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Hydrolysis of tetracalcium phosphate under a near-constant-composition condition—effects of pH and particle size

Laurence C. Chow*, Milenko Markovic, Stanislav A. Frukhtbeyn, Shozo Takagi

Paffenbarger Research Center, American Dental Association Foundation, National Institute of Standards and Technology, Gaithersburg, Maryland, MD 20899, USA

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Abstract

Tetracalcium phosphate (TTCP) is a component of a number of calcium phosphate cements used clinically for bone defect repairs. The strength, phase composition, and solubility of the set cement are highly dependent on the reactions of the cement components during setting. This study investigated hydrolysis reactions of TTCP under solution compositions chosen to mimic the compositions of the cement liquid during setting. The study utilized a pseudo-constant-composition technique that allowed both the rate and stoichiometry of the reaction to be determined while the reaction proceeded under a specific, constantly held solution pH, thereby keeping a constant calcium-to-phosphate ratio in solution. The hydrolysis experiments were conducted using either a fine (median particle size 3.5 μm) or coarse (median particle size 13.2 μm) TTCP powder at pH 7, 8 and 10. Low crystalline calcium (Ca)-deficient hydroxyapatite (HA) was the product in all experiments. Both the solution pH and TTCP particle size produced significant effects on all aspects of the hydrolysis reaction. At a given pH, the fine TTCP produced a HA product with a greater Ca deficiency than did the coarse TTCP. For a given particle size, the Ca deficiency generally decreased with increasing pH. Hydrolysis reaction rate generally decreased with increasing pH or TTCP particle size. At pH 7 and 8, the solution was undersaturated with respect to TTCP and supersaturated with respect to HA, suggesting that the reaction rate was limited by TTCP dissolution. In contrast, at pH 10, the solution was approximately saturated with respect to TTCP and highly supersaturated with respect to HA, suggesting that HA formation was the rate-determining step of the reaction. The findings provided useful insights into the setting reaction mechanisms of TTCP-containing calcium phosphate cements.

Keywords: Hydrolysis; Tetracalcium phosphate; Hydroxyapatite; Calcium-deficient apatite; Constant-composition titration; Bone graft material

1. Introduction

Although a large number of calcium phosphate cements form hydroxyapatite (HA) as the product, there are wide variations in the properties of the HA products formed. These include composition (Ca/P molar ratio, Ca deficiency, carbonate and sodium contents), crystallinity, and solubility properties. TenHuisen and Brown [1] reported the formation of Ca-deficient HA (CD-HA) in a slurry system consisting of tetracalcium phosphate (TTCP), $Ca_4(PO_4)_2O$, and dicalcium phosphate dihydrate (DCPD), $CaHPO_4 \cdot 2H_2O$, with a TTCP/DCPD molar ratio of 1/2. Another study [2] suggested the formation of nearly stoichiometric HA (S-HA), $Ca_5(PO_4)_3OH$, when excess TTCP was present, and formation of CD-HA when excess dicalcium phosphate anhydrous (DCPA), $CaHPO_4$, was present in a TTCP + DCPA cement.

It is possible that the HA products formed in a given cement system may have a range of Ca/P molar ratios rather than a single Ca/P value. This is because the stoichiometry of the HA formed at a given time during the reaction is influenced by the composition of the liquid phase, which is not constant but is affected by the relative rates of TTCP and DCPA dissolution and HA precipitation. The dissolution rates, in turn, depend on the amounts and the particle sizes of the TTCP and DCPA present. Finally, the amounts of TTCP and DCPA that are present at a given time would depend on

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*Corresponding author.

E-mail address: laurence.chow@nist.gov (L.C. Chow).

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the amounts of these components that have been consumed by the reaction, which are functions of time and the stoichiometry of the HA product that had been formed. The large number of interacting variables in the cement setting reaction makes the system too complex for elucidating mechanistic information relating to the factors that control the rate and course of the setting reactions. This is probably why little such information exists in the literature. We believe that useful information can be obtained by studying hydrolysis reactions of the individual cement components under solution compositions chosen to mimic the compositions of the cement liquid during setting. The variables may include the particle size of the reacting calcium phosphate compound and composition of the solution. The present paper describes a study of TTCP hydrolysis reactions with TTCP particle size and solution pH as the independent variables. The study utilized a pseudo-constant-composition technique that allowed both the rate and stoichiometry of the reaction to be determined while the reaction proceeded under a specific, constantly held solution pH.

2. Principle of the pseudo-constant-composition method

Because TTCP is more soluble than HA under all pH conditions [3], dissolution of TTCP in water would lead to a solution composition that is supersaturated with respect to HA and, consequently, HA precipitation. Hydrolysis of TTCP, a process consisting of dissolution of TTCP and precipitation of a less soluble phase, e.g., HA, may be represented by Eq. (1), assuming that S-HA is the product

$$Ca_4(PO_4)_2O + H_2O \rightarrow \tfrac{2}{3}Ca_5(PO_4)_3OH + \tfrac{2}{3}Ca^{2+} + \tfrac{4}{3}OH^-. \quad (1)$$

Because OH^- ions are released as a byproduct, the pH of the reaction slurry would increase from the original value, e.g., 7, as the reaction proceeds. If a titrator added a H_3PO_4 solution to the slurry to keep the pH of the solution constant, the hydrolysis reaction should follow Eq. (2), again assuming that S-HA is the product

$$Ca_4(PO_4)_2O + \tfrac{2}{5}H_3PO_4 \rightarrow \tfrac{4}{5}Ca_5(PO_4)_3OH + \tfrac{1}{5}H_2O. \quad (2)$$

It is noted that because of the low solubility of TTCP and HA under neutral and alkaline solutions, the amounts of Ca and P present in the solution were neglected in the equation. In the cases where the HA precipitation is a slower process than TTCP dissolution, the solution would be nearly saturated with respect to TTCP as the hydrolysis reaction proceeds. Gibb's phase rule [4] dictates that, under fixed temperature and pressure, a three-component system, such as $Ca(OH)_2$–H_3PO_4–H_2O, with two phases (a solution and a solid) in equilibrium has one degree of freedom. Thus, as long as the solution remains saturated with TTCP, the solution composition is completely defined by fixing the values of one compositional parameter, such as the pH. In the present study, by maintaining the pH at a fixed value, the titration system described here would allow the TTCP hydrolysis to proceed under a near-constant-composition condition, and the rate of reaction can be determined from the rate of titration. As will be seen in the Results section, the solution composition was not held strictly constant in some cases because HA precipitation occurred more rapidly than TTCP dissolution, and the solution became undersaturated with TTCP to varying degrees. In these cases, keeping the solution pH constant would lead to a constant [Ca]/[P], the molar ratio of solution calcium concentration, [Ca], and phosphate concentration, [P], instead of a constant solution composition.

In the present study, the initial reactant solution was 0.15 mol/l in KNO_3 rather than water to simulate the ionic strength of physiological fluids. Although the system contained a component that is additional to $Ca(OH)_2$, H_3PO_4, and H_2O, the system can be made to be equivalent to three-component system by having the same KNO_3 concentration (0.15 mol/l) in both the initial reactant solution and the H_3PO_4 titrant solution and due to the fact that neither K^+ nor NO_3^- was consumed or released in the hydrolysis reaction. This was the reason why NaCl, which is the salt present in physiological fluids, was not chosen as the background electrolyte in the study because both Na^+ and Cl^- are known to be incorporated into the apatitic hydrolysis products.

TTCP hydrolysis may not follow Eq. (2) because CD-HA instead of S-HA was the product [9]. Assuming that the CD-HA has the general formula of $Ca_{5-x}H_{2x}(PO_4)_3OH$, the hydrolysis reactions of TTCP can be represented by

$$\begin{aligned} &Ca_4(PO_4)_2O + yH_3PO_4 \\ &\quad \rightarrow [4/(5-x)]Ca_{5-x}H_{2x}(PO_4)_3OH \\ &\qquad + [(2-2x)/(5-x)]H_2O, \end{aligned} \quad (3)$$

where $y = (2+2x)/(5-x)$. The Ca/P molar ratio of the hydrolysis product can be expressed in terms of x or y, i.e., $(5-x)/3$ or $4/(2+y)$. For $x = 0$, y equals to 2/5, the Ca/P ratio is 5/3 (the product is S-HA), and Eq. (3) becomes Eq. (2). For $x = 1$, y equals 1.0, and the Ca/P molar ratio is 1.33, the Ca/P ratio of octacalcium phosphate, $Ca_8H_2(PO_4)_6 \cdot 5H_2O$. Thus, the amount of H_3PO_4 that would be consumed per mole of TTCP to complete the hydrolysis reaction, i.e., the value of y in Eq. (3), would vary depending on the product formed.