

Ionic Concentrations in Calcium Phosphate Solutions. II. The Solubility of Hydroxylapatite in Water or Salt Solutions at 37 °C

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A table of calcium and phosphate concentrations in solutions saturated with respect to hydroxylapatite $[\text{Ca}_5\text{OH}(\text{PO}_4)_3]$ at 37 °C and at various concentrations of an indifferent salt has been computed; pH is the independent variable, with $5 \leq \text{pH} \leq 8$. Two different values of the solubility product have been used, one equal to ten times the other, the higher one corresponding to approach to equilibrium from supersaturation. An order-of-magnitude calculation of the surface Helmholtz function of hydroxylapatite has been carried out on the basis of the ratio between the solubility products and a typical value of crystal size, using the Gibbs-Kelvin equation.

The most important compound among the calcium phosphates is hydroxylapatite, $\text{Ca}_5\text{OH}(\text{PO}_4)_3$, mainly because it is the major inorganic constituent of hard tissue in higher animals. Its solubility has been the subject of numerous publications, yet reliable values of its solubility product at ordinary temperatures have not been obtained until recently. Unlike the first paper in this series,¹ the present one does not report new measurements; we shall use Bjerrum's results² in the calculations. In addition, we shall discuss some important factors affecting the solubility of hydroxylapatite.

THE SOLUBILITY PRODUCT OF HYDROXYLAPATITE

The process of dissolution of hydroxylapatite in an aqueous system is



and the solubility product is defined as

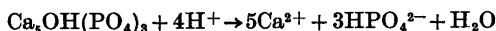
$$K_{\text{sp}} = a(\text{Ca}^{2+})^5 a(\text{OH}^-) a(\text{PO}_4^{3-})^3$$

which may also be written

$$\text{p}K_{\text{sp}} = 5\text{pCa} + \text{pOH} + 3\text{pPO}_4$$

where $\text{p}X = -\log a(X)$ (analogous to pH).

Bjerrum² used a different formulation, particularly suitable for salts of weak acids dissolved in acid solutions and originally applied to the solubility of CaCO_3 .³ He wrote the dissolution process



and determined the quantity

$$\text{p}K_{\text{sp}}' = 5\text{pCa} + 3\text{pHPO}_4 - 4\text{pH}$$

which is related to $\text{p}K_{\text{sp}}$ as follows:

$$\text{p}K_{\text{sp}}' = \text{p}K_{\text{sp}} - 3\text{p}K_3 - \text{p}K_w$$

where K_3 is the third dissociation constant of phosphoric acid, and K_w is the dissociation constant of water. The advantage of using $\text{p}K_{\text{sp}}'$ lies in the fact that it is obtained from the directly measured quantities $[\text{Ca}^{2+}]$, $[\text{P}]$ (total phosphate concentration), and pH with the aid of only one equilibrium constant, *viz.* $\text{p}K_2$ of phosphoric acid; $\text{p}K_3$ is not known with the same precision as $\text{p}K_2$.

Table 1 gives the values found by Bjerrum together with the results of more recent determinations.

Bjerrum's two values represent approach to equilibrium from super- and unsaturated solutions, respectively. The same two different values were invariably found even with an equilibration time of several weeks. The other

Table 1.

<i>T</i> , °C	<i>pK</i> _{sp} '	<i>pK</i> _{sp}	Ref.
37	6.5; 7.5	56.7; 57.7	2
25		54.6; 57.4	4
25		58.3; 60.0	5
37		59.1	6

values in the table correspond to the lower one of Bjerrum's values. Wier, Chien, and Black⁵ used a column-elution technique, which may, perhaps, not allow for sufficient time for the establishment of equilibrium. Moreno, Gregory, and Brown⁴ stated that the value obtained depended on the treatment of samples prior to the experiment.

We conclude that one value of the solubility product must be used when it is desired to calculate the amount of hydroxylapatite, which may precipitate from a given solution, and another value when dissolution is considered, and that there is a "dead zone" of concentrations at which neither precipitation nor dissolution occurs at a measurable rate. Of course, hydroxylapatite, like any other well-defined sparingly soluble salt, possesses one, and only one, thermodynamic solubility product at any given temperature, but at present we do not know the proper value at, say, 25 °C.

In all the above determinations, calcium-phosphate complexes in solution have been neglected. This does not, however, lead to erroneous results unless the values are used far outside the pH range in which they have been determined, approximately $5 \leq \text{pH} \leq 8$.

CALCULATIONS OF ION CONCENTRATIONS

The calcium and total phosphate concentrations as functions of pH in the range $5 \leq \text{pH} \leq 8$ were calculated from Bjerrum's values of *pK*_{sp}' and the value 7.182 for *pK*_{a2} of phosphoric acid at 37 °C.⁷ The set of equations used is: electroneutrality

$$2[\text{Ca}^{+2}] = [\text{H}_2\text{PO}_4^-] + 2[\text{HPO}_4^{2-}] \quad (1)$$

and equilibria

$$[\text{HPO}_4^{2-}]\alpha(\text{H}^+)/[\text{H}_2\text{PO}_4^-] = K_{\text{ac2}} \quad (2)$$

$$[\text{Ca}^{2+}]^5[\text{HPO}_4^{2-}]^3/\alpha(\text{H}^+)^4 = K_{\text{csp}'} \quad (3)$$

The solution for $[\text{Ca}^{2+}]$ is

$$[\text{Ca}^{2+}] = \left\{ \frac{1}{5} \left[\frac{\alpha(\text{H}^+)}{K_{\text{ac2}}} + 2 \right]^3 \alpha(\text{H}^+)^4 K_{\text{csp}'} \right\}^{1/8}$$

from which the other concentrations are easily found. $\alpha(\text{H}^+)$ is defined as $10^{-\text{pH}}$. *K*_{ac2} and *K*_{csp'} depend on the ionic strength *I* of the solution and are found by iteration. For activity coefficients, the Güntelberg⁸ (or Guggenheim-Schindler⁹) formula has been used:

$$\log \gamma_i = A z_i^2 I^{1/2} / (1 + I^{1/2})$$

where *z*_{*i*} is the charge of ion species No. *i* in units of the electronic charge, and *A* is the constant of the Debye-Hückel equation.

The calculations were carried out on a Hewlett-Packard electronic calculator model 9100A with a model 9101 extended memory, both for solutions in pure water and for solutions containing an indifferent salt contributing to the ionic strength by an amount *I*₀. The results are given in Table 2 for *I*₀ = 0 and 0.15, respectively, the latter corresponding roughly to isotonic salt solution. Copies of tables for intermediate values of *I*₀ as well as a copy of the program may be obtained from the author on request.

DISCUSSION

It is evident from a comparison of the present data with those obtained earlier for brushite and tetracalcium monohydrogen phosphate¹ that hydroxylapatite is considerably less soluble than both other compounds throughout the whole pH range investigated. During precipitation of hydroxylapatite the quantity $5[\text{P}] - 3[\text{Ca}^{2+}]$ is constant, and the pH at saturation as well as the amount precipitated from a given supersaturated solution may be found by interpolation. The direct application of the table is limited to cases, where the condition (1) is fulfilled; however, as the fraction of total phosphate which occurs as HPO_4^{2-} is a function only of pH and *I*, the product $[\text{Ca}^{2+}]^5[\text{P}]^3$ also depends on these two parameters only. Hence one may determine whether a given solution is saturated, unsaturated, or supersaturated by calculating this product and comparing it with the value found from the tabulated data for the actual values of pH and *I*.

Table 2. Calcium and total phosphate concentrations in mmol/l.

$I_0 =$ $pK_{sp}' =$ pH	0				0.15			
	6.5		7.5		6.5		7.5	
	[Ca ²⁺]	[P]	[Ca ²⁺]	[P]	[Ca ²⁺]	[P]	[Ca ²⁺]	[P]
5.0	4.797	9.552	3.231	6.431	16.563	33.054	11.838	23.632
5.1	3.634	7.226	2.484	4.938	13.079	26.086	9.438	18.823
5.2	2.784	5.526	1.926	3.822	10.403	20.732	7.564	15.073
5.3	2.153	4.263	1.505	2.979	8.321	16.568	6.087	12.118
5.4	1.678	3.314	1.183	2.336	6.687	13.297	4.914	9.772
5.5	1.317	2.591	.936	1.840	5.393	10.709	3.979	7.900
5.6	1.040	2.037	.744	1.455	4.464	8.648	3.229	6.399
5.7	.826	1.608	.594	1.155	3.540	6.998	2.626	5.191
5.8	.659	1.275	.476	.920	2.878	5.673	2.139	4.216
5.9	.529	1.014	.383	.734	2.344	4.604	1.745	3.428
6.0	.426	.808	.310	.587	1.914	3.741	1.427	2.788
6.1	.345	.646	.252	.471	1.565	3.041	1.168	2.269
6.2	.281	.517	.205	.378	1.282	2.474	.957	1.848
6.3	.229	.415	.168	.304	1.052	2.013	.786	1.504
6.4	.189	.333	.139	.245	.865	1.638	.647	1.225
6.5	.156	.268	.115	.197	.714	1.333	.534	.988
6.6	.129	.216	.095	.160	.590	1.085	.442	.812
6.7	.108	.175	.080	.129	.489	.883	.366	.661
6.8	.091	.142	.067	.105	.407	.719	.305	.539
6.9	.077	.115	.057	.085	.340	.586	.254	.439
7.0	.065	.094	.048	.070	.285	.477	.213	.358
7.1	.056	.078	.041	.058	.240	.389	.180	.292
7.2	.048	.064	.036	.048	.203	.318	.152	.238
7.3	.041	.053	.031	.040	.173	.261	.129	.195
7.4	.036	.045	.027	.033	.148	.214	.111	.161
7.5	.031	.038	.023	.028	.127	.177	.095	.133
7.6	.027	.032	.020	.024	.109	.147	.082	.110
7.7	.024	.027	.018	.020	.095	.123	.071	.092
7.8	.021	.024	.016	.018	.083	.103	.062	.077
7.9	.019	.020	.014	.015	.072	.087	.054	.065
8.0	.016	.018	.012	.013	.063	.074	.047	.056

The difference in solubility resulting from the two values of pK_{sp}' is not so great as it appears at first sight. Consider for instance a solution with $I_0 = 0$, $pH = 6.0$ and $5pCa + 3pHPO_4 - 4pH = 6.5$. If hydroxylapatite is precipitated from this solution, until the latter quantity attains the value 7.5, then pH will be 5.86, and $1.59 \mu\text{mol/l Ca}_5\text{OH}(\text{PO}_4)_3$ will have been precipitated. This amounts to only 1.87 % of the calcium and 0.57 % of the phosphate.

The most plausible explanation of the two different solubility products is that the two ways of approaching equilibrium produce crystals of different size. In an unsaturated solution the smallest crystals are dissolved first, and in this case the crystals will, in general, be larger than in the other case. X-Ray diffractometric investigations show¹⁰ that the crystals obtained by direct precipitation at 37 °C are 500–1000 Å long and 100–200 Å thick. The

solubility of a small crystal is found from the Gibbs-Kelvin equation for solids:

$$\Delta\mu = 2\gamma_j \bar{V}/h_j$$

where $\Delta\mu$ is the excess chemical potential, γ_j is the solid-liquid interfacial Helmholtz function of crystal face No. j , h_j is the perpendicular distance of this face from the center of gravity of the crystal, and \bar{V} is the volume occupied by one formula unit in the crystal. Hydroxylapatite belongs to the hexagonal system, $a = 9.432 \text{ \AA}$, $c = 6.881 \text{ \AA}$, and $Z = 2$. The crystals are hexagonal prisms terminated by hexagonal pyramids. We have $\Delta\mu = kT \ln 10 = 9.85 \times 10^{-21} \text{ J/formula unit}$, and $\bar{V} = 2.65 \times 10^{-28} \text{ m}^3/\text{formula unit}$; if we put $h_j = 100 \text{ \AA}$ for the prismatic faces, we find $\gamma_j = 0.186 \text{ J/m}^2$. Though nothing but a rough estimate, this value is in excellent agreement with the relation between solubility and interfacial Helmholtz function found by

Nielsen and Söhnel ¹¹ from nucleation data.

The persistent supersaturation in solutions in contact with solid hydroxylapatite is explained by assuming that the crystals grow by twodimensional nucleation, in which case there is no observable growth below a certain critical supersaturation. The spiral growth mechanism is ruled out for two reasons: 1° The presence of a screw dislocation in a crystal of the size in question will increase its energy and thereby its solubility to an extent at least as great as the surface effect. 2° Analyses by Wagner ¹² and Kahlweit ¹³ show that if the growth rate is proportional to some power of the supersaturation (1 or 2 in this case), then the latter will decrease steadily with a limiting value of 0.

On the other hand, point defects – vacancies and substitutions – are very frequent in hydroxylapatite, and they cause an increase in solubility, too. Careful preparation and treatment of the samples used for solubility measurements are vital for obtaining a reliable solubility product; results from unspecified commercial products are of no value.

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