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The effect of excess phosphate on the solubility of hydroxyapatite

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Abstract

The solubility of hydroxyapatite (HA) is critical in fields such as medicine, dentistry and geochemistry. Previously, it had been found that it was apparently slightly increased with 1 mmol/L excess phosphate present. This study was to determine the solubility of HA over the pH range 3.3–5.4 with a series of concentrations of such 'excess' phosphate with solid titration (ST), and to identify the precipitate formed at equilibrium with SEM, TEM, EDX, FTIR and XRD. For $[PO_4]_{XS}$ = 0–0.3 mmol/L, results followed closely the already-reported ST 'low' solubility isotherm. At $[PO_4]_{XS}$ = 0.5 mmol/L, the solubility surface switched abruptly to a 'high' position that could not be reconciled with either the 'low' isotherm or conventional calculations. Thus, HA solubility is critically dependent on the presence of excess phosphate. Such excess may account for the discrepancy between ST and excess-solid results, although the crystallographic explanation is as yet lacking.

Keywords: Biomaterials; Solubility; Solid titration; Phosphates

1. Introduction

The archetype of the apatite mineral family, hydroxyapatite (HA) is of fundamental importance in a variety of fields, such as soil science, purification processes, medicine, and biological materials. Its solubility has been much studied over several decades due to its importance as a model for biological hard tissue, but in particular in the context of dental caries, fluoridation and remineralization. However, results have varied markedly from one report to another. But whether as a result of differences in methods, raw materials, test solutions, or other factors, a definitive statement of its true solubility is still lacking. This can be ascribed to the rather complicated dissolution process of calcium phosphates in general, and even for well-characterized synthetic pure HA, despite considerable effort over a long period [1–10].

The conventional approach to the determination of HA solubility uses a relatively large amount of solid immersed in an aqueous medium for between a few hours and a few days. When equilibrium is assumed to have been reached, the pH is noted and the mass or the solution concentration of calcium is checked so as to determine solubility [6,11–14]. However, superficial phase transformation leading to a lower Ca/P ratio can occur, and this has often been ignored. The apparent solubility cannot then reflect the true behavior HA due to this incongruent dissolution [2]–the solution composition does not match that of the solid in contact. Incongruent dissolution invalidates all such 'solubilities' because the value depends on the amount of solid present, in violation of the underlying thermodynamic assumption.

The dissolution mechanisms of apatite are thought to be extremely complex, involving several simultaneous aqueous and surface reactions, so that a single solubility product could not govern the whole process if it involves several solid phases. Consequently, a surface complex has been proposed to explain the phenomenon [15,16]. However, the exact identity of such a material is controversial due to difficulties with the

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model and the poor sensitivity of the test methods, there being no direct evidence of such a material.

Given all this, and to avoid transformations, Leung and Darvell developed solid titration (ST) [17], since confirmed as reliable and precise in determining the solubility of HA and related substances under closely-defined conditions [3,18–23]. It is a key finding that the solubility of HA as determined by ST is substantially lower than commonly reported [3,20]. In addition, the equilibrium precipitate has shown no sign of a special coating or complex, although its Ca/P ratio decreases slowly with lowering equilibrium pH [20]; this has also been observed elsewhere [24,25].

The effect of other solution ions (*i.e.*, through speciation effects) has not drawn much attention, or at least its importance has been underestimated. Although interaction between HA and ions such as K^+, Na^+, and Cl^- can ordinarily be neglected [2], the effect of 'extra' (analytical) background [Ca] and [PO_4], and ions such as Sr^{2+}, F^- and CO_3^{2-} should be considered. For example, it has previously been shown that the solubility of HA is significantly increased by solution carbonate and phosphate [3]. Although it is a different mechanism, ions incorporated in the apatite lattice, where the substitution may cause crystal lattice distortions, result in changes in physicochemical properties, including solubility [19,23]. Indeed, it has been shown that the solubility of bovine bone mineral, a carbonated apatite, is significantly higher than that of pure HA [18]. Likewise, solubility in a simulated saliva is substantially higher than in 100 mmol/L KCl, with or without CO_2 present [3,26]. Hence, any attempt to investigate the behavior of HA by immersing the solid in a simulated body fluid or buffer solution, which necessarily contains various ions whose roles have not been investigated, should be considered with caution [11,13,14,27]. Similarly, but with the greater force, the use of phosphoric acid as a pH regulator or test background solution [28–32] is incorrect, or unsuitable at the very least, in the absence of a proper recognition and characterization of its effects.

A preliminary observation of the effect of phosphate on HA solubility was of slight increase for pH 4.2 to 5.0, with 1 mmol/L excess phosphate [3]. However, it is clear from the above that more detailed investigation is required. Hence, the aim now was to determine the solubility of HA in the presence of a range of background [PO_4] concentrations, and to identify the equilibrium solid.

2. Materials and methods

Solid titration was used as previously described [3,18–23] to determine the solubility of HA in the test solution at 37.0 ± 0.1 °C. In essence, the method depends on determining, by a laser-scattering detector, the point at which no further solid may dissolve, or at which a new precipitate forms, using small increments of solid that must dissolve completely before a further increment is added.

Pure HA, prepared by a standard precipitation method in a closed borosilicate glass reaction vessel flushed with N_2, was the titrant solid. High-purity KCl and KH_2PO_4 (ARISTAR, BDH, Poole, England) were used to prepare the test solutions with ultra-pure deionized water (arium 631; Sartorius, Goettingen, Germany). All solutions contained 100 mmol/L KCl, in which was included 0, 0.1, 0.2, 0.3, 0.5, 1, 2, 10, 50, 100, or 500 mmol/L KH_2PO_4 (*i.e.*, to provide 'excess' phosphate, $[PO_4]_{XS}$, where the form [PO_4] refers to analytical phosphate, without regard to speciation), the pH being adjusted as required with 5 mmol/L HCl or KOH solution. The reaction vessel and its contents were purged slowly and continuously with water-saturated nitrogen at 37 °C through an immersed capillary to eliminate and exclude CO_2 [20]. The vessel contents were stirred with a magnetic bar at ~60 rpm, sufficient to keep solid particles suspended. Runs were interlaced, randomized in groups, and many replicated on several distinct occasions over three years, to ensure repeatability.

The solid titration process entailed the following. When thermal (± 0.01 K) and pH (± 0.001) stability was attained for 600 mL of the test medium, and the scattering detector output on a chart recorder seen to be stable, the first increment of solid was added. Dissolution gave a quasi-exponential decline in scattering signal after the initial abrupt rise. When the scattering signal had returned to baseline, as near as could be judged, the system was allowed to equilibrate for at least a similar interval to ensure dissolution of the increment. The next and subsequent increments were treated similarly, until the scattering signal remained elevated with no indication of decline over several hours. Having established that the end-point had been exceeded, a further small increment was added such that after equilibration approximate interpolation for both solid added and end-point pH could be made using the scattering signal as a guide [3]. When this process was complete, a quantity of 5 mmol/L HCl was added, enough to dissolve completely the solid and enable the commencement of the next run from a new initial pH, eventually covering the pH range ~3.3–5.4. Above about that limit, the solubility is too low to be determined reliably. Likewise, at low pH, the solubility becomes rather high and more difficult to determine with ST.

To obtain a sufficient quantity of end-point, equilibrated precipitate for characterization, the ST was extended on selected occasions by continuing the incremental addition to a total of a further 6–10 mg, as described in detail elsewhere [20] (it has been previously been shown that all such added material also dissolves to be reprecipitated–no remnants are detectable). This was done for end-points both above and below pH 3.9 where the break in the continuity of the isotherm occurs [20]. After a further 10 days' equilibration, precipitates were collected by centrifugation (2000*g*, 15 min), rinsed quickly by several droplets of ultra-pure deionized water (to reduce the amount of KCl and KH_2PO_4 carried over; this had been found not to have any detectable effect on the precipitate), and dried in air at 60 °C overnight [18].

The ST here was in three stages. Firstly, using HA in 100 mmol/L KCl only, to reconfirm the reproducibility of the standard ST isotherm for HA [3,20] with the current set-up, materials and operator. Secondly, solubility was determined