

An Analysis of Hydroxyapatite Surface Layer Formation

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A mechanism for the formation of hydroxyapatite (HAp) surface layers compositionally different from the bulk compositions is described. Surface layer formation is a consequence of HAp being a compound of variable composition: $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ to $\sim\text{Ca}_9\text{HPO}_4(\text{PO}_4)_5\text{OH}$, existing over Ca/P ratio from 1.67 for stoichiometric to ~ 1.5 for fully calcium-deficient HAp. One consequence of this compositional variability is that only one HAp composition (Ca/P ratio) dissolves congruently (the solution and solid have the same Ca/P ratio). HAp compositions having Ca/P ratios different from the congruently dissolving composition will form surface layers. Equilibration of stoichiometric HAp with water will result in the formation of a surface layer having a Ca/P ratio of less than 1.67. In general, for solid HAp compositions having Ca/P ratios greater than that of the congruently dissolving composition, a nonstoichiometric surface layer will form and the Ca/P ratio in solution will exceed that of the surface layer. For solid compositions having lower Ca/P ratios than the congruently dissolving composition, the opposite will be true.

Introduction

Because of its importance as a hard tissue analogue, the phenomena involved in the crystallization and dissolution of hydroxyapatite (HAp) have received considerable attention. Elliot¹ has provided a comprehensive review of this literature. However, the phenomena accounting for the formation of HAp surface layers at the interfaces between HAp crystallites and the solution have not been explicitly discussed. One objective of this article is to describe the mechanisms by which HAp surface layers, having Ca/P ratios different from the Ca/P ratio in the bulk solid, form during HAp equilibration with water at low temperatures (e.g., 25° and 37.4 °C).

HAp surface layers having indeterminate compositions have been reported to influence the solubility behavior of hydroxyapatites² and fluoridated apatites.³ A further objective is to illustrate that the compositions of these layers are predictable. The thermodynamic principles governing the driving force for equilibration of magnesium carbonate–calcium carbonate solid solutions have been previously established⁴ and apply to the present analysis. The present analysis is also based on our prior work describing the solubility behavior of calcium phosphates.^{5–7} Those studies demonstrated that $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ (DCPD) and CaHPO_4 (DCP) exhibit incongruent solubilities with respect to HAp, HAp is not a compound of fixed composition, and “nonstoichiometric” HAp compositions are thermodynamically stable solids.

The solubility behavior of HAp is related to those of CaHPO_4 and $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ because these are phases with which HAp can exist in stable and metastable equilibrium. The following sequence of events occurs during the formation of a solution saturated with respect to DCP or DCPD [expressed as DCP(D) for convenience] when crystals of either solid are immersed in water. Initial DCP(D) dissolution introduces Ca and phosphate ions to the solution in a molar ratio of 1:1. With continuing dissolution, this solution becomes saturated with respect to HAp. However, because the solution remains undersaturated with respect to DCP(D), its dissolution continues. Consequently, supersaturation with respect to HAp occurs, which results in

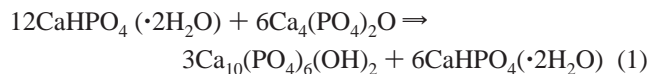
its precipitation. HAp precipitation decreases the Ca/P ratio of the solution to less than 1. Eventually, an invariant point between HAp and DCP(D) is reached, a solution saturated with respect to DCP(D) is achieved, and further DCP(D) dissolution ceases.⁵ The HAp–DCP invariant point is stable; that involving HAp and DCPD is metastable. Because DCP(D) dissolution does not result in a saturated solution without the formation of a second solid phase, its dissolution is incongruent.⁸

HAp formed in aqueous solutions at low temperatures can incorporate a variety of substituents. Among these are sodium, carbonate, and fluoride. However, compositional variations in HAp can be achieved in the absence of substitution. This occurs by the coupled phenomena of vacancy formation on Ca and OH sites and the protonation of a phosphate group. Thus, the crystal–chemical relationship between stoichiometric HAp, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ (Ca/P = 1.67), and a calcium-deficient HAp, such as $\text{Ca}_9\text{HPO}_4(\text{PO}_4)_5\text{OH}$ (Ca/P = 1.5), is the result of the creation of a vacancy on one of the ten Ca sites, the creation of a vacancy on one of the two hydroxyl sites, and protonation of one of the six PO_4 groups with the formation of a HPO_4 group. The range of compositions which can be achieved in this way may be expressed as: $\text{Ca}_{(10-x)}(\text{HPO}_4)_x(\text{PO}_4)_{(6-x)}(\text{OH})_{(2-x)}$ $x = 0-1$. Because the CaO/P₂O₅ ratio of calcium-deficient HAp is 3:1 where Ca/P = 1.5, this HAp sometimes has been referred to erroneously as tricalcium phosphate. However, on heating to ~ 700 °C, Ca-deficient HAp with a Ca/P = 1.5 will convert to tricalcium phosphate, $\text{Ca}_3(\text{PO}_4)_2$.⁹

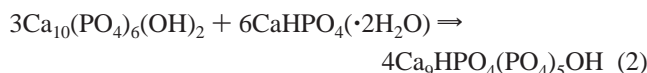
As a result of the creation of vacancies and the rupture of P–O bonds, nonstoichiometric HAp compositions have solubility products significantly different than stoichiometric HAp. For example, the solubility products reported for stoichiometric and calcium-deficient (Ca/P = 1.5) HAp have been reported to be $\sim 118^3$ and $\sim 85^{10}$ respectively. The solubility differences between stoichiometric and calcium-deficient HAp have been demonstrated recently.⁷

The formation of nonstoichiometric HAp has been well documented.^{11–15,26–28} Although this view is not universally accepted, the nonstoichiometric compositions formed are not

metastable with respect to stoichiometric HAp. Our prior work has demonstrated that calcium-deficient HAp will form in preference to stoichiometric HAp when the bulk Ca/P ratio is 1.5.^{16–18} For example, DCP(D) reacts with $\text{Ca}_4(\text{PO}_4)_2\text{O}$ (TetCP) to form nonstoichiometric HAp as follows:¹⁹



then



If nonstoichiometric HAp were metastable, the principle of free energy minimization would preclude its formation according to eq 2. Thus, nonstoichiometric HAp formation is not merely the consequence of the Ostwald–Gay Lussac law of progressive crystallization. Although the solubilities of nonstoichiometric HAp compositions are higher than those of stoichiometric HAp, nonstoichiometric hydroxyapatites are equilibrium solids.

The limiting composition of nonstoichiometric HAp is somewhat uncertain. It is generally accepted that the limiting composition is near $\text{Ca}_9\text{HPO}_4(\text{PO}_4)_5\text{OH}$ (Ca/P = 1.5). However, nonstoichiometric HAp with the composition $\text{Ca}_8(\text{HPO}_4)_2(\text{PO}_4)_4$ (Ca/P = 1.33) has been described.²⁰ Other work suggests the limiting ratio may be near 1.4.¹¹ Forming HAp from DCP(D) and TetCP precursors at 25° or 37.4 °C in the absence of foreign ions suggests that the limiting Ca/P ratio in HAp is 1.5.⁷

Analysis

Overview. Analyses previously published and based on empirical determinations were the basis for the construction of the $\text{CaO}-\text{P}_2\text{O}_5-\text{H}_2\text{O}$ ternary diagram.^{5,6,21} In the published diagrams, HAp was represented as a compound of variable composition. However, consideration was not given to the implications of the compositional variability of HAp. In this article we discuss the stability region of HAp in the context of the relationship between its solubility isotherms and the compositions of stoichiometric and nonstoichiometric (e.g., Ca/P = 1.5) HAp at 25° and 37.4 °C. Figure 1 illustrates the solubility behavior of HAp at 25° and 37.4 °C. The solubility isotherms for HAp, $\text{Ca}(\text{OH})_2$, and DCP are illustrated. These solubility isotherms define the compositions at which single solids are in equilibria with solutions saturated with respect to those solids. The points A–a–b–c–B define the solubility isotherm for HAp. Points A and D define the solubility isotherm for $\text{Ca}(\text{OH})_2$, and points C and B define the solubility isotherm for DCP. A, B, and C are ternary invariant points. A is the invariant point: $\text{Ca}(\text{OH})_2-\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ –solution. B is the invariant point: $\text{DCP}-\text{Ca}_9\text{HPO}_4(\text{PO}_4)_5\text{OH}$ –solution. C is the invariant point: $\text{DCP}-\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$ –solution. D is the binary invariant point: solution– $\text{Ca}(\text{OH})_2$. The compositional points for the various solids are labeled. Tie lines connect the compositions of solids and liquids which coexist in equilibrium. Because DCP and $\text{Ca}(\text{OH})_2$ are compounds of fixed compositions, all liquid compositions along their solubility isotherms are in equilibrium with those solids. Alternatively, HAp has variable composition, and the tie lines illustrate the compositional relationships between the solutions and solid HAp compositions in equilibrium.

Lines connecting the water origin and the compositional points for various compounds (lines of congruent dissolution) illustrate the compositional paths taken by the liquid during the

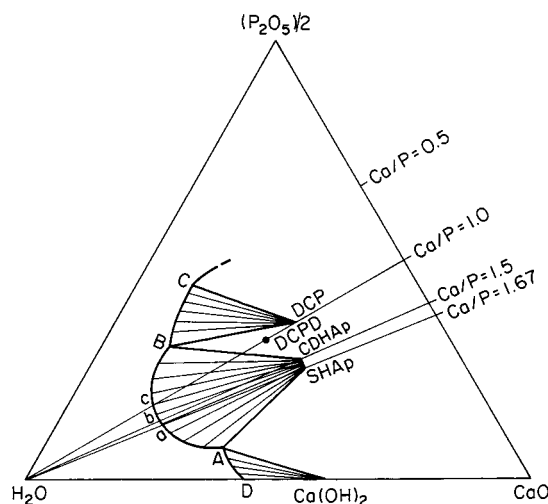


Figure 1. Schematic $\text{CaO}-\text{P}_2\text{O}_5-\text{H}_2\text{O}$ diagram at (or near) physiological temperature showing the compositional points and solubility isotherms for $\text{Ca}(\text{OH})_2$, HAp, and DCP. The diagram is represented to scale with regard to the Ca/P ratios for various solids. The compositions of the solids that exist in this system can be expressed as linear combinations of CaO , P_2O_5 , and H_2O . For example stoichiometric HAp is $10\text{CaO} \cdot 3\text{P}_2\text{O}_5 \cdot \text{H}_2\text{O}$, whereas DCP is $1/2(2\text{CaO} \cdot \text{P}_2\text{O}_5 \cdot \text{H}_2\text{O})$, and DCPD is $1/2(2\text{CaO} \cdot \text{P}_2\text{O}_5 \cdot 5\text{H}_2\text{O})$. For this reason the axes on the diagram are plotted in terms of CaO , $\text{P}_2\text{O}_5/2$, and H_2O . The extent of the solution region is exaggerated for purposes of representation. Tie lines connect compositions of solids and solutions in equilibrium. Invariant points A, B, C, and D are shown. Lines of congruent dissolution of DCP ($\text{H}_2\text{O}-\text{c}-\text{DCP}$), of calcium-deficient HAp ($\text{H}_2\text{O}-\text{b}-\text{CDHAp}$), and of stoichiometric HAp ($\text{H}_2\text{O}-\text{a}-\text{SHAp}$) are shown.

initial dissolution of DCP, calcium-deficient HAp, and stoichiometric HAp. The points at which each of these lines intersects a solubility isotherm indicate the compositions of the saturated solutions that form when DCP, calcium-deficient HAp, or stoichiometric HAp dissolve. These points are labeled c, b, and a, respectively. For initial saturation, the calcium and phosphate concentrations at point b are 0.5 mM and 1.2 mM, and the pH is ~5 at 25 °C. At 37.4 °C these values are 0.8 mM and 2.0 mM, respectively with a pH of 4.5. The Ca/P ratio for point b is 1.512 at 25 °C and 1.520 at 37.4 °C.⁷ The Ca/P ratio for point a was not determined empirically because the phosphate concentrations were below the limit of detection by DC plasma spectrometry. However, the pH values are ~9.5 at 25 °C and ~8.5 at 37.4 °C. As Figure 1 indicates, dissolution of calcium-deficient and stoichiometric HAp (along with that of DCP) are incongruent. Incongruity of DCP dissolution^{5,21} is indicated by an intersection between the HAp isotherm and a line extending from the water origin to the compositional point for DCP. The composition of a saturated solution in equilibrium with stoichiometric HAp is that at point A, not that at point a. In an equivalent manner, the solution composition in equilibrium with calcium-deficient HAp is that at point B, not at point b.

For the purpose of discussion, the dissolution behaviors of calcium-deficient and stoichiometric HAp will be analyzed together. The analysis will treat HAp dissolution as occurring in discrete steps until a saturated solution is reached, whereas the process is continuous. However, this convenience does not require any alteration in the mechanistic paths taken. The analysis also assumes equilibrium compositions form during the dissolution/precipitation events. Figure 2 shows the relevant details of Figure 1 when the compositional relationships are illustrated using orthogonal axes. Figure 2 retains the feature that monocalcium phosphate monohydrate (MCPM) dissolution is incongruent with respect to HAp.⁶ Thus, the solubility

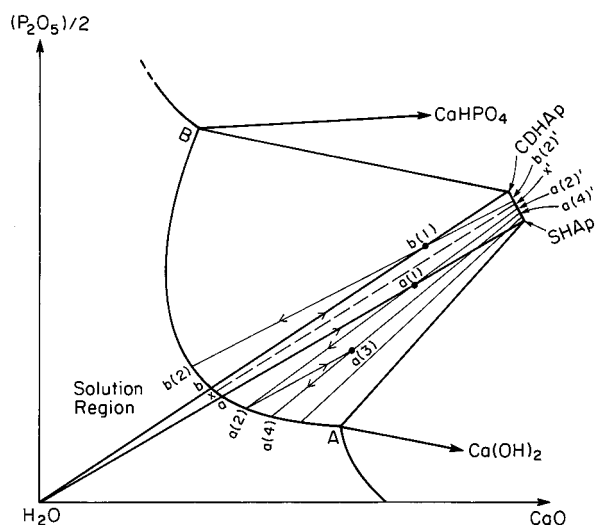


Figure 2. Schematic of the $\text{CaO-P}_2\text{O}_5\text{-H}_2\text{O}$ diagram represented with use of orthogonal axes and with emphasis on the solubility isotherm of HAP. Invariant points A and B are shown. The following tie lines have been drawn to illustrate paths taken in surface layer formation: $b(2)'-b(2)$, $a(2)'-a(2)$, $a(4)'-a(4)$. The tie line $x'-x$, along which HAP dissolves congruently (Ca/P ratio in solution = Ca/P ratio in the solid), is represented by a dashed line. Because SHAp is dissolving, the line $a(2)-a(3)$ representing the second dissolution step is parallel to the line $\text{H}_2\text{O}-a\text{-SHAp}$; this is a consequence of SHAp dissolution causing Ca and phosphate ions to enter solution in a ratio of 10:6 in both steps.

isotherm for HAP extends beyond the Ca/P ratio of 0.5. Of particular interest are the geometric relationships between the lines of congruent dissolution of stoichiometric and calcium-deficient HAP and the tie lines connecting solution and HAP compositions which coexist in equilibrium. These relationships may be used to describe the mechanistic paths followed during HAP dissolution, surface layer formation, and precipitation.

Surface Layer Formation. Stoichiometric HAP. Moreno et al.²¹ studied the dissolution of stoichiometric HAP in phosphoric acid solution and reported a Ca/P differing from 1.67. Ingram²³ pointed out that such behavior could also be attributed to compositional changes in the apatite associated with the low pH and the presence of phosphate. The following analysis illustrates a mechanistic path consistent with these observations.

The dissolution behavior of stoichiometric HAP can be analyzed as initially occurring along the line of congruent dissolution having a fixed Ca/P ratio of 1.67. This line is defined by the points $\text{H}_2\text{O}-a\text{-SHAp}$ in Figure 2. However, the solution composition that intersects the HAP solubility isotherm at this Ca/P ratio (point a) is not saturated with respect to stoichiometric HAP. Therefore, the dissolution of stoichiometric HAP is occurring incongruently. In other words, a solution saturated with respect to stoichiometric HAP cannot be formed in the absence of the precipitation of a second solid. Hence, stoichiometric HAP dissolution exhibits behavior analogous to that of DCP(D). Because the solution at point "a" is not saturated with respect to stoichiometric HAP (the dissolving composition), its continued dissolution will result in supersaturation with respect to some other HAP composition. This is represented as occurring along the line $a-a(1)$ in Figure 2 (exaggerated in the figure for the purposes of illustration). If it is assumed that a solution whose composition is represented by point a(1) is critically supersaturated with respect to a hydroxyapatite, precipitation will occur. However, the HAP that precipitates will not be stoichiometric HAP. Rather, it will have the composition defined by the point a(2)'. During the relief of supersaturation, the

composition of the solution will move along the tie line from point a(1) to point a(2) as a result of the precipitation event. Thus, precipitation of this HAP composition will result in the solution achieving point a(2) on the HAP solubility isotherm. These events result in an HAP surface layer of composition a(2)' establishing an equilibrium with solution of composition a(2). A materials balance is retained because the HAP surface layer has a lower Ca/P than does stoichiometric HAP, and the Ca/P ratio in solution is greater than that of point a. The compositional path taken by the solution $a \Rightarrow a(1) \Rightarrow a(2)$ during HAP surface layer formation is a consequence of the incongruent dissolution of stoichiometric HAP.

Regardless of whether these events occur by dissolution and reprecipitation or by leaching, they indicate the mechanistic path by which an HAP surface layer forms and has a composition different from the bulk, stoichiometric composition. A consequence of this dissolution behavior of stoichiometric HAP is the formation of an HAP surface composition having a Ca/P ratio different from that of the dissolving solid. As will be discussed, the thickness of the surface layer formed will depend on its effectiveness in isolating the underlying stoichiometric HAP from the solution, as well as on the proportion of solution present. A similar phenomenon has been described with regard to the equilibration of hydroxyapatite-fluorapatite solid solutions.²⁴ To the extent that calcium-deficient, fluoride-substituted apatites exist, similar behavior may be anticipated with regard to surface layer formation.

The analysis above treated the formation of a surface layer as occurring in a single step. This step resulted in the formation of an HAP surface layer having a composition represented by a(2)' and a solution of composition a(2). Because these compositions lie on the same tie line, equilibrium between the surface layer and the solution has been achieved. If an HAP surface layer of composition a(2)' is an effective barrier, further dissolution of the underlying stoichiometric HAP will not occur. Because the HAP, which precipitates as a consequence of the dissolution of stoichiometric HAP, will have a Ca/P ratio less than 1.67, the Ca/P ratio of the solution becomes different from that of the dissolving solid.

However, as previously mentioned, the process of equilibration with the solution likely involves more than a single discrete step. Thus, there is benefit in extending the analysis to consider the formation of surface layer involving more than a single step. Such an analysis assumes that the surface layer of composition a(2)' is an inadequate barrier to further dissolution of stoichiometric HAP. In that event, the solution again will become enriched with calcium and phosphate through additional dissolution of stoichiometric HAP. This is represented as occurring along the line $a(2)-a(3)$. Because stoichiometric HAP is dissolving, this line is parallel to the initial line of congruent dissolution for stoichiometric HAP (the line $\text{H}_2\text{O}-a\text{-SHAp}$). If it is assumed that the solution attaining the composition at point a(3) will result in HAP precipitation, its composition moves from point a(3) to point a(4) as precipitation proceeds. This equilibration step results in a saturated solution of composition a(4) on the HAP solubility isotherm coexisting in equilibrium with an HAP surface layer of composition a(4)'. Although the analysis assumes the previously formed HAP of composition a(2)' adjusts its composition to a(4)', such an assumption is not critical to the mechanism of surface layer formation. In the absence of such compositional adjustment, the surface layer will exhibit a compositional gradient (with the first-formed and more calcium-deficient HAP in the layer actually being closer to the underlying stoichiometric HAP).

Surface Layer Formation Calcium-Deficient HAp. As Figure 2 shows, the dissolution behavior of calcium-deficient HAp is also incongruent. Because of this, its dissolution behavior can be analyzed in the same manner as for stoichiometric HAp. Dissolution initially occurs along a line of congruent dissolution having fixed a Ca/P ratio 1.5 (the line H_2O –b–CDHAp in Figure 2). In this instance, the dissolution event produces a supersaturated solution of composition b(1). Surface layer formation then occurs as the solution composition attains point b(2) on the HAp solubility isotherm, which results in an HAp surface layer of composition b(2)'. In this instance the HAp, which precipitates as a consequence of the dissolution of calcium-deficient HAp ($\text{Ca/P} = 1.5$), will have a Ca/P ratio greater than 1.5, whereas the Ca/P ratio of the solution becomes lower than that at point b.

Congruent Dissolution. An HAp composition exists which dissolves congruently; the Ca/P ratio of the solid and the solution are the same. This composition is labeled as point x' in Figure 2. Dissolution of HAp having this Ca/P ratio equilibrates with solution in the absence of surface layer formation. Thus, the tie line between the HAp solubility isotherm and point x is coincident with the line of congruent dissolution for that composition (the line H_2O –x–x'). Any HAp having a bulk Ca/P ratio higher than the congruent composition will exhibit dissolution behavior comparable with that described for stoichiometric HAp. Alternatively, any HAp having a bulk Ca/P ratio lower than the congruent composition will exhibit dissolution behavior comparable with that described for calcium-deficient HAp.

Surface Layer Composition. Regardless of whether calcium-deficient or stoichiometric HAp is dissolving, surface layers having Ca/P ratios different from the bulk composition will form. However, the compositions of the surface layers will be indeterminate because the extent of surface layer formation will depend on the surface area of the equilibrating HAp. Thus, the variations in Ca/P ratios between solutions and HAp preparations having relatively low surface areas will be small. On the other hand, if an HAp preparation has a high surface area, surface layer formation could result in a significant difference between the Ca/P ratio in the solid and in solution. Because of incongruent HAp dissolution, washing precipitated HAp (particularly that having a high surface area) will result in a surface layer of composition different from the bulk composition. Such behavior was observed by Eanes and Gever²⁵ for HAp containing fluoride. The more extensive the washing, the greater this departure will be.

Isothermal Evaporation of Water and the Formation of Stoichiometric HAp. An analysis similar to that above can be performed to describe the consequence of the isothermal evaporation of water from a solution with which stoichiometric HAp has equilibrated. Isothermal evaporation of water from a solution in equilibrium with HAp will cause the solution Ca/P ratio to vary in a manner that is the reverse of when HAp dissolves. For convenience, and with reference to Figure 2, stoichiometric HAp forms a surface layer of composition a(2)' which is in equilibrium with solution of composition a(4) in Figure 3. Isothermal evaporation of water will cause disequilibrium between the surface layer and the solution in a manner equivalent to that described for the dissolution of stoichiometric HAp. The analysis will again treat the events as occurring in stepwise fashion, whereas they occur continuously. As before, however, such a convenience does not require that the mechanistic path be altered. Thus, removal of water from solution a(4) will supersaturate that solution to point a(5) in Figure 3.

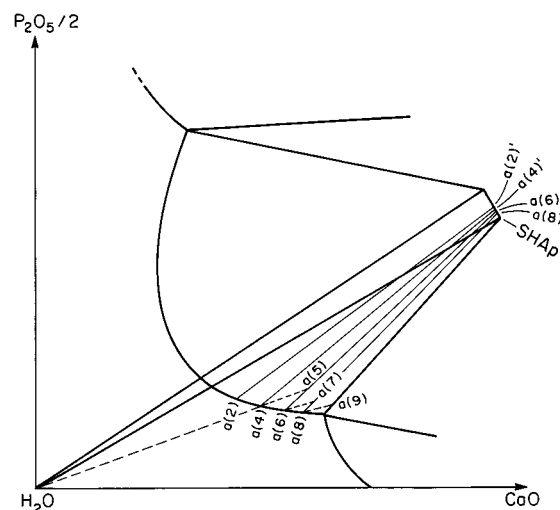


Figure 3. The extension of Figure 2 to illustrate of the mechanistic path taken during the isothermal evaporation of water from a solution in equilibrium with stoichiometric HAp. From Figure 2, equilibrium occurred when a surface layer of composition a(4)' equilibrated with a solution of composition a(4). Events involving tie lines a(6)–a(6)' and a(8)–a(8)' facilitate illustration. Variations in solution composition with evaporation of water occur along lines intersecting the water origin and the equilibrium solution compositions. In the figure these are lines H_2O –a(4)–a(5), H_2O –a(6)–a(7), and H_2O –a(8)–a(9).

This is represented as occurring along an extension of the line H_2O –a(4) consistent with the removal of one of the components from an open thermodynamic system. Precipitation results in the formation an HAp surface layer of composition a(6)' having a higher Ca/P ratio than that which was in equilibrium with solution a(4). Relief of supersaturation results in a solution of composition a(6). Continued water evaporation forms solution a(7) which equilibrates to a(8) with a commensurate change in the surface layer composition to a(8)'. During each evaporation event, the solution attains supersaturation by moving along a line extending from the water origin, through the relevant compositional point on the solubility isotherm [e.g., a(4), a(6), or a(8)], and into the two-phase HAp solution region.

The assumption that the surface layer attains an equilibrium composition after each supersaturation step requires it to adjust its composition from a(4)' to a(6)' to a(8)'. With cyclic supersaturation and equilibration events, the solution composition follows the path to a(9) and eventually to point A. Attendant to these events is the continuing change in the composition of the HAp surface layer toward that of stoichiometric HAp resulting in its Ca/P ratio approaching 1.67. As the solution composition approaches point A, it becomes exhausted. Thus, only when the solution has disappeared through the complete isothermal evaporation of water are the HAp surface layer composition and the bulk composition the same, namely the composition of stoichiometric HAp.

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