The calcium orthophosphate solubilities as represented by a model in three dimensions

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The construction of a model of the calcium orthophosphate solubilities has been described in detail. The model gives a true and easily comprehensible visualization of the complex interrelationships existing in phosphate systems. Examples of its application have been given as regards the stability fields, the biologic metastability, the congruent solubility, and the kinetics of dissolution and precipitation processes. As an instrument of assessing the solubilities in practical work, the usefulness of the model is further increased by including diagrammatic representations of the solubilities of Fap, CaF_2, and $CaCO_3$. The model virtually covers the whole field usually encountered in solubility studies. It is based upon an ionic strength of 0.05, and any complexation, ionic interaction, or specific ionic effects have been disregarded It is possible, however, to make the model to any scale and to construct it with a view to any purpose required.

Key-words: Calcium phosphates; hydroxyapatite; solubility

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The mineral metabolism of hard tissues is primarily a question of calcium orthophosphate solubility. These solubilities are also of immense importance for the fertilizer industry and for the solution of present-day pollution problems, and they are basic to an understanding of the pedodontic development.

Within physiologic research these solubility problems have been controversial ever since they were introduced some 50 years ago (*Holt et al.* 1925, *Sendroy & Hastings* 1926—27). In principle, tissue mineral behavior is governed by physicochemical law relating to liquid-solid phase interplay. However, the overwhelming majority of studies on bone mineralization and demineralization, on dental caries and dental calculus, have been performed in terms of biologic parameters: hormones, enzymes, microorganisms, nutrients. These parameters are generally considered as a goal in themselves, and not as a means of changing the thermodynamically conditioned solubility equilibria.

Consequently, the solubility behavior of hard tissues, and the effect of the biological parameters, has almost exclusively been assessed by empirical means, e.g. by determining the amount of calcium or phosphate dissolved, or by estimating the weight loss or gain. All these methods circumvent the very complex problems connected with calcium orthophosphate solubility, and they may be grossly misleading.

In some very few studies the solubility product principle has been used. The

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solubility product may be suited for evaluating the behavior of one and the same phosphate under different conditions, but not for comparing different phosphates. The only exception is that pairs of phosphates may be arranged in order of their saturation states by calculating transitional pH values.

The relative solubility of any phosphate may be calculated by the n-concept of *Schmidt-Nielsen* (1946). These relative solubilities may be compared. »Solubility» is then defined as »the absolute amount of solid dissolved in the liquid phase at equilibrium». On the assumption that the solubility is strictly stoichiometric and congruent, i.e. the Ca/P ratio is the same in the solid and the liquid phases, the theoretical, absolute solubility may also be calculated (*Hagen*, 1975b). The solubility of any number of phosphates may be represented on a single diagram as functions of the chemical potentials of $Ca(OH)_2$ and H_3PO_4. This method should be convenient for practical work, but it has the inherent drawback that the experimentally determined variables ((Ca^{2+}), (P), pH, ionic strength) cannot be readily visualized on the diagram.

In recent years the ADA Research Unit in Bethesda has carried on fundamental work on solubility problems (see *Brown*, 1973, 1974). This work is not easily accessible to physiologic and dental researchers and has not been utilized.

The model to be presented summarizes the ideas and concepts developed over the years in a way which, it is hoped, may make the model a practical instrument for assessing the solubilities.

THEORETICAL BACKGROUND

The phosphates of interest are:

hydroxyapatite (Hap) or $Ca_5(PO_4)_3OH$,

dicalcium phosphate dihydrate (DCPD) or $CaHPO_4 \cdot 2H_2O$,

octacalcium phosphate (OCP) or $Ca_4H(PO_4)_3 \cdot 2\frac{1}{2}\ H_2O$

β-tricalcium phosphate (TCP) or β-$Ca_3(PO_4)_2$

In addition, some other salts will play a part under conditions where calcium orthophosphates appear, notably fluorapatite (Fap) or $Ca_5(PO_5)_3F$, fluorite or CaF_2, and calcite or $CaCO_3$.

When solubility equilibrium is established, the free energy of the solid phase plus the free energy of dissolution must equal the free energy of the ions in solution:

$$\triangle G_f^o \text{ (solid)} + \triangle G_d^o = \Sigma v_i \triangle G_f^o \text{ (ion)},$$

where $\triangle G_f^o$ (solid) is the standard free energy of formation for the solid, $\triangle G_d^o$ is the standard free energy of dissolution, and where v_i is the stoichiometric coefficient for the ith ion, which has a standard free energy of formation equal to $\triangle G_f^o$ (ion).

Expressed in terms of the chemical potentials, this equation changes into

$$\triangle G_d^o = \Sigma v_i\, RT \ln [\text{activity}]_{ion} = -RT \ln K,$$

adopting the convention that the ion activities are unity under standard conditions. The constant K is the solubility product. Activities are in the following given in brackets, and concentrations in parentheses.

The solubility product derived in this way is functionally related to three variables, two of which are independent. These three variables are: (1) the calcium ion activity, (2) the hydronium ion activity, and (3) the activity of the pertinent phosphoric ion. This latter ion is uniquely determined from the total phos-

phorus activity by means of the dissociation constants of phosphoric acid and the pH.

In terms of negative logarithms the solubility product is then functionally given by

$$pK = \varphi p\,[Ca^{2+}] + \varphi\, p\,(Q_i[P]) + \varphi\, pH \quad (1)$$

where Q has the values

$$Q_1 = \frac{[H_3O^+]^3 K_1}{[H_3O^+]^3 + [H_3O^+]^2 K_1 + [H_3O^+] K_1K_2 + K_1K_2K_3} \quad (2a)$$

$$Q_2 = \frac{[H_3O^+] K_1K_2}{[H_3O^+]^3 + [H_3O^+]^2 K_1 + [H_3O^+] K_1K_2 + K_1K_2K_3} \quad (2b)$$

$$Q_3 = \frac{K_1K_2K_3}{[H_3O^+]^3 + [H_3O^+]^2 K_1 + [H_3O^+] K_1K_2 + K_1K_2K_3} \quad (2c)$$

When multiplied by the total phosphorus activity, these Q quantities give the activities of the $H_2PO_4^-$ ion, the HPO_4^{2-} ion, and the PO_4^{3-} ion, respectively. The K_1, K_2, and K_3 are the first, the second, and the third dissociation constants of phosphoric acid.

In the ternary system $Ca(OH)_2$—H_3PO_4 — H_2O balanced equations may therefore be written for the formation of any phosphate. These equations are given in a coordinate system with $p[Ca^{2+}]$, p[P], and pH as the three axes in accordance with Equation (1). If the pH and p[P] are chosen as the free variables the $p[Ca^{2+}]$ necessary to obtain exact saturation is calculated to:

$$p[Ca^{2+}]_{Hap} = 0.2\ pK_{Hap} - pK_w - 0.6\ pQ_3 - 0.6p[P] + 0.2\ pH;$$

$$p[Ca^{2+}]_{OCP} = 0.25\ pK_{OCP} - 0.75\ pQ_3 - 0.75\ p[P] - 0.25\ pH;$$

$$p[Ca^{2+}]_{DCPD} = pK_{DCPD} - pQ_2 - p[P];$$

$$p[Ca^{2+}]_{TCP} = 0.33\ pK_{TCP} - 0.67\ pQ_3 - 0.67\ p[P].$$

The limitless number of points calculated from these equations are — for each equation — located on a surface in space. Each of these *saturation surfaces* has a curvature and a direction different from the other ones.

When activity units are used, the saturation surfaces have a general validity. However, from a practical point of view it is more convenient to employ the ordinary concentration units. The coordinates are then expressed in terms of calcium ion concentration and total phosphorus concentration, whereas the pH, which is the negative logarithm of the $[H_3O^+]$ may be retained since the pH is measured routinely. These conventions imply that the solubility product constants and the dissociations constants become so-called »incomplete constants», i.e. they are based on activities as far as the H_3O^+ and the OH^- ions are concerned, but on concentrations with regard to other ions involved. The location of the saturation surfaces in relation to the $p(Ca^{2+})$ and p(P) axes will then be a function of the ionic strength. This relationship has only a slight practical importance.

The electroneutrality requirements put an additional restriction on the equilibrium conditions. In a pure $Ca(OH)_2$ — H_3PO_4 — H_2O system the ionic species are connected by the relation

$$2(Ca^{2+}) + (H_3O^+) = (H_2PO_4^-) + 2\,(HPO_4^{2-}) + 3\,(PO_4^{3-}) + (OH^-) \quad (3)$$

Neglecting the small difference between (H_3O^+) and $[H_3O^+]$, and between $(OH)^-$ and $[OH^-]$, this equation may be transformed and plotted as a *neutrality surface*

on the same concentration axes as the saturation surfaces:

$$p(Ca^{2+}) = 0.301 + p\left\{10^{pK_w + pH} - 10^{-pH} + (Q_1 + 2\ Q_2 + 3\ Q_3)\ (P)\right\} \quad (4)$$

The neutrality surface will intersect all the saturation surfaces and form a line with each of them, a *solubility isotherm*. Any phosphate can be in a solubility equilibrium only at these isotherms, which means that the whole system is uni-variant.

When extraneous salts are added to the pure ternary system, which will always be the case in biological systems, Equation (3) assumes the form

$$(Ca^{2+}) = \tfrac{1}{2}\left\{(H_2PO_4^-) + 2\ (HPO_4^{2-}) + 3\ (PO_4^{3-}) - [(H_3O^+) - (OH^-)] - U\right\}$$

The quantity U is termed the *electroneutrality unbalance* and is defined by

$$U = \Sigma v_i \cdot \text{cations} - \Sigma v_i \cdot \text{anions} = \Sigma v_i C_i$$

where v_i is the valency of the ith ion, and the concentrations, C_i, are taken over all the ions in the system except calcium, phosphate, hydronium, and hydroxyl ions.

In the presence of neutral salts, e.g. NaCl, the added equivalents will cancel, and the electroneutrality unbalance will not count. When an acid (HCl) or calcium-containing salt ($CaCl_2$) is added, the U will get a negative value, and the calculated (Ca^{2+}) will increase by the amount of $0.5\ 10^{-3}$ for each milliequivalent of acid added (»positive unbalance»). When a base (NaOH) or a phosphate-containing salt (Na_2HPO_4) is added, the U will get a positive value, and the calculated (Ca^{2+}) will decrease by the amount of $0.5\ 10^{-3}$ for each equivalent of base added (»negative unbalance»).

The electroneutrality surface will move towards the $p(Ca^{2+})$-axis when an acid or additional calcium is added, and move toward the p(P)-axis when a base or extra phosphate is added.

The hydronium and hydroxyl ions may be included in the electroneutrality unbalance, and

$$(Ca^{2+}) = \tfrac{1}{2}\left\{(H_2PO_4^-) + 2\ (HP_4^{2-}O) + 3\ (PO_4^{3-}) - U_a\right\}$$

The electroneutrality surface may then be plotted with the vertical axis expressed in pU_a-units instead of in pH-units. It is then possible to get the »generalized four component phase diagram» (*Brown*, 1974), because the U_a may be regarded as a fourth component in addition to $Ca(OH)_2$, H_3PO_4, and H_2O. The pertinent problems will not be dealt with here except by remarking that the electroneutrality surface will assume the same form in a pure ternary system whether the vertical axis is given in pH-units or pU_a-units.

CONSTRUCTION OF THE MODEL

The saturation surfaces

The dissociation constants for phosphoric acid were taken from *Bjerrum & Unmack* (1929):

$$pK_1 = 2.232 - 0.515\ \sqrt{\mu} - 0.54\ \mu$$
$$pK_2 = 7.165 - 1.545\ \sqrt{\mu} + 1.12\ \mu$$
$$pK_3 = 12.18 - 2.575\ \sqrt{\mu} + 2.62\ \mu$$

These constants are valid at 38°C and for ionic strength up to 0.1.

In cases where activity coefficients had to be calculated, this was done from the formula derived by *Debye & Hückel* (1923). The following values were used:

the charge of a univalent cation was taken to be $4.803 \cdot 10^{-10}$ e.s.u., the dielectric constant 74.31 at 38°C, R was put equal $8.314 \cdot 10^{7}$ erg/deg, and Avogadros number $6.023 \cdot 10^{23}$. Assuming an average solute diameter of 3 Ångström, a general activity coefficient assumed valid at an ionic strength of 0.05 was calculated to

$$\log f_i = 0.0958 \cdot z_i^2,$$

where z_i is the valency of ith ion.

The activity solubility products used were:

pK_{Hap} : 57.43 (*Moreno et al.* 1968)

pK_{OCP} : 46.90 (*Moreno et al.* 1960)

pK_{DCPD}: 6.63 (*Gregory et al.* 1970).

pK_{TCP} : 29.66 (*Moreno et al.* 1970).

With the constants given and $pK_W = 14$, the equations for the saturation surfaces at an ionic strength of 0.05 and for temperatures of 37—38° C are:

Hap:

$$p(Ca^{2+}) = -4.6528 - 0.6\ p(P) + 0.2\ pH + 0.6\ pY \quad (5a)$$

OCP:

$$p(Ca^{2+}) = -5.1024 - 0.75\ p(P) - 0.25\ pH + 0.75\ pY \quad (5b)$$

DCPD:

$$p(Ca^{2+}) = -3.1056 - p(P) - pH + pY \quad (5c)$$

TCP:

$$p(Ca^{2+}) = -4.8716 - 0.67\ p(P) + 0.67\ pY \quad (5d)$$

where

$$Y = 10^{-3pH} + 10^{-2pH-2.0896} + 10^{-pH-8.9645} + {}^{-20.6992} \quad (6)$$

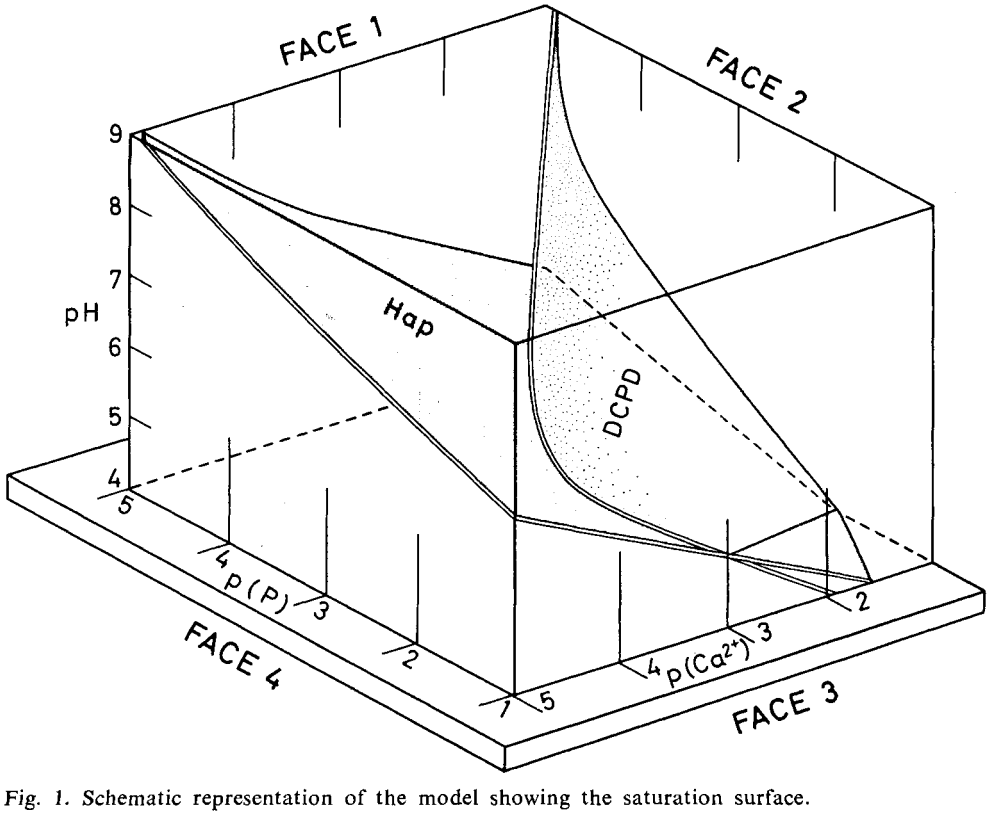

Fig. 1. Schematic representation of the model showing the saturation surface.

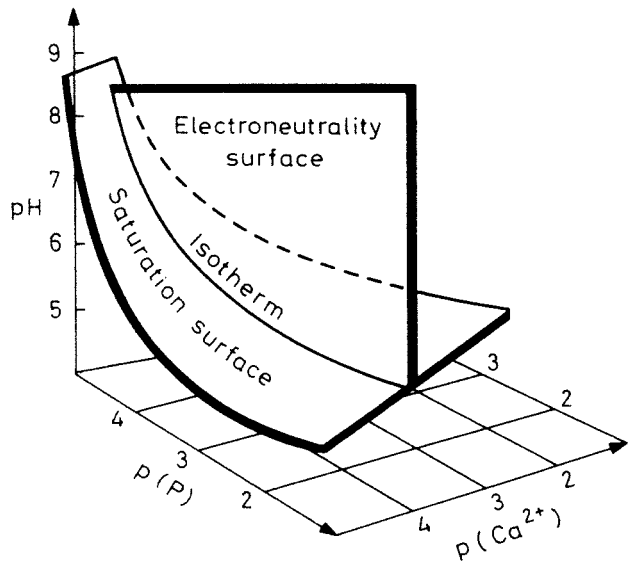

Fig. 2. Schematic representation of the saturation and electroneutrality surfaces.

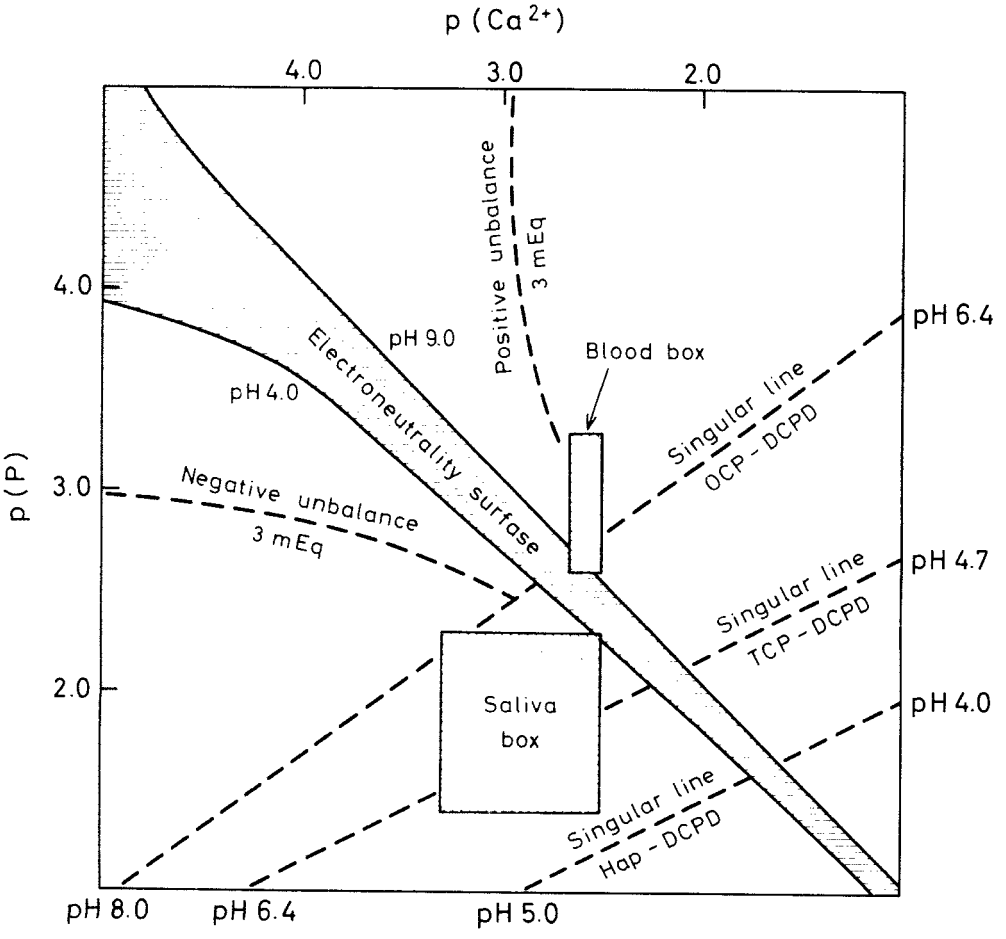

Fig. 3. Projections on the p(P) — p(Ca^{2+}) surface. Vertical axis: pH from 4.0 to 9.0.

A schematic representation of the model has been shown in Fig. 1. When the (Ca^{2+}) and p(P) values are plotted in decreasing order, and the pH's in increasing order away from the origo of the coordinate system, any point located above any surface represents a state of supersaturation with respect to that surface. Similarly, any point below a surface represents a state of undersaturation.

The region incorporated in the model has pH values from 4.0 to 9.0, and $p(Ca^{2+})$ and p(P) values from 1.0 to 5.0, i.e. they cover a concentration range from 0.01 to 100 mM. All biologic and most inorganic systems will be found within these limits.

The electroneutrality surface

This surface is calculated from Equation (4) with the appropriate constants introduced (Fig. 2). At an ionic strength of 0.05 we get

$$p(Ca^{2+}) = 0.301 + p\left\{10^{-14+pH} - 10^{-pH} + \frac{X}{Y}(P)\right\} \quad (7)$$

where Y is given by Equation (6) and

$$X = 10^{-2pH-2.0896} + 10^{-pH-8.6635} + 10^{-20.2221}$$

When the concentrations of total phosphorus and the activity of hydronium are approximately similar (and equal to 10^{-pH}), or the concentration of calcium and the activity of hydroxyl are both about 10^{-pK_W+pH}, the mathematical solution of Equation (7) makes no practical, chemical sense. This is so because the cationic equivalents will come from the dissociation of water and phosphoric acid at low pH values, whereas the anionic equivalents will essentially consist of hydroxyl ions at high pH's under these conditions. The results is the presence of so-called »knees» in the electro-neutrality surface as plotted. Fortunately, these complications are not of interest with regard to the saturation surfaces.

When the electroneutrality unbalance enters, the left side of Equation (7) must be given an addition for plotting purposes. The $p(Ca^{2+})$ must be changed to

$$p\left\{(Ca^{2+} \pm \tfrac{1}{2}\ U)\right.$$

$$\text{or } p\left\{(Ca^{2+}) \pm mEq\ 10^{-3.301}\right\},$$

where mEq is number of milliequivalents of extra calcium or extra phosphate. These corrections will make themselves especially conspicuous at low concentrations of ionic calcium and total phosphate, and will then lead to definite »knees» in the electro-neutrality surface.

Fig. 3 gives a projection on the basal plane of the model, illustrating the relationship mentioned.

The solubility isotherms

Any phosphate can be in solubility equilibrium only where the electroneutrality surface intersects the pertinent saturation surface. The solubility isotherms are formed by these intersections.

For the following calculations it is convenient to transform Equations (5a), (5b), (5c), and (7) into an operational form. This transformation is done from the tabulated data by means of the general relation:

$$\frac{pH-pH_1}{pH_2-pH_1} = \frac{p(Ca^{2+}) - p(Ca^{2+})_1}{p(Ca^{2+})_2 - p(Ca^{2+})_1} = \frac{p(P) - p(P)_1}{p(P)_2 - p(P)_1} \quad (8)$$

And the vector equation

$$a \cdot pH + b \cdot p(Ca^{2+}) + c \cdot p(P) + k = 0 \quad (9)$$

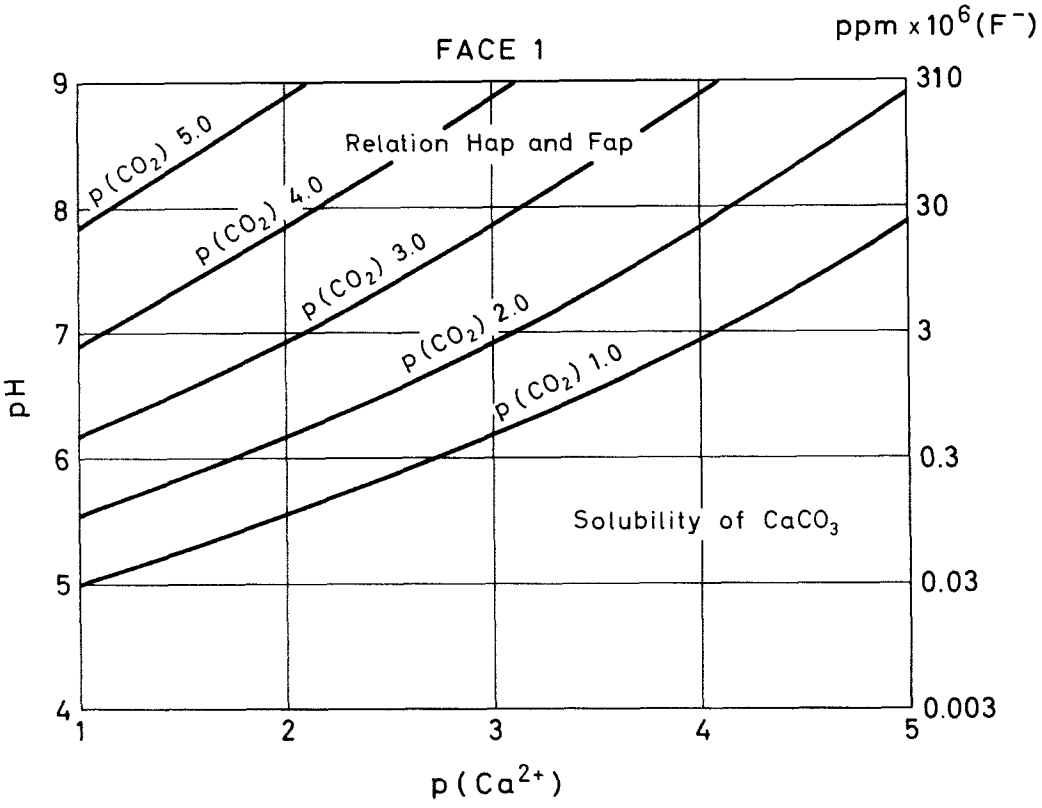

Fig. 4. Surface representing the solubility of $CaCO_3$ and the solubility relation of Hap and Fap.

Equations for the solubility isotherms relating to saturation conditions in the model

Phosphate	Equation of the isotherm
Hap	$0.4702\ p(Ca^{2+}) - 0.1240\ p(P) - 0.2235\ pH + 0.3409 = 0$
OCP	$0.5774\ p(Ca^{2+}) - 0.1319\ p(P) - 0.2698\ pH + 0.6083 = 0$
DCPD	$3.1298\ p(Ca^{2+}) - 0.2845\ p(P) - 0.6616\ pH - 2.0756 = 0$
TCP	$0.8187\ p(Ca^{2+}) - 0.1489\ p(P) - 0.3540\ pH + 0.5446 = 0$

Equations for the singular lines in the model

Pairs of phosphates	Equation of the singular line
Hap — DCPD	$0.5\ p(Ca^{2+}) + 3\ p(P) + 2\ pH - 14.3680 = 0$
OCP — DCPD	$0.5\ p(Ca^{2+}) + 2.3666\ p(P) + 2.4635\ pH - 24.5785 = 0$
TCP — DCPD	$0.5\ p(Ca^{2+}) + 2.9508\ p(P) + 2.0252\ pH - 17.9352 = 0$

Coordinates for the singular points in the model

Pair of phosphates	pH coordinate	$p(Ca^{2+})$ coordinate	p(P) coordinate
Hap — DCPD	4.3979	1.8222	1.5537
TCP — DCPD	5.3168	2.2308	2.0512
OCP — DCPD	6.8862	2.6797	2.6512

The equation for the electroneutrality surface is thus changed into

$$p(Ca^{2+}) = p(P) - 0.0963\ pH + 0.6919 \qquad (10)$$

equating Equation (10) with the operational equations for the four phosphates gives equations for the solubility isotherms relating to saturation conditions in the model (p. 74).

The coordinates of the isotherms at a particular pH are found by means of Equation (10) which gives the Ca/P ratio at the pH in question. The number of unknown is then reduced to one.

The singular lines and the singular points

When any pair of the four Equations (5a) —(5d) is equal, the corresponding saturation state must be described equally well by the two equations. This leads to the presence of *singular lines* in the model. Theoretically, six such singular lines are possible, but only three of which will occur within the region of the model, namely that between Hap and DCPD, that between OCP and DCPD, and that between TCP and DCPD. The pertinent calculations give equations for the singular lines in the model (p. 74). The equations are solved by choosing the pH and calculating the (Ca^{2+}) — (P) relation from Equation (5c).

When the solubility isotherm intersects a singular line, a *singular point* will appear. Only at this point can any two phosphates be in equilibrium simultaneously. The coordinates of the singular points are determined by the fact that the operational equations of the solubility isotherms and those of the singular lines must have the same value for $p(Ca^{2+})$, p(P), and pH. The calculations give coordinates for the singular points in the model (p. 74).

Representation of the solubilities of Fap, $CaCO_3$, and CaF_2

1. The relation between the solubilities of Fap and Hap is

$$\frac{K_{Fap}}{K_{Hap}} = \frac{(F^-)}{[OH^-]} = (F^-) \cdot \frac{[H_3O^+]}{10^{-14}} \qquad (11)$$

and

$$p(F^-) = 16.7864 - pH$$

The constants used (ionic strength 0.05) were $pK_{Fap} = 55.6698$ (*Hagen*, 1975a) and $pK_{Hap} = 52.8832$. The fluoride values given along the pH axis of the model will indicate the minimum fluoride concentration required to make Fap and Hap saturated simultaneously at the pH in question (Fig. 4).

2. The activity solubility product of $CaCO_3$ was assumed to be 8.766 (*Hastings et al.*, 1926—27). The values of 6.304 (*Harned & Davies*, 1943) and of 10.13 (*Kauko & Airola*, 1937) were used as the first and second dissociation constants of carbonic acid, respectively.

At an ionic strength of 0.05 the relation between the solubilities of calcite and Hap, in terms of total P, total CO_2, and pH, is

$$p(CO_2) = 0.6\ p(P) - 0.2\ pH - 3.4986 + pZ - 0.6pY$$

where pY is given by Equation (6) and

$$z = 10^{-2pH} + 10^{-pH-6.2084} + 10^{-16.0510} \qquad (12)$$

A plotting of the calculated (CO_2) values on the pH — p(P) surface of the model will indicate the minimum CO_2 concentration required to make $CaCO_3$ saturated at the same time as Hap (Fig. 5).

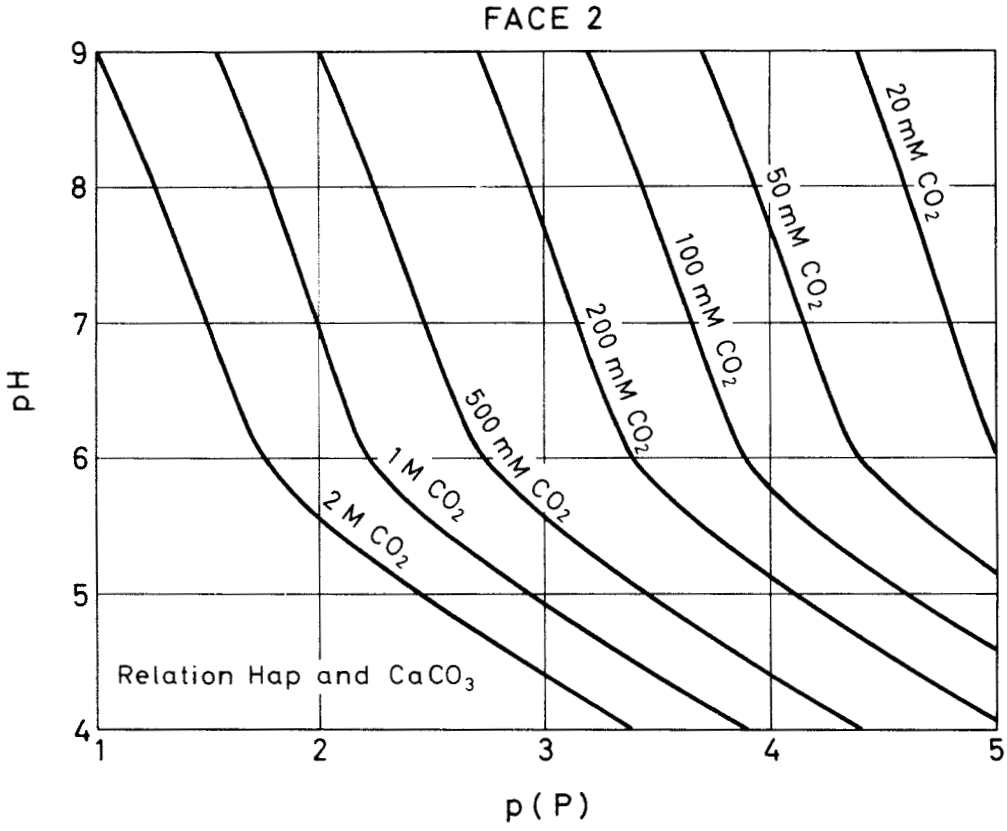

Fig. 5. Surface representing the solubility relation of Hap and $CaCO_3$.

3. A diagrammatic representation of the solubility of $CaCO_3$ itself is given on the $p(Ca^{2+})$— pH surface, calculated from the relation

$$p(CO_2) = 8.1514 - p(Ca^{2+}) - pZ \qquad (13)$$

The CO_2 isotherms show the CO_2 concentrations needed to make $CaCO_3$ saturated at the pH's and $p(Ca^{2+})$'s given on the axes (Fig. 4).

4. The solubility of fluorite is plotted separately along the $p(Ca^{2+})$ axis of the model according to

$$p(F^-) = 4.9376 - 0.5\ p(Ca^{2+}) \qquad (14)$$

The activity value of pK_{CaF_2} was taken to be 10.45 (*McCann*, 1968). The (F^+) values plotted will indicate the fluoride concentration (in ppm) needed to make CaF_2 saturated at the $p(Ca^{2+})$ in question (Fig. 6).

5. The solubility of fluorite may also be related to that of Fap. In a solution (ionic strength 0.05) simultaneously saturated with CaF_2 and Fap, the calcium concentration is given by

$$p(Ca^{2+}) = 9.8752 - 2\ p(F^-).$$

Substituting this expression in the solubility product of Fap($pK_{Fap} = 55.6698$) gives

$$p(P) = 2.0979 - 3\ p(F^-) - pQ_3,$$

where Q_3 is defined by Equation (2c). For selected values of $p(F^-)$, p(P) may be found as a function of pQ_3 and the pH. The

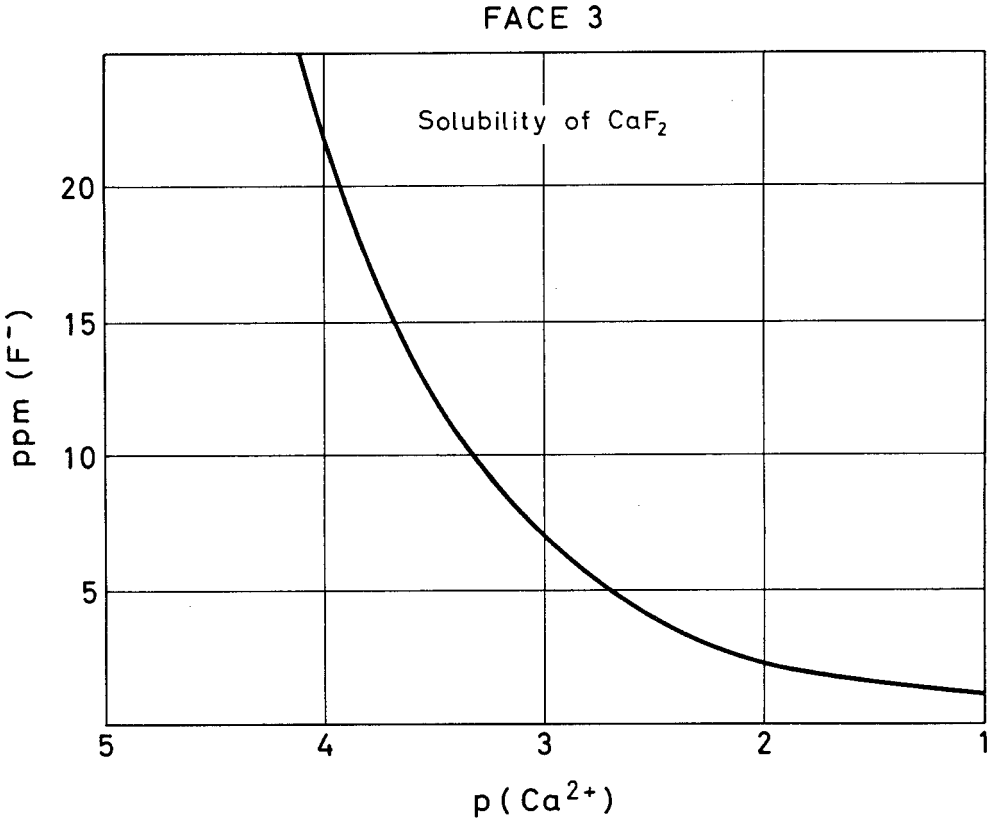

Fig. 6. Surface representing the solubility of CaF_2.

results are plotted as a graph on the p(P)—pH surface of the model, from which may be read off the fluoride concentration (in ppm) needed to make CaF_2 and Fap saturated simultaneously at the pH and p(P) in question (Fig. 7).

The solubilities in saliva and plasma

The regions in the model pertaining to conditions in saliva and plasma have been projected on the basal plane in Fig. 3. The constructions were based on the variations in these two fluids as given on p. 78. It is to be noted that the ionic strength in plasma is higher than 0.1, which is considered the upper limit for the validity of the constants used.

DISCUSSION

The present discussion will be limited to the general principles of solubility. Readers interested in the applications of the model on the caries process are referred to *Brown* (1973, 1974).

The crystallographic and thermodynamics studies of later years have made it fairly certain that the solubilities in calcium orthophosphate systems such as saliva are restricted to those seven compounds represented in the model. The possibility of solid solutions has been indicated (*Driessens*, 1973), but these solid solutions will probably only act as intermediary phases in the change from one equilibrium state to another.

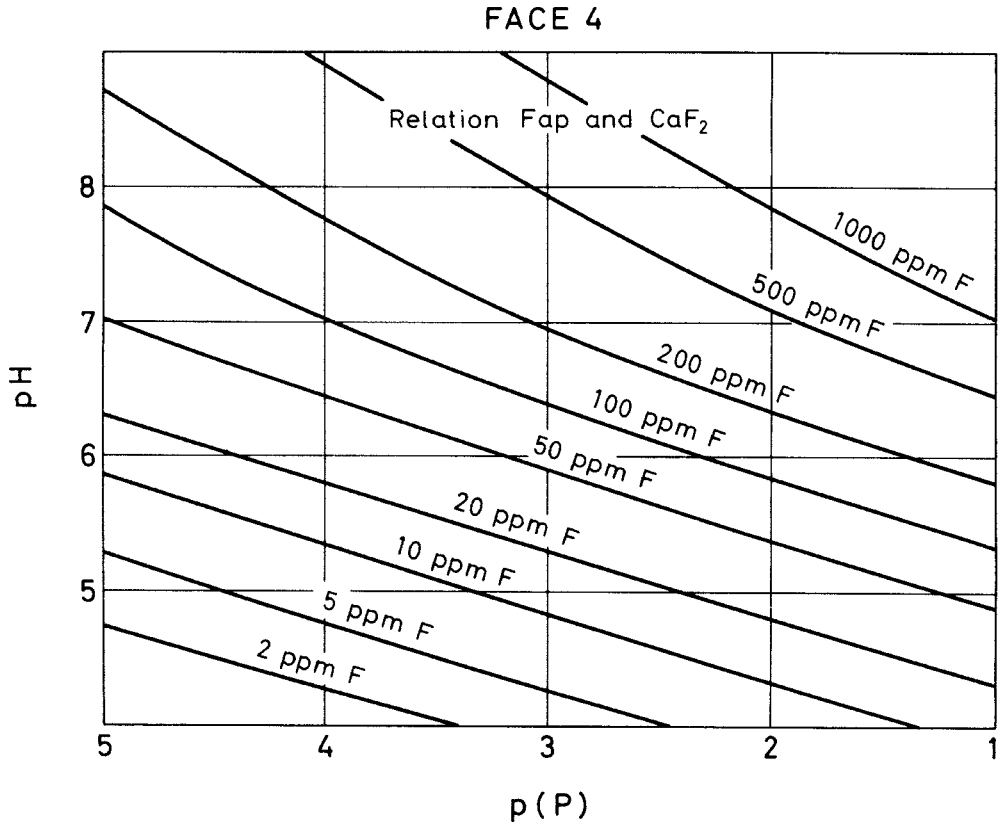

Fig. 7. Surface representing the solubility relation of Fap and CaF_2.

The solubilities in saliva and plasma

Fluid	Total Ca	Total P	pH	Ionic strength
Saliva	0.5—3.0 mM	3.0—40.0 mM	4.0—9.0	0.02—0.12
Plasma	2.0—3.0 mM	0.5— 2.5 mM	6.5—8.0	0.14—0.17

Discussion

Compound	$\triangle H_f^o$ kcal/mole	$\triangle G_f^o$ kcal/mole	S cal/deg/mole	p(S.p.)
$Ca_{10}(PO_4)_6(OH)_2$	—3221	—3030	186.6	114.86
$CaHPO_4$ 2 H_2O	— 574.47	— 515.00	45.28	6.63
$Ca_8H_2(PO_4)_6$5 H_2O		—2931		93.80
β-$Ca_3(PO_4)_2$	— 984.9	— 928.5	56.4	29.66
$Ca_{10}(PO_4)_6F_2$	—3285	—3103	185.4	117.84
CaF_2	— 291.5	— 279.0	16.46	10.45
$CaCO_3$	— 299.46	— 269.80	22.2	8.766

Some thermodynamic data (National Bureau of Standards, 1971) and the activity solubility products used have been assembled in the table on p. 78.

Some variation in these thermodynamic values is encountered in the literature. However, this variability definitely falls within any analytic and experimental error of ordinary laboratory work, i.e. to all practical intents and purposes the values given may be regarded as true constants. The model, which is directly built on these constants is therefore a generally valid representation of the solubilities in calcium orthophosphate systems. It is pointed out, however, that the theoretical assumptions cannot be physically realized in every part of the model, e.g. it is impossible to maintain an ionic strength of 0.05 at the low pH values.

The stability fields

These fields are clear-cut only at pH values above 6—7. Under these physiologic conditions Hap is by far the most stable solid phase, which explains why this phosphate is the backbone mineral in all hard tissues. Next in order follow TCP and OCP with DCPD as the most soluble phosphate. The practical implication of this finding is that the dental enamel-saliva relationship is normally governed by the Hap solubility.

By decreasing the pH or increasing the P concentration in the systems the singular line will be reached, and a solubility shift will take place. *Ericsson* (1949) observed that saliva-dental enamel systems remained unsaturated with respect to Hap at pH's of 5.0 and lower. This finding is explained by the fact that DCPD, and not Hap, is the governing phase in these acid regions, as shown also by crystallographic evidence (*Hagen*, 1965, *Newesely*, 1966). *Moreno et al.* (1960) found a solubility shift between Hap and OCP at pH 6.38. The effect of merely changing the P concentration was observed by *Elliott et al.* (1959). On the whole, the mass of earlier experimental data are in harmony with the predictions of the model. The solubility shifts will explain the presence of non-apatitic phosphates in carious lesions.

Only minute quantities of F^- is necessary for the formation of Fap, which is the least soluble of all the phosphates. This fact is a contributing cause to the expressed effect of fluoride ingestion on hard tissue metabolism, and explains why Fap is the apatite prototype found in nature. At low pH's and low P concentrations relative to (F^-), fluorite will form at the expense of Fap (*Hagen*, 1975a). The conditions necessary for the formation of CaF_2 can probably not be obtained in the human body except in the oral cavity, where fluoride from highly acidulated and highly concentrated topical agents is initially fixed as CaF_2 (*Hagen*, 1972).

Calcite will hardly form at the expense of phosphates under physiologic conditions since the CO_2 concentrations will be too low. Only under exceptional circumstances, e.g. in states of acidosis or at the openings of the salivary ducts, might the presence of $CaCO_3$ be expected. In sea-water and in geologic formations the precipitation of $CaCO_3$ may be favored as evidenced by the abundance of carbonates in nature.

The biologic metastability

In current publications the saturation state in biological fluids is described as metastabile. In general, however, no precise and physico-chemically defined meaning is attached to this metastability concept; often it is simply implied that biological

fluids contain more calcium and phosphorus than corresponding inorganic solutions do. In this sense saliva and plasma is »metastabile», supersaturated, since the salivary and plasma boxes in the model are for the most part located above the saturation surfaces. However, it is forbiddingly difficult to vizualize these states as true, thermodynamic supersaturations, because the concentration of Hap in these fluids would then be 10—20 times higher than thermodynamics would allow.

The explanation for this apparent supersaturation is that saliva and plasma are always analyzed for the gross concentrations of calcium and phosphorus, whereas the solubility equilibria refer to the activities of the participating ions. When adequate corrections are made for complexing processes and ionic strength effects, human saliva seems to be approximately saturated with regard to Hap (*Hagen*, 1965).

Because the thermodynamic properties of biological fluids are largely unknown, the total contents of calcium and phosphorus in saliva and plasma, and the various »products» derived from these quantities, have only an empirical value as a measure of the biological solubility. Whether the total calcium (or phosphorus) concentration is high or low, says virtually nothing about the saturation state, and thereby about the dynamics of hard tissue metabolism.

In Gibb's notations several equilibrium states may be proposed:

a) a *stable equilibrium* is present when the three experimental parameters (pH, $p(Ca^{2+})$, p(P)) exactly correspond to an isotherm;
b) a *metastabile epuilibrium* is characterized by the fact that any two of the parameters fall on an isotherm, whereas the third one does not;
c) an *unstable equilibrium* is present when only one of the parameters corresponds to an isotherm, whereas the other two do not;
d) when none of the parameters fall on any isotherm, the system is in *non-epuilibrium.*

The logical basis of this classification is the fact that the statistical probability of reaching a defined stabile equilibrium is increasing in the order d), c), and b), i.e. to some extent it is possible to predict the direction of change.

The above-mentioned terms relate to the isotherms much in the same way as »supersaturation» and »undersaturation» relate to the saturation surfaces. Also in this latter case the probability is that a supersaturated solid phase will be approached rather than an undersaturated solid phase.

The congruent or stoichiometric solubility

The stoichiometric nature of the solubility reaction is evidenced by the general formula

$$m \cdot \mu Ca(OH)_2 + n \cdot \mu H_3PO_4 = F_f \text{ (phosphate)} + y \cdot \mu H_2O \qquad (15)$$

where $\mu Ca(OH)_2$, μH_3PO_4, and μH_2O are the chemical potentials of the respective components. These potentials are defined in terms of an activity product, e.g. for $\mu Ca(OH)_2$:

$$\mu Ca(OH)_2 = \mu^{\circ} Ca(OH)_2 + RT \ln [Ca^{2+}] [OH^-]^2$$

Assuming the chemical potential of water to be constant, Equation (15) is changed into

$$\log [Ca^{2+}] [OH^{-2}] = -\frac{n}{m} \log [H^+]^3 [PO_4^{3-}] + K \qquad (16)$$

A plotting of log $[Ca^{2+}]\,[OH^-]^2$ versus log $[H^-]^3\,[PO_4^{3-}]$ will give a slope equal to the negative reciprocal of the Ca/P of the solid phase, i.e. for Hap the slope will be $-3/5 = \frac{1}{1.67}$, for TCP $-\frac{1}{1.5}$, for OCP $-\frac{1}{1.33}$, and for DCPD $-\frac{1}{1}$.

This thermodynamically determined relation between the chemical potentials of the components and the Ca/P ratio of the equilibrating solid, has often been interpreted to mean that the Ca/P ratios themselves should be equal in the liquid and solid phases at equilibrium. However, thermodynamics puts no such restrictions on the system. It is seen from the model that the saturation surfaces have a limitless variation of the Ca/P ratios.

The Ca/P ratio in the liquid phase is primarily determined by the electroneutrality surface. For a pure ternary system it is calculated from Equation (10) that the Ca/P ratio will vary between 0.5 at pH 4.0 to 1.5 at pH 9.0, whatever phosphate is present. To obtain a Ca/P ratio of, say, 1.67 for Hap, would necessitate the presence of a positive electroneutrality unbalance, and excess calcium, in the system.

By the term »stoichiometry of dissolution» is often implied that the Ca/P ratio in the mater dissolved must be the same as that in the matter not dissolved. Consequently, there should be a 1 : 1 correspondence between the Ca/P ratios in the liquid and solid phases. It must be noted, however, that the phosphates are anisotropic and exhibit directional tendencies. Thus the different planes in the crystals will be expected to possess different solubilities (*Tyler*, 1970; *Jongebloed et al.*, 1973). Moreover, it is important to distinguish between the concentration of a component and its chemical potential. At equilibrium the chemical potential of the PO^{3-} must be the same in the solution and the solid. In the liquid phase, however, the chemical potential will vary with the acidity, being higher in alkaline than in acid solutions. Concequently, more PO_4^{3-}groups will tend to dissolve relative to Ca^{2+} as the pH decreases. The result will be a decreasing Ca/P ratio with decreasing pH. It is also noted that the exchange properties of Fap indicate that the ion in the solid to some degree behave independently (*Hagen*, 1973). The term »stoichiometric solubility», which has been used synonimously with »congruent solubility», should probably be reserved for cases where the solubility is expressed in terms of »grams pr liter» (*Hagen*, 1975b).

The kinetics of dissolution and precipitation

The model only describes the states existing under thermodynamic, equilibrium conditions. The fundamental equilibrium, which eventually will be reached, is represented by some point on the isotherm located lowest in the model. Given time, Hap is bound to appear as the only solid phase when the pH is above 6.0—7.0.

The many metastabile and unstable equilibria in the system are all of a transient character, but may nevertheless play a significant part in the formation of solids during their short-lived existence (cp. »caries crystals» in carious lesions). These processes are in principle matters of kinetics. The rate or rapidity of a reaction is dependent upon a number of physical factors (viscosity of the solution, the presence of organic matter, etc.) which, however, cannot initiate or stop any process, but may only impede reactions going on between given energy states.

The energy difference which is needed for any process to proceed, is termed »the

driving force» (*Lewis & Randall* 1923), and may for the present purpose be defined as:

$$\text{Driving force} = RT \ln (\text{ionic product}) - RT \ln (\text{solubility product})$$

$$= RT \ln \frac{(\text{ionic product})}{(\text{solubility product})} \quad (17)$$

The driving force, or rate, will be increasing with the difference between the experimentally determined ionic product and the thermodynamically derived solubility product. If the sign is negative, a dissolution is taking place, whereas a positive sign shows that a precipitation is going on. The relation of the experimental points to the isotherms in the model will, therefore, also give information about the rates. Conversely, the model shows that any change in the experimental variables also affects the rate of reaction. By lowering the pH, a highly supersaturated solution will become less supersaturated and the rate of precipitation will decrease simultaneously. When the pH is such that the ionic product = the solubility product, the system is just saturated, and the net rate is zero (»critical pH»). By lowering the pH further, the system will become increasingly unsaturated. The rate will assume a negative value, i.e. it will become the rate of dissolution.

In addition to the driving force, each phosphate has its specific rate of reaction which may be denoted by $K_{phosphate}$. *Huffman et al.* (1957) and *Hagen* (1975a) have shown that Fap has a much lower rate of dissolution than has Hap, which in turn is more inert than the water-containing OCP and DCPD. The specific rates are therefore arranged in much the same order as the saturation surfaces in the model.

The total rate may then be described by:

$$\frac{\text{d (solid diss. or prec.)}}{\text{d (time)}} = K_{phosphate} \pm \text{driving force}$$

It is conceivable that the $K_{phosphate}$ and the driving force may combine in such a way that OCP or DCPD will form instead of the inherently more stable Hap. As may be inferred from the model, this formation of OCP and DCPD will preferably take place at lower pH values, where the low specific rate of Hap has a less probability of being compensated by a high driving force.

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