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Invited Conference Paper

Thermodynamics of Hydroxyapatite Surfaces*,[1]

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A new model for equilibria at the interface of a sparingly soluble crystal is reviewed. It provides that several kinds of equilibria are present and each type is characterized by (i) a set of species that are transported across the phase boundary, (ii) a set of chemical reactions which describe this transport process, and (iii) a set of thermodynamic expressions which define equilibrium. Three types are envisaged: 1. *Stoichiometric equilibrium* provides the thermodynamic communication between the lattice and the bulk solution, occurs at a kink site, preserves the composition of the solid phase, defines a solubility product, leads to an isotherm in the phase diagram, and is unaffected by Galvani potentials. The equilibrium is defined by a single equation. 2. *Gibbsian equilibrium* in which the chemical potential of each component is stated to be equal across the phase boundary, but does not define an actual chemical process. There is one such equation for each component in the system. 3. *Electrochemical equilibrium* provides thermodynamic communication between ions in the bulk phase and those in the outer layer of the crystal, is nonstoichiometric, is profoundly affected by Galvani potentials, does not lead to a solubility product constant nor to an isotherm, and requires one more equilibrium condition than there are components in the system. Equilibrium between the lattice and the surface is limited to reactions via the aqueous phase, one of which is stoichiometric and the other nonstoichiometric. This model provides a clarity of description of interfacial events heretofore unattainable.

This paper is concerned with thermodynamic models of surface equilibria.[1] It is based on the idea that there is more than one type of equilibrium at the interface, and that for each equilibrium there is a one-to-one correspondence between the *physical process,* the *chemical equation* that describes the transport process, and the *thermodynamic expression* for equilibrium.

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Thermodynamics of Surface Equilibria

These considerations apply to a sparingly soluble salt under saturated conditions. More specifically, they are applied to hydroxyapatite (OHAp), $Ca_5(PO_4)_3OH$, in the ternary system, $Ca(OH)_2$—H_3PO_4—H_2O, as the example. The Gibbs phase rule requires that a system at constant temperature and pressure containing three components and two phases, a solid and a liquid, in equilibrium has one degree of freedom.[2] In this case, the condition of saturation reduces the degrees of freedom by one. This is very important because it is the sine qua non that makes possible the following treatment. The single degree of freedom expresses itself in the form of an isotherm in a phase diagram (Figure 1) representing the compositions of solutions saturated with respect

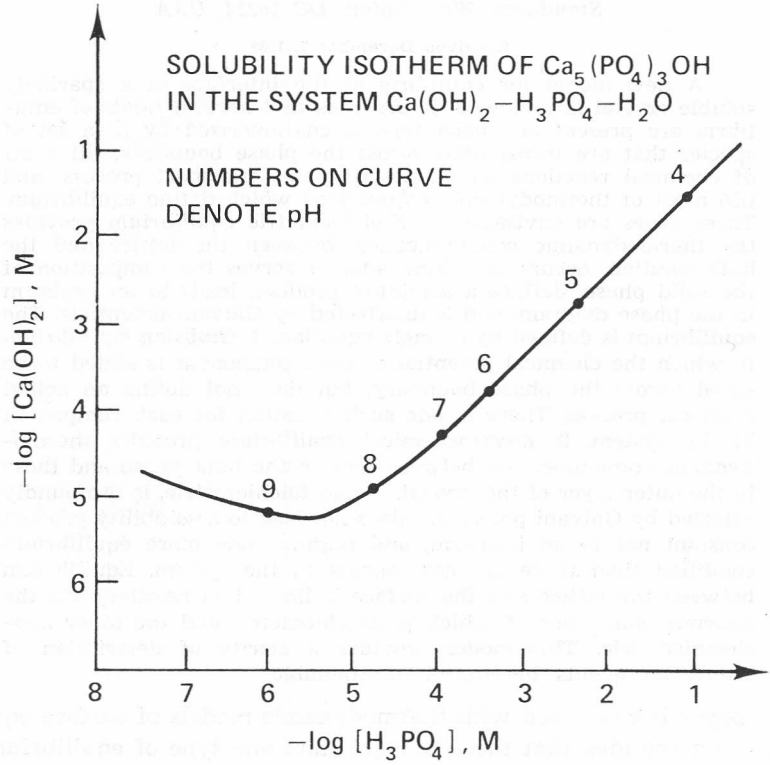

Figure 1. Solubility isotherm of $Ca_5(PO_4)_3OH$ in the system $Ca(OH)_2$—H_3PO_4—H_2O. Numbers on curve denote pH.

to OHAp. Solutions above the isotherm are supersaturated, and those below the isotherm are undersaturated, as indicated in the diagram. Integral values of pH are listed along the isotherm. If one were able to continuously change the composition of the solution so that it shifted along the isotherm, we would know[1] that: (1) The solubility product constant for OHAp would be satisfied in all of these solutions; (2) the chemical potential of any neutral component capable of being transmitted across the phase boundary would be the same in both the solid and the bulk liquid phase; and (3) the electrochemical po-

tential of any ionic component transportable across the phase boundary would be the same in both phases. Having said the above, we leave unanswered at this time where in the solid phase or in the interface these equilibrated constituents are located, this being a major consideration in the following treatment.

Model of the Interface

In Figure 2 is shown a model of a crystal depicting the various types of regions that may be involved in the equilibria. These include:

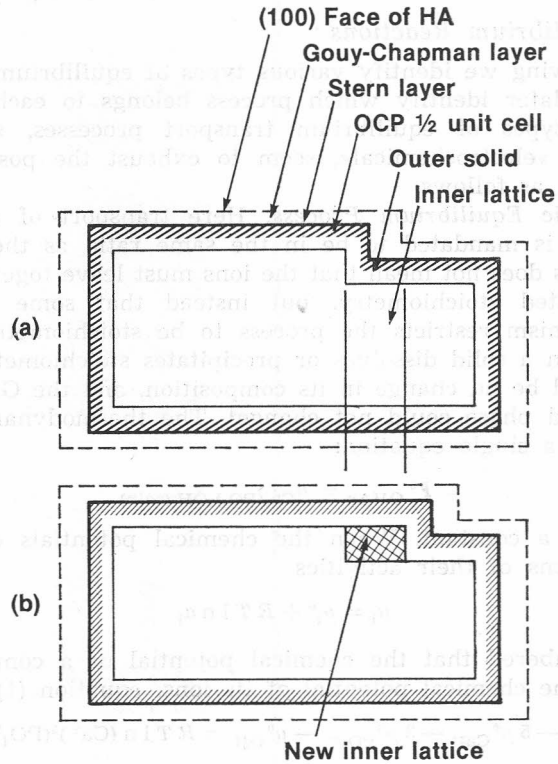

Figure 2. A hydroxyapatite crystal in a saturated solution before (a) and after (b) an increment of growth of the inner lattice at the kink site.

(1) *The bulk solution* which we take to be the reference state. It is essentially electrically neutral, but it can carry a Galvani potential.

(2) *The Gouy-Chapman layer* in which the ions are mobile, can carry a substantial electrical charge unbalance, and the composition varies continuously from that immediately adjacent to the solid phase to that in the bulk liquid phase.

(3) *The outer layer* of the crystal comprising three contiguous zones which, in the ternary system, are inseparable. These could be (i) the Stern layer, (ii) a zone in which the structure may be different from that of the interior of the crystal (e. g., a half unit cell of OCP[3]), and finally (iii) a zone in which the structure is very much the same as that in the interior

of the crystal except that it is strained and, therefore, may have a Gibbs energy different from that of the interior. We refer to this combined layer as the »outer layer« of the crystal. It is quite possible that this layer is too thick for all of it to be in chemical equilibrium with the aqueous phase, so we further subdivide it into »active« and »passive« layers.

(4) *The inner lattice,* which in the ideal OHAp crystal has the monoclinic structure but in fact it may be considered to be either the monoclinic form or the disordered hexagonal form. As noted later, the inner lattice probably is not in chemical equilibrium with the outer layer.

Models of Equilibrium Reactions

In the following we identify various types of equilibrium transport processes, and we later identify which process belongs to each region of our system. Three types of equilibrium transport processes, »stoichiometric«, »Gibbsian«, and »electrochemical«, seem to exhaust the possibilities. These can be described as follows.

Stoichiometric Equilibrium Process: Here transport of ions across the phase boundary is mandated to be in the same ratio as they occur in the ideal lattice. This does not mean that the ions must leave together in a packet with the indicated stoichiometry, but instead that some feature of the transport mechanism restricts the process to be stoichiometric. Such would be the case when a solid dissolves or precipitates stoichiometrically, because then there would be no change in its composition, and the Gibbs energy per mole of the solid phase could not change[4]. The thermodynamic equilibrium is expressed by a single equation:

$$F^0{}_{\mathrm{OHAp}} = \mu_{\mathrm{Ca_5(PO_4)_3OH\ (soln)}} \tag{1}$$

where $F^0{}_{\mathrm{OHAp}}$ is a constant. When the chemical potentials of the ions are expressed in terms of their activities

$$\mu_i = \mu_i{}^0 + R\,T \ln a_i \tag{2}$$

and it is remembered that the chemical potential of a compound is equal to the sum of the chemical potential of its ions, equation (1) becomes

$$F^0{}_{\mathrm{OHAp}} - 5\,\mu^0{}_{\mathrm{Ca^{2+}}} - 3\,\mu^0{}_{\mathrm{PO_4^{3-}}} - \mu^0{}_{\mathrm{OH^-}} = R\,T \ln (\mathrm{Ca^{2+}})^5(\mathrm{PO_4^{3-}})^3(\mathrm{OH^-}) \tag{3}$$

The left-hand side is equal to a constant, K', so that

$$\frac{K'}{R\,T} = \ln K_{sp} = \ln (\mathrm{Ca^{2+}})^5(\mathrm{PO_4^{3-}})^3(\mathrm{OH^-}) \tag{4}$$

Thus this type of equilibrium defines a solubility constant.

Gibbsian Equilibrium: The word »Gibbsian« is used here because the equilibria are expressed in terms of the components as originally defined by Gibbs. For OHAp in the ternary system, $Ca(OH)_2$—H_3PO_4—H_2O, the equilibria are defined by three equations:

$$\mu_{\mathrm{Ca(OH)_2\ (solid)}} = \mu_{\mathrm{Ca(OH)_2\ (soln)}} \tag{5}$$

$$\mu_{\mathrm{H_3PO_4\ (solid)}} = \mu_{\mathrm{H_3PO_4\ (soln)}} \tag{6}$$

$$\mu_{\mathrm{H_2O\ (solid)}} = \mu_{\mathrm{H_2O\ (soln)}} \tag{7}$$

The Gibbsian-type equilibria contain information about the individual chemical potentials of the components in the solid phase which is left moot by the condition for stoichiometric equilibrium, equation (1). Since the equilibria can be expressed equally well in terms of other components, (e. g., CaO, P_2O_5, H_2O), it seems unlikely that there would be a unique mechanism which would involve transport of entities such as $Ca(OH)_2$ and H_3PO_4 across the phase boundary. Thus equations (5) to (7) do not represent equilibrium transport processes, but instead, they appear to derive from the more basic electrochemical equations described later.

The chemical potentials of the components (which can be expressed in terms of ion activity products once the ion activities in a solution are known) vary as the composition shifts along the isotherm. In the case of OHAp, the quantity $\mu_{Ca(OH)_2}$ decreases, $\mu_{H_3PO_4}$ increases, and μ_{H_2O} remains essentially constant for a shift in composition along the isotherm in the direction towards higher concentrations and lower pH values.

Electrochemical Equilibrium Processes: When ions instead of neutral compounds are used as components, the ternary system becomes quaternary, say, Ca^{2+}, PO_4^{3-}, OH^-, and H_2O[5]. In terms of these components, the thermodynamic expressions for equilibrium are:

$$\bar{\mu}_{Ca^{2+}\,(solid)} = \bar{\mu}_{Ca^{2+}\,(soln)} \tag{8}$$

$$\bar{\mu}_{PO_4^{3-}\,(solid)} = \bar{\mu}_{PO_4^{3-}\,(soln)} \tag{9}$$

$$\bar{\mu}_{OH^-\,(solid)} = \bar{\mu}_{OH^-\,(soln)} \tag{10}$$

$$\mu_{H_2O\,(solid)} = \mu_{H_2O\,(soln)} \tag{11}$$

Here the electrochemical potential of the ith species of ion, $\bar{\mu}_i$, in any phase or compartment is defined as usual

$$\bar{\mu}_i = \mu_i + n_i F \Delta \Phi \tag{12}$$

where n_i is the valence and $\Delta \Phi$ *is* the Galvani potential difference relative to the bulk solution. Because of the electrical term, $n_i F \Delta \Phi$, it is not necessary for the *chemical* potential of a given species of ion to be the same in two parts of the system that are in equilibrium. Furthermore, it is conceivable for the chemical potential of an ionic species to remain constant in a given compartment of the solid or interface while the composition of the bulk solution is shifted along the isotherm. In such a case the entire change in $\bar{\mu}_i$ would occur in the Galvani potential term.

The Gibbsian equations can be derived from the electrochemical equations. For example,

$$\mu_{Ca(OH)_2} = \bar{\mu}_{Ca^{2+}} + 2\,\bar{\mu}_{OH^-} \tag{13}$$

because the Galvani potential terms always cancel for neutral components. Similarly the stoichiometric equilibrium expression can be derived from electrochemical expressions

$$\Delta F^0_{OHAp} = 5\,\bar{\mu}_{Ca^{2+}\,(soln)} + 3\,\bar{\mu}_{PO_4^{3-}\,(soln)} + \bar{\mu}_{OH^-\,(soln)} \tag{14}$$

once it is specified that the solid has an invariant composition $Ca_5(PO_4)_3OH$. However, it is not possible to derive the electrochemical expressions from those for stoichiometric or Gibbsian equilibria under any assumption. Thus there is a hierarchy of information content in the three sets of equilibrium equations.

Kinds of Reactions at the Interface

The ions from the bulk solution strike the interface in a random manner, but their retention on crystal growth (or release on crystal dissolution) can be either ordered or random. Two types of situations can arise:

(1) Ions randomly reaching the kink site (Figure 2a) during growth will be retained in a sequence governed by the structure of the crystal. Even though these ions seem to be entering the outer layer (which is distorted and possibly of variable composition), the net growth process creates inner lattice (cross-hatched area in Figure 2b). Furthermore, the amount of outer layer is not changed significantly by the growth, because the portion at the bottom of the step appears at the top after the growth has taken place and the area of the step face remains unchanged. Thus the reaction at the kink site (i) is stoichiometric, so that the phase formed does not carry a charge unbalance, (ii) is not affected by Galvani potential differences, (iii) is representative of true crystal growth (or dissolution) and (iv) provides the thermodynamic communication mechanism between the bulk solution and the inner lattice. Clearly these are the properties one associates with the stoichiometric equation (1).

(2) Random retention and release of ions is characteristic of processes which take place away from kink sites. Such a process (i) can be non-stoichiometric, (ii) may deliver a charge, (iii) does not regiment movement of ions, and (iv) is strongly affected by differences in Galvani potential. Thus, the electrochemical equations (8) to (11) best describe the equilibria between the bulk solution and the outer layer. We believe that these processes do not represent crystal growth or dissolution, but instead are means for adjusting the composition of the active part of the outer layer so that it can be in equilibrium with the bulk solution.

The randomness of the mechanisms described for the outer layer apply equally well to the Gouy-Chapman layer, so that the electrochemical equations also describe its equilibria with the bulk solution.

Interactions Between Inner Lattice and Outer Layer

With a solid as dense as OHAp, it is unlikely that diffusion between the inner lattice and the active part of the outer layer can occur at an appreciable rate at physiological temperatures. This view is in accord with the radioactive ion exchange results of Kukura, Bell, Posner and Quirk[6]. Thus, the primary interactions between these two regions will be through their equilibria with the bulk solution, one stoichiometric and the other electrochemical. At equilibrium, the former assures that the solution composition will be on the isotherm, and the latter, through an adjustment of the outer layer composition, fixes the Galvani potential difference so that the electrochemical potentials of the ions in the active part of the outer layer and the bulk solution are equal.

DISCUSSION OF SURFACE EQUILIBRIA

We have seen from the above that there are basically three types of chemical reactions that can be written for the equilibria between the bulk solution, the interior lattice, and the interfacial compartments. One of these sets, the Gibbsian equilibria, although valid, do not represent physical mechanisms or processes, but instead are derivative from the electrochemical equations. There are as many of these equations as there are components in the system. The stoichiometric equilibrium is represented by a single equation because all of the components are involved with fixed ratios in a single chemical process. When ionic components are used, which must be the case with electrochemical equilibria, the system which is nominally ternary becomes quaternary[5]. With bulk phases, the condition of electroneutrality provides an appropriate constraint. In the following we summarize the essential properties of the stoichiometric and the electrochemical type equilibria.

Stoichiometric model: This model provides the mechanism for equilibrium between the interior of the crystal and the bulk solution, and even though the reaction takes place at the surface, the stoichiometry and Gibbs energy change of the process is controlled by the inner lattice and not by the surface layer. This explains why the 100 face of OHAp could have a half unit cell of octacalcium phosphate in its outer layer[3] and still have the solubility of OHAp. This type of process is consistent with well accepted crystal growth and dissolution mechanisms[7-9]. Because it is a stoichiometric process, it is not affected by Galvani potential differences, nor can it generate such potentials.

Another feature of the stoichiometric model which is appealing is that it provides that all the faces of the crystal have the same solubility, because in each case it is interior lattice that dissolves or is created, and not outer layer, during dissolution-growth. Despite this equality of solubility properties of the various types of faces, this model does not invalidate Wulff's law because the Gibbs energy stored in the passive part of the outer layer could determine the relative areas of the crystallite faces thereby providing a most stable morphology. As noted earlier, it is essential for the reaction to be stoichiometric if it is to define a solubility product constant. Because of the stoichiometric feature of the model, it is assured that (i) if there is a Galvani potential difference between lattice and solution, it will not affect the solubility; and (ii) when the composition of the lattice cannot change, the Gibbs--Duhem equation assures that the Gibbs energy of the lattice will remain constant[4]. Also, the model provides a rational approach to showing how particle size can affect the solubility of the crystallites because when the crystals are sufficiently small it would not be possible to create or destroy undistorted inner lattice by an increment of growth or dissolution.

Electrochemical model: This model is consistent with the random, gas-like, kinetic processes that are known to take place at interfaces, and the ion distributions obviously will be affected by Galvani potential differences; conversely, they will generate Galvani potential differences which are known to exist between crystals and the bulk solution (e. g., specific ion electrodes). Because this type of process is in general non-stoichiometric, it does not generate a solubility product constant nor an isotherm in the phase diagram. This permits the composition of the outer layer to change as the solution composition shifts along the isotherm. Under some conditions (probably

when the shift is from a saturated solution of low pH to a solution of high pH), calcium and phosphate ions may be released in sufficient amounts so that the resulting solution becomes supersaturated. This would account for apparent nonstoichiometric and incongruent dissolution processes and for anomalous solubility constants that have been encountered. Since this type of process involves, in its essence, adsorption of ions to simply modify the composition of the non-stoichiometric outer layer, it is not a true crystal growth or crystal dissolution process involving the lattice. It apparently would never involve more than a fraction of a unit-cell thick layer on the surface.

An Application to Dissolution Kinetics

The usefulness of a valid model for surface equilibria can be illustrated by an example. Higuchi and coworkers use a »two-site« model to explain their dissolution-kinetics data[10,11]. They associate two parameters with each site: (1) an »apparent ion activity product« for dissolution at that site, K_{ap}, such that the ion activity product in the solution must be below this value before dissolution can proceed at an appreciable rate, and (2) a rate-of-dissolution constant which is independent of the ion activity product of the solution. Their dissolution results indicate that the rate constant associated with the site with the larger K_{ap} (site 1) is the only one that is active when the degree of undersaturation is low. However, the site with the smaller K_{ap} (site 2) takes over when the degree of undersaturation is very high because its rate constant is relatively large. The Higuchi two-site model has not received wide acceptance, in part because it lacked a rigorous model to account for the assignment of the characteristic thermodynamic and kinetic constants for each site. In the following, we show that through the use of our stoichiometric equilibrium model it is possible to develop a rational two-site model.

The model is based on the idea that each of the two sites is associated with a given type c^f face, say the (100) and the (101) of hydroxyapatite. It accepts the idea that the thermodynamic solubility is the same for all types of faces, but that each type of face can have a different activation energy for dissolution. Thus, the difference between the solubility product constant and K_{ap} would be related to the activation energy for dissolution. The rate constant associated with each site would then be a function of such factors as (i) the total area of that kind of face, (ii) the number of kink sites per unit area of the face, and (iii) the mobilities of ions on that face. The fact that most hydroxyapatite crystals are acicular and have only two types of faces, the prism faces (100), which dominate, and the terminal faces, (101), is in accord with the relative values of the four adjustable parameters of a two-site model, as is the suggestion by Higuchi (personal communication) that the prism face is the locus of site 2 and the terminal face is the locus of site 1. The relatively large area of the prism face would tend to make its rate constant large, as required for site 2, and the observation that hydroxyapatite crystals dissolve from within, forming tubular crystals, when the undersaturation is low, would be in accord with properties of site 1. This model requires additional development and confirmation. For example, the apparent activation energy of site 1, $K'_{ap} = 10^{-120}$, would be about 4 Kcal, which appears reasonable; that for site 2, $K''_{ap} = 10^{-128}$ to 10^{-131}, would be about 15 to 20 Kcal. The latter values appear high, but perhaps not for a process involving a total of 18 atoms plus some waters of hydration.

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SAŽETAK

Termodinamika površina hidroksiapatita

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Opisan je novi model postizavanja ravnoteže na površini slabo topljivog kristala u otopini. Model pretpostavlja više simultanih tipova ravnoteže, a svaka od njih je ovisna o: (1) vrsti koja se prenosi preko granice faza, (2) kemijskim ravnotežama koje opisuju taj proces prijenosa, i (3) termodinamičkim parametrima koji određuju pojedinu ravnotežu. Model uočava tri tipa ravnoteža: 1. Stehiometrijska ravnoteža, koja je izraz termodinamičke komunikacije između čvrste faze i mase otopine. Ta stehiometrijska ravnoteža održava se na mjestu defekta površine, održava stalni sastav čvrste faze, određuje produkt topljivosti, određuje jednu od izotermi faznog dijagrama, i neovisna je o Galvanijevim potencijalima. Ravnoteža je određena jednom jedinom jednadžbom. 2. Gibbsova ravnoteža, koja zahtijeva da kemijski potencijal svake komponente bude jednak preko čitave granice faza, ali ne definira neki stvarni kemijski proces. 3. Elektrokemijska ravnoteža izražava termodinamičku vezu između iona u masi otopine i onih na vanjskoj površini kristala. Ta je ravnoteža nestehiometrijska, ovisna je o Galvanijevu potencijalu, nije određena izotermom u faznom dijagramu niti dovodi do konstante produkta topljivosti. Njezina definicija zahtijeva broj uvjeta ravnoteže koji je za jedan veći nego broj komponenata u sistemu.

Ravnoteža između kristalne rešetke i površine uvjetovana je reakcijskim putem kroz tekuću fazu. Ovaj model predstavlja nov, do sada nedostignut stupanj jasnoće opisa površinskih reakcija.