, 1.0 M solutions of CaCl₂ and H₃PO₄ of chemically pure or reagent grade (Reachim) were used as precursors of the synthesis. The calcium phosphate precipitation was performed by varying the pH of the solutions in the range of 3 to 11 and the molar ratio of Ca/P 0.5 to 1.67. 500 mL of distilled water was placed in the reaction flask and the pH was adjusted to the target value using solutions of hydrochloric acid or ammonia. The solutions of CaCl₂ and H₃PO₄ prepared with a given ratio of Ca/P. The solution was continuously stirred using a blade stirrer at a speed of 300 rpm and 1.0 M ammonia solution was simultaneously added to the solution using peristaltic Micro-Dosers at a flow rate of 0.05-1 mL/min. The flow rate of the reagent solutions was selected based on the stoichiometry of precipitation reactions and based on pilot experiments so that the pH of the solution remained at a given level with an accuracy of ±0.1 pH using a pH meter Adwa AD8000 (accuracy of ±0.05 pH units) throughout the precipitation process. After precipitation, the products were kept under stirring in the reactor for additional 6 h. This process of “maturation” contributes to the crystallization of precipitates, and allows proper identification by powdered X-ray diffraction. The resulting suspensions were filtered under vacuum, washed with small portions of cold distilled water and then freeze dried to constant weight before analysis.

To determine the Ca/P molar ratio, synthesized precipitates were dried to constant weight and homogenized by grinding in an agate mortar. A weighed quantity of the precipitates were dissolved in a concentrated HCl in volumetric flasks. Concentration of orthophosphate was performed in separate aliquots by using colorimetric method in which reduction reaction of heteropolyacid formed by the reaction of orthophosphate ions with ammonium molybdate in acidic condition. Concentration of calcium ion was determined by

inductively coupled plasma optical emission spectroscopy (ICP-OES) using an Optima 8000 spectrometer (PerkinElmer, Norwalk, CT, USA).

X-ray phase analysis was performed using a DRON-2 diffractometer in monochromatic Co-K $_{\alpha 1}$ radiation. To identify the phase composition from the PCPDFWIN database, the diffraction patterns were recalculated on Cu-K $_{\alpha 1}$ radiation. The degree of crystallinity (X_C), corresponding to the fraction of the crystalline phase in the test volume, was evaluated by the equation:

$$B_{hkl} \sqrt[3]{X_C} = K,$$

where K is a constant equal to 0.24, used for different hydroxyapatite in powder diffraction, and B_{hkl} is the width (hkl) of the reflex at its half-height¹⁶.

The solubility of calcium phosphate precipitates was calculated by using the formula for the solubility product, as:

$$K_S = [Ca^{2+}]^{10} [PO_4^{3-}]^6 [OH^-]^2 = (10\beta_0 S)^{10} (6\alpha_3 S)^6 (S + C_{OH})^2,$$

where S is the solubility (mol/l), α_i and β_i are the proportions of anions and cations of the precipitate. Similarly, K_1 , K_2 , are K_3 are acid dissociation constants and K_1^* and K_2^* are stability constants of the cation hydroxy complexes. The expression for α_3 and β_0 are as follows:

$$\alpha_3 = \frac{K_1 K_2 K_3}{[H^+]^3 + [H^+]^2 K_1 + [H^+] K_1 K_2 + K_1 K_2 K_3},$$

$$\beta_0 = \frac{1}{1 + [OH^-] K_1^* + [OH^-]^2 K_1^* K_2^*}.$$

The following values of solubility products were used in the calculations (negative logarithms of their values are indicated in brackets): Ca(H₂PO₄)₂·2H₂O (1.14), DCPD (6.59), DCPA (6.90), amorphous calcium phosphates Ca_xH_y(PO₄)_znH₂O with Ca/P = 1.2-2.2 (26-33), α - and β -Ca₃(PO₄)₂ (40), Ca-deficient hydroxyapatites Ca_{10-x}(HPO₄)_x(PO₄)_{6-x}(OH)_{2-x} with Ca/P = 1.5-1.67 (114-155), Ca₈(HPO₄)₂(PO₄)₄ (96.6), HA (155)¹⁷.

Results and discussion

The summary of experimental conditions and compositions of the synthesized products are reported in Table 1. At the early stage of precipitation, the maturation of precipitates at lower pH and at 15-30°C lead to the formation of well crystalline forms of

DCPD and DCPA. The degree of their crystallinity varies in the range of 17-35% and can be considered as a result of chemical precipitation. With a decrease in pH of the reactant mixture, a progressive decrease in the degree of crystallinity of the precipitates was found.

In acidic solutions at room temperature, crystal hydrate of DCPD (PCPDFWIN No. 72-0713) is formed. However, its anhydrous form, DCPA (PCPDFWIN No. 77-0128), is crystallized directly in the solution during precipitation at 50°C and above. The conversion of DCPD to DCPA has been reported earlier¹⁷. This process proceeds at a noticeable rate already at a temperature of 37°C. The dehydration of DCPD is reported to occur at temperature above 80°C¹, which, however, has been found at a much lower temperature in this study.

Fig. 1 shows the diffraction patterns of calcium orthophosphates synthesized at temperatures range from 15 to 90°C. The change in diffraction patterns of precipitates matured at $\geq 50^\circ\text{C}$ indicates a significant rearrangement of the crystal lattice in DCPD. In fact, the conversion of DCPD to DCPA is caused by the rearrangement of the crystal lattice. According to reference data, DCPD has a monoclinic crystal lattice with the parameters $a = 5.812$, $b = 15.18$, and $c = 6.239$, while DCPA has triclinic with $a = 6.900$, $b = 6.650$, and $c = 7.000$.

Diffraction patterns in Fig. 1 from the PCPDFWIN reference database show an apparent low angle shift by 0.3-0.45 degrees of all diffraction peaks relative to their reference values. Additional studies have shown that the magnitude of shift of peaks decreases with increasing time of maturation of precipitates in the supernatant¹⁷. It should be noted that this effect is only observed in precipitates that have not been thermally treatment after precipitation, such as reference calcium phosphates presented in the PCPDFWIN. These differences are better explained based on the solid-state chemistry principle that lattice strain decreases with an increase in temperature or time of maturation. During thermal treatment of crystalline or partially crystalline precipitate in hydrated media, crystallites continue to grow, which in turn reduces the lattice strain of the crystal structure and consequent decrease in interplanar spacing. Contrarily to acidic synthesis, the precipitation in an alkaline medium showed stable amorphous precipitate, which practically does not crystallize at 15-30°C, even if they are kept in solution for several days (Fig. SI 1-3). They did not show any shift in peak position on the diffraction patterns.

Given that the structure of the precipitate is determined by the precipitation rate (r), which is a function of the degree of supersaturation of the product in the solution, the relationship could be written as follows:

$$r = k(\Omega^{1/3} - 1)^n,$$

where k is the rate constant, n is the order of precipitation (as a rule of thumb, $n > 10$), Ω is the degree of supersaturation (the ratio of the ion activities product in the supersaturated solution to the thermodynamic solubility product of the precipitate¹⁸). In acidic solutions, the degree of supersaturation of the reagent mixture is relatively small due to excess of protonated H_2PO_4^- over HPO_4^{2-} species. This reduces the growth rate of DCPD nuclei and thus creates the conditions for the formation of the most thermodynamically stable crystal lattice at given pH. As the degree of supersaturation increases, the precipitation rate increases and the precipitate is formed in a less energetically favorable crystal lattice. With a further increase in pH, the size of the DCPD particles decreases with the eventual formation of amorphous products in alkaline solutions.

As illustrated from data reported in Table 1, the phase compositions of calcium phosphate precipitates do not depend on the starting Ca/P molar ratio. For example, mixing aqueous solutions of reagents with molar ratios of Ca/P = 0.5 and 1.5 at pH = 3-4 and pH = 6, formed the solid precipitate of DCPD with Ca/P ratio of 1.00 ± 0.05 . Similarly, mixing aqueous reagents with a molar ratio of Ca/P = 1.0 and 1.67 at pH 8, amorphous precipitates with a molar ratio of Ca/P ca. 1.50-1.61 were obtained. An increase of the maturation temperature to 50°C improved the degree of crystallinity of the precipitates and formed Ca-deficient hydroxyapatite (Fig. SI 4). A further increase in synthesis pH to 11 with an initial molar ratio of reagents of Ca/P = 0.5, an amorphous precipitate was formed with Ca/P = 1.67 ± 0.05 . However, PXRD diffraction peaks confirmed the presence of some long-range atomic order of hydroxyapatite (Fig. SI 3).

The role of differences in the Ca/P ratios in the reagent mixture in the products have been repeatedly noted in the literature. For example, Zyman et al.¹² prepared phosphate products with Ca/P ratio 1.5 at pH = 10 from a reagent mixture with an initial ratio of Ca/P = 1: 1. They explained this discrepancy by the hydrolysis of the fraction of DCPD during washing of precipitates after synthesis. These results indicate that when mixing solutions of calcium and orthophosphate salts with the ratio Ca/P = 1, the formation of hydroxyapatite with Ca/P ratio = 1.5 is possible. In our study, mixing solutions with Ca/P ratio as low as 0.5 in alkaline solutions formed an amorphous precipitate with a ratio of Ca/P = 1.67 ± 0.05 (Table

1). This amorphous phase is a precursor for the crystallization of apatite, although the rate of crystal growth is very low at 20°C. Thus, in contrast to the pH of the reaction medium- a master variable, the molar Ca/P ratio of initial reagents does not play a critical role in determining the final composition of calcium phosphate precipitates. The differences in Ca/P ratio between the initial reagent mixture and resulted precipitate at the end of crystallization should be only induced by minor presence of CaCO₃ from atmospheric air at the impurities level because the magnitude of coprecipitation of certain ions depends on their concentration in solution and the order of mixing of solutions of synthesis precursors. It is noteworthy to mention that even if Ca/P ratio of initial reagents used for synthesis is equal to the stoichiometric hydroxyapatite (i.e., 1.667), non-stoichiometric precipitates, such as amorphous phosphates, are still formed as a side product. ¹.

The effect of pH on the composition of chemically pure calcium orthophosphate precipitates can be illustrated in a solubility isotherm (Fig. 2). As shown, the optimal pH for the synthesis of calcium phosphates can be chosen based on the need of solubility and stability of crystalline phases, which, however, depends on the precipitation method, synthesis temperature, and aging condition. According to thermodynamic calculation on phase precipitation, hydroxyapatite is the least soluble in the entire range of pH values from 0 to 14 (Fig. 2).

The variable range of solubility of precipitates are shown by shaded zones (4 and 7 in Fig. 2). The actual loci of these isotherms depend on chemical composition and the equilibrium constant (K_{sp}) of the precipitate. A range of solubility isotherms of amorphous calcium phosphates $Ca_xH_y(PO_4)_z \cdot nH_2O$ with a molar ratio of Ca/P = 1.2-2.2 lie between curves 3 and 5. At pH < 6, calcium phosphates are precipitated in crystalline form due to the relatively low concentration of HPO₄²⁻ ions. Suitable time of maturation and temperature can promote their conversion into less soluble and more thermodynamically stable forms of calcium phosphates. The range of thermodynamic states of isotherms lies between curves 6 and 8 for Ca-deficient hydroxyapatites with a molar ratio of Ca/P = 1.5-1.67. All of them are metastable in hydrated conditions, which means in the presence of excess calcium ions, they transform into stoichiometric hydroxyapatite.

As shown in Fig. 2, the precipitates of DCPD and DCPA are metastable, which transform into more stable phosphates over time or increase in temperature. This conclusion was based on series of experimentation. Heating DCPA precipitates at pH = 6 in an autoclave at 250 °C for 6 h resulted in a mixture of anhydrous DCPA and hydroxyapatite HA. This

partial transformation of DCPA is well explained by the kinetic inhibition of the reaction. The irreversibility of the phase transition from DCPD to DCPA was reported earlier ¹⁷. However, other authors ¹⁹ have shown that DCPA is fairly resistant to hydration and does not transform to DCPD at a temperature of 4-50 °C for as long as seven months. The solubility isotherms in Fig. 2 explain these patterns well. The change of thermodynamic state from isotherm 6 to 8 is energetically favorable. However, activation energy could be a barrier to this transformation. It is obvious that an increase in temperature is required to overcome this barrier, which is confirmed by our experimental results and literature data. For example, Ca-deficient hydroxyapatite can be obtained by simultaneous addition of calcium and phosphoric acid salts in the ratio Ca/P = 1.50-1.67 in boiling water at pH = 6.5-9.5, followed by boiling the suspension for several hours. Similarly, stoichiometric hydroxyapatite can be synthesized at a temperature of ~90° at the ratio of Ca/P = 1.67 and pH = 9.5-12 ²⁰.

Considering that the intensity of diffraction peaks is proportional to the planar density of all crystallites formed under specific crystallization conditions, activation energies (minimum energy required for growing the crystalline phase) are calculated. To a first approximation, the rate of transformation of the crystal lattice and the rate of conversion of certain interplanar distances are described by a kinetic equation of pseudo-first order:

$$\frac{dI}{dt} = \pm kI,$$

or in integral form:

$\ln I = \ln I_0 \pm kt$, where k is the rate constant, I is the current intensity of the diffraction pattern, which reflects the state transformation (i.e., transition from the metastable state to the next, second thermodynamically more stable state of precipitate in the process of maturation in the supernatant), I_0 is the intensity of diffraction peak at time $t = 0$. The equations are expressed in \pm sign because the intensity of the reflection can both increase and decrease. It is clear that at $t = \text{const}$ the logarithm applied to reflection peaks is proportional to rate constant of phase transition. Assuming that activation energy (E_a) does not depend on temperature the calculated values of logarithm of intensity from reflections provide a beneficial tool that allows for comparison between different states of phase transition.

After integrating the Arrhenius equation in a narrow temperature range T_1 and T_2 (assuming that the activation energy (E_a) does not depend on the temperature), the revised expression of the equation:

$$\ln \frac{k_2}{k_1} = \frac{E_a}{R} \left(\frac{1}{T_1} - \frac{1}{T_2} \right).$$

The above equation can be expressed using the logarithms of the peak intensities of the diffraction patterns instead of the rate constants for precipitates that are present in the supernatant for the same time but at different temperatures. Given that peak intensity can increase or decrease, the expression above can be expressed in a modulus form:

$$\left| \ln \left(\frac{\ln I_2}{\ln I_1} \right) \right| = \frac{E_a}{R} \left(\frac{1}{T_1} - \frac{1}{T_2} \right).$$

This formula allows to calculate the activation energies at any given value of 2θ diffraction patterns of precipitates that undergo phase transition after precipitation. The results of calculated values of E_a for diffractograms in Fig. 1 are reported in Fig 3. In present calculations the ranges of diffractograms with typical reflections of DCPD and DCPA were used whereas areas with no diffraction peaks were excluded due to significant contribution of error in estimation of E_a and thus irrelevant in representation of crystalline lattice structures of the studied here phases.

Based on the results obtained from calculations using equations above and presented in Fig. 3, we conclude that the change of each interplanar distance in the crystal lattice is characterized by its activation energy. The appearance and disappearance of certain peaks on the diffraction pattern require overcoming a specific activation energy barrier. Fig. 3 show the upper limit of the activation energy, which is a more appropriate estimate of the crystallization process than the average values. Crystallization (growth of long-range atomic order in particles due to diffusion of ions from solution), recrystallization (growth of long-range atomic order in particles due to diffusion of ions within the solid phase of particles), or phase transformation are interconnected and complementary and cannot exist, in most cases, without each other. Fig. 3 show a notable difference in activation energies for the recrystallization process, which in turn, will determine the overall rate of this reaction. Thus, the transformation of the interplanar distances in the crystal lattice with the largest E_a value will be the limiting factor for all reactions.

The maximum activation energy calculated using the above relationship for DCPD recrystallization 10.2 kJ/mol. Similarly, the energy for the recrystallization of anhydrous DCPA – 13.1 kJ/mol, transition DCPD to DCPA phase – 36.7 kJ/mol, and for recrystallization to HA – 5.2 kJ/mol. These results suggest that the reconstruction of the crystal lattice requires much more energy than the crystal growth or hydrolysis of certain

faces of the crystal or crystallite of the polycrystalline material. The kinetics of the DCPD crystallization in supersaturated solutions at pH = 5.4-6.2 was calculated by measuring the concentrations of calcium ions and phosphates at temperatures of 15, 25, and 37 °C²¹. These authors found that the activation energy of DCPD crystals growth is 44.0 kJ/mol, which indicates the process of crystallization was in the kinetic mode. Similarly, activation energy of the dissolution of DCPD crystals in unsaturated solutions at pH = 5.0-5.6 was 15.9 kJ/mol²². These authors concluded that the dissolution rate of DCPD is controlled by the site of calcium ions and diffusion rate of phosphates from crystal surface.

It should be noted that in our experiments, both the precipitation and maturation of calcium phosphates were carried out under continuous stirring with a blade stirrer at a speed of ~ 300 rpm. Herewith, the precipitates were present in saturated solution, which means the content of the precipitate is determined by the solubility. The growth of crystals under such conditions is possible only due to two steps: dissolution of nano- or microparticles and crystallization of larger particles, Ostwald Ripening. It is obvious that the total crystal growth rate under such conditions should be controlled at the lowest (limiting) rate. On the other hand, increasing the degree of crystallinity (long-range atomic order) can be considered as a process of recrystallization, when, for example, the amorphous portion of the precipitate at the boundary with the crystallites gradually turns into a crystalline state, thus extending the length of atomic order. This process can take place not only on the surface, but also in the volume of the solid phase, where the diffusion processes are not associated with gradients of concentrations of calcium and phosphates in solution. It is more likely that in both processes: Ostwald ripening on the surface and recrystallization in the volume of precipitate particles occur side by side. Comparable and low activation energies (10.8 kJ/mol for DCPD and 11.2 kJ/mol for DCPA) suggest that the limiting reaction is likely the diffusion of ions. For the phase transition of DCPD to DCPA, the activation energy of 36.7 kJ/mol indicates the kinetic nature of reaction, which induces a conversion of the monoclinic crystal lattice of DCPD into a triclinic lattice of anhydrous DCPA. Overall, these results conclude that a caution needed to compare the literature data^{21,22} with current results on activation energy. To make a distinction, we used the term “recrystallization”, to represent the growth of crystallites of polycrystalline material at the expense of others.

Conclusion

The study on kinetics of crystallization and transformation of metastable calcium orthophosphates under different synthesis conditions (pH, temperature, and molar ratio Ca/P),

specifically the phase composition and degree of crystallinity, generated insightful outcomes. In acidic solutions (pH = 3-6, t=15-90°C), DCPD and DCPA precipitates are formed in the crystalline state (degree of crystallinity =17-35%). In alkaline solutions (pH = 8-10, t=15-30°C) calcium orthophosphates are precipitated only in amorphous state. This is due to a high degree of supersaturation of solutions, and consequently, the higher precipitation rate compared to that in acidic media. A shift of all diffraction peaks of DCPD and DCPA by 0.3-0.45 2θ degrees relative to the reference data was found to be related to time for maturation. Our data shows that the magnitude of the shift decreases with the increase in time of maturation of precipitates in the supernatant, analogous to commonly described solid state chemistry principle in which decrease of lattice strain as a result of growth of long-range atomic order.

We conclude that, unlike pH as the master variable of the form, the initial molar ratio of Ca/P reagents in the media has a minor role in determining the fundamental composition of calcium phosphate precipitates. Differences should be expected only at level of minor impurities, because the magnitude of coprecipitation of certain ions depends on their concentration in solution and the order of mixing of solutions of synthesis precursors.

The effect of pH on the composition of precipitates is illustrated by the solubility isotherms of known calcium orthophosphate phases. Based on this calculations, for the entire range of pH (0-14), hydroxyapatite is the least soluble phosphate. The solubility isotherms allowed to establish energetically possible phase transitions between metastable states of calcium phosphates with activation energy being a barrier of transition. An increase in temperature is often the factor to overcome this activation barrier. Since the intensity of diffraction peaks is proportional to planar density of given plane in the material, we proposed an equation to calculate the values of activation energy of phase transformation, for the first time, from X-ray diffraction patterns. The calculated activation energy for DCPD recrystallization is 10.2 kJ/mol, for recrystallization of anhydrous DCPA is – 13.1 kJ/mol, and phase transition of DCPD to DCPA is– 36.7 kJ/mol, and for recrystallization of hydroxyapatite $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ to be – 5.2 kJ/mol. These results, overall, show that the physical model of calcium phosphate transformation where reconstruction of the crystal lattice requires more energy than that in the crystal growth or dissolution.

References

- 1 Dorozhkin, S. V. Calcium orthophosphate-based bioceramics. *Materials* **6**, 3840-3942 (2013).
- 2 Dorozhkin, S. V. Calcium orthophosphates (CaPO₄): occurrence and properties. *Progress in biomaterials* **5**, 9-70 (2016).
- 3 Ślósarczyk, A., Czechowska, J., Cichoń, E. & Zima, A. New Hybrid Bioactive Composites for Bone Substitution. *Processes* **8**, 335 (2020).
- 4 Dorozhkin, S. V. Calcium orthophosphate-containing biocomposites and hybrid biomaterials for biomedical applications. *Journal of functional biomaterials* **6**, 708-832 (2015).
- 5 Lett, J. A. *et al.* Drug Leaching Properties of Vancomycin Loaded Mesoporous Hydroxyapatite as Bone Substitutes. *Processes* **7**, 826 (2019).
- 6 Wang, L. & Nancollas, G. H. Calcium orthophosphates: crystallization and dissolution. *Chemical reviews* **108**, 4628-4669 (2008).
- 7 Brown, P. W. Phase Relationships in the Ternary System CaO—P₂O₅—H₂O at 25° C. *Journal of the American Ceramic Society* **75**, 17-22 (1992).
- 8 Martin, R. I. & Brown, P. W. Phase equilibria among acid calcium phosphates. *Journal of the American Ceramic Society* **80**, 1263-1266 (1997).
- 9 Lin, R. & Ding, Y. A review on the synthesis and applications of mesostructured transition metal phosphates. *Materials* **6**, 217-243 (2013).
- 10 Omelon, S. J. & Grynopas, M. D. Relationships between polyphosphate chemistry, biochemistry and apatite biomineralization. *Chemical reviews* **108**, 4694-4715 (2008).
- 11 McDowell, H., Gregory, T. & Brown, W. Solubility of Ca₅{P₄hOH in the System Ca {OH} 2-H₃P₄-H₂O at 5, 15, 25, and 37 C. (1977).
- 12 Zyman, Z., Goncharenko, A., Khavroniuk, O. & Rokhmistrov, D. Crystallization of metastable and stable phases from hydrolyzed by rinsing precipitated amorphous calcium phosphates with a given Ca/P ratio of 1: 1. *Journal of Crystal Growth* **535**, 125547 (2020).
- 13 Ferreira, A., Oliveira, C. & Rocha, F. The different phases in the precipitation of dicalcium phosphate dihydrate. *Journal of Crystal Growth* **252**, 599-611 (2003).
- 14 El Briak-BenAbdeslam, H., Ginebra, M., Vert, M. & Boudeville, P. Wet or dry mechanochemical synthesis of calcium phosphates? Influence of the water content on DCPD—CaO reaction kinetics. *Acta Biomaterialia* **4**, 378-386 (2008).
- 15 Nikolenko, N. & Esajenko, E. Surface properties of synthetic calcium hydroxyapatite. *Adsorption Science & Technology* **23**, 543-553 (2005).
- 16 Bakan, F. A Systematic Study of the Effect of pH on the Initialization of Ca-deficient Hydroxyapatite to β-TCP Nanoparticles. *Materials* **12**, 354 (2019).
- 17 Nikolenko, M. V., Vasylenko, K. V., Myrhorodska, V. D., Kostyniuk, A. & Likozar, B. Synthesis of Calcium Orthophosphates by Chemical Precipitation in Aqueous Solutions: The Effect of the Acidity, Ca/P Molar Ratio, and Temperature on the Phase Composition and Solubility of Precipitates. *Processes* **8**, 1009 (2020).
- 18 Nikolenko, M., Kostyniuk, A., Goutenoire, F. & Kalashnikov, Y. V. Chemical precipitation of iron (III) molybdate+ molybdenum trioxide mixtures through continuous crystallization. *Inorganic Materials* **50**, 1140-1145 (2014).
- 19 Miyazaki, T., Sivaprakasam, K., Tantry, J. & Suryanarayanan, R. Physical characterization of dibasic calcium phosphate dihydrate and anhydrate. *Journal of pharmaceutical sciences* **98**, 905-916 (2009).
- 20 Norton, J., Malik, K., Darr, J. & Rehman, I. Recent developments in processing and surface modification of hydroxyapatite. *Advances in Applied Ceramics* **105**, 113-139 (2006).

- 21 Marshall, R. W. & Nancollas, G. H. Kinetics of crystal growth of dicalcium phosphate dihydrate. *The Journal of Physical Chemistry* **73**, 3838-3844 (1969).
- 22 Nancollas, G. H. & Marshall, R. W. Kinetics of dissolution of dicalcium phosphate dihydrate crystals. *Journal of dental research* **50**, 1268-1272 (1971).

Acknowledgment

This work was supported by a R&D project 24/200490 (state registration number 0120U101971) of the Ukrainian State University of Chemical Technology . A part of this work was also supported from a research grant from the U.S. Department of Agriculture (NIFA award 2018-67021-27965).

Author contributions

M.N. designed the study and interpreted results; D.J. analyzed results and edited text; K.V. performed synthesis; Y.S. plotted figures, performed literature review and edited text. All authors contributed to the draft manuscript writing and approved the final version.

Additional information

The authors declare no competing interests.

Correspondence and requests for materials should be addressed to M.N.

Figure legends

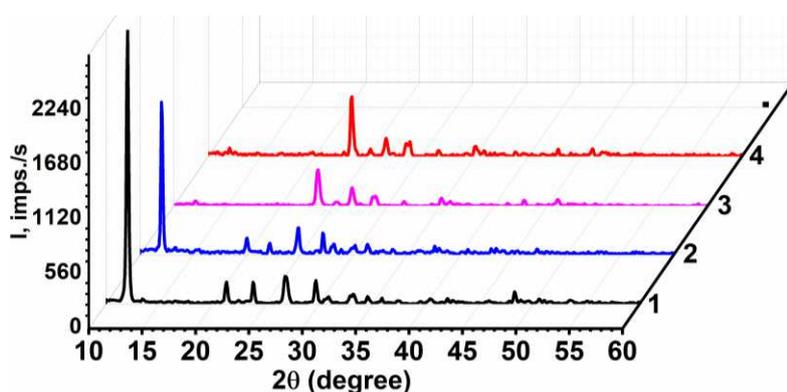


Fig. 1. Diffraction patterns of calcium orthophosphate synthesized at a constant pH (3.8) and initial Ca/P ratio (0.5) but at four different temperatures: 15 °C (1), 30 °C (2), 50 °C (3), and 90 °C (4). The products were kept in the reaction medium for 6 h after precipitation.

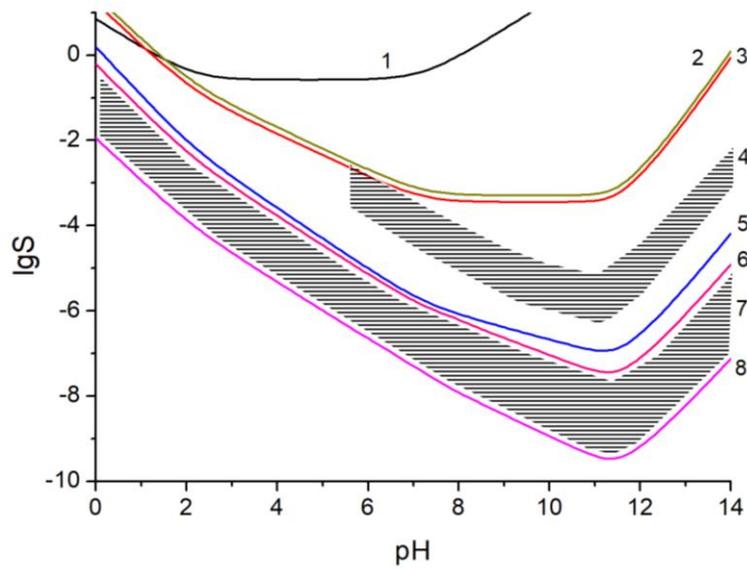


Fig. 2. Solubility isotherms of different calcium phosphates: 1) $\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$, 2) DCPD, 3) DCPA, 4) amorphous precipitates $\text{Ca}_x\text{H}_y(\text{PO}_4)_z \cdot n\text{H}_2\text{O}$, 5) $\text{Ca}_8(\text{HPO}_4)_2(\text{PO}_4)_4 \cdot 5\text{H}_2\text{O}$, 6) $\text{Ca}_9(\text{HPO}_4)(\text{PO}_4)_5(\text{OH})$, 7) Ca-deficient (non-stoichiometric) hydroxyapatites $\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}$, and 8) stoichiometric hydroxyapatite HA.

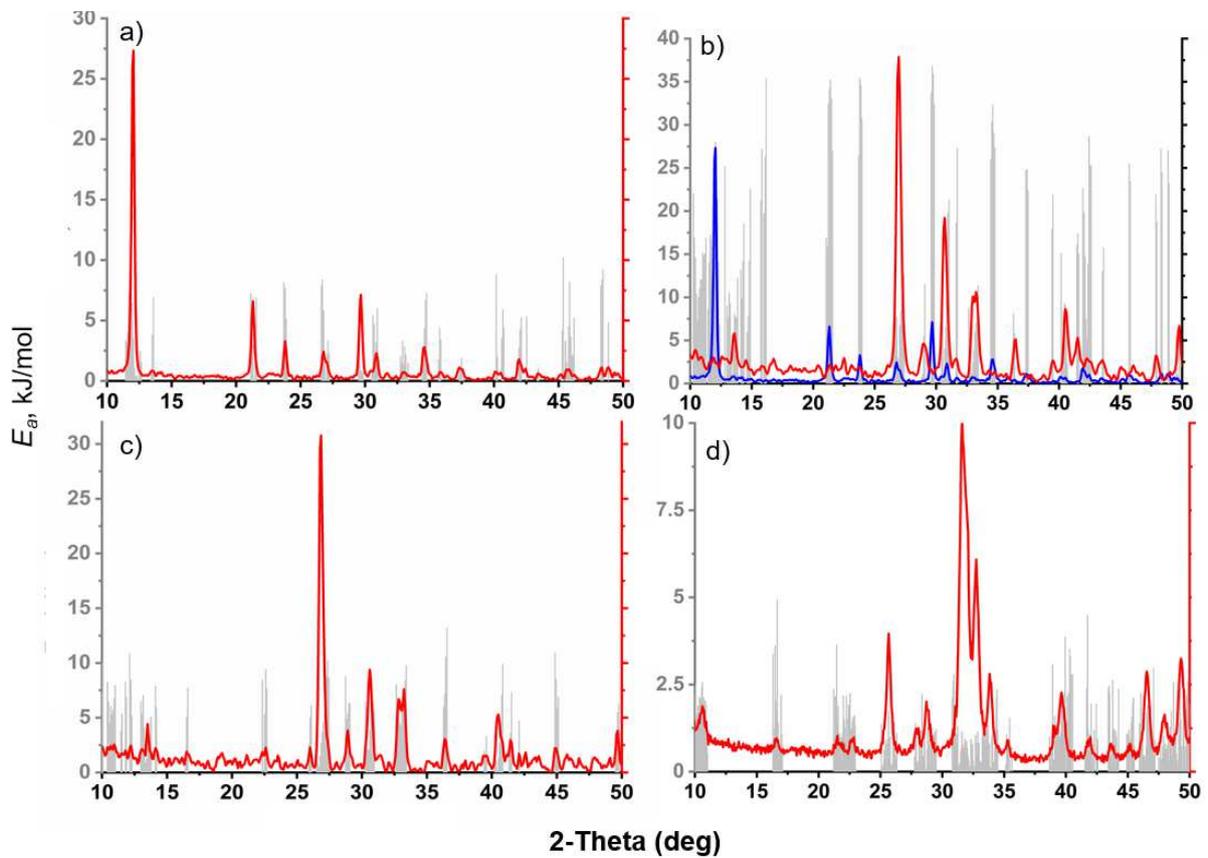


Fig. 3. PXRD diffractogram of pure DCPA (red) and DCPD ((blue) and calculation based on activation energies bars (grey). a) 14 and 30°C, b) 30 and 50°C, c) 50 and 90°C and d) at 50°C.

Table

Table.1. Synthesis conditions, phase composition, and degree of crystallinity (X_c) of calcium orthophosphate precipitates.

pH of the precipitation	Ca/P in solution	T, °C	Phase composition of the precipitate	Ca/P in precipitate	X_c , %
3.0	0.5	20	DCPD	1.00±0.05	35
3.8	0.5	15	DCPD	1.00±0.05	17
		30	DCPD	1.00±0.05	17
		50	DCPA	1.00±0.05	18
		90	DCPA	1.00±0.05	32
6.0	1.5	20	DCPD	1.00±0.05	12
8.0	1.0	15	Amorphous precipitate	1.50±0.05	0
		30	Amorphous precipitate	1.51±0.05	0
		50	Ca-deficient hydroxyapatite	1.55±0.05	3
8.0	1.67	15	Amorphous precipitate	1.53±0.05	0
		30	Amorphous precipitate	1.59±0.05	0
		50	Ca-deficient hydroxyapatite	1.61±0.05	9
11.0	0.5	20	Amorphous precipitate	1.67±0.05	0

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupportinginformationMay172021formatted.docx](#)