

## 3.2: Basic Facts About Calcium- Its Compounds and Reactions

### Basic Facts

Calcium was first recognized as an element in 1808 by Humphry Davy, and the name was given after the Latin for lime: *calx*. Several isotopes of calcium are known. The stable isotopes are, in order of decreasing natural abundance,  $^{40}\text{Ca}$  (96.94%),  $^{44}\text{Ca}$  (2.1%),  $^{42}\text{Ca}$  (0.64%), and  $^{43}\text{Ca}$  (0.145%).  $^{43}\text{Ca}$  is the only isotope with a nuclear spin ( $I = \frac{7}{2}$ ) different from zero, which makes it amenable to NMR studies.  $^{45}\text{Ca}$  is a radioactive isotope of some importance ( $\beta^-$  decay; 8.8 min half life).<sup>3</sup> It has been used in studies of calcium localization and transport in biological systems.

Calcium constitutes about 3 percent by weight of the Earth's crust, mostly in the form of sedimentary rocks of biological origin dating back some three billion years. In sea water the total concentration of calcium ranges from 5 to 50 times higher than in fresh water, which, in turn, has a calcium concentration ten times that of rain water (see Table 3.1). This explains the pleasant feeling when ordinary soaps are used in rain water. The calcium concentration in ordinary tap water varies with location; calcium is usually added to water in distributing networks in order to prevent corrosion of iron pipes. Tap water with a calcium concentration above 1.5 mM is usually classified as "hard." Interestingly, the taste of beer seems related to the calcium concentration, and it is claimed that "good" beer should have a concentration higher than that of "hard" tap water.

In the body fluids of higher organisms the total calcium concentration is usually on the order of a few millimolar (see Table 3.1). In adult human serum, the concentration is observed to be, within narrow limits, 2.45 mM.

Table 3.1 -  $\text{Ca}^{2+}$  concentrations in fluids and tissues.<sup>6-9</sup>

Specimen	Units are mM if not otherwise stated
Sea water	10
Fresh water	0.02 - 2
Rain water	0.002 - 0.02
"Hard" tap water	1.5
"Good" beer	4
Adult human serum	$2.45 \pm 0.05$
Serum of other vertebrates	1.5 - 5
Nematode body fluids	6
Molluscan serum - marine	9 - 15
Molluscan serum - fresh water	1.5 - 7.8
Molluscan serum - land	3.3 - 12.3
Milk	70
Bone	0.8 - 1.0
Mitochondria from rat liver	$0.8 \pm 0.1$ mmol/kg
Endoplasmatic reticulum	8 - 10 mmol/kg
Cytoplasm of a resting mammalian cell	0.0001
Cytoplasm of <i>E. coli</i>	0.0001

### Essentials of $\text{Ca}^{2+}$ Chemistry

Since the  $\text{Ca}^{2+}$  ion accomplishes its biological tasks in an environment with 1 to 3 mM  $\text{Mg}^{2+}$ , it is of particular interest to compare the properties of these two ions in order to understand how a discrimination is made in biological systems. In addition, the coordination chemistry of  $\text{Ca}^{2+}$  is closely related to that of  $\text{Mg}^{2+}$  (as well as  $\text{Cd}^{2+}$ ), though there are several obvious differences.

First of all, the ionic radius of a  $\text{Ca}^{2+}$  ion with a given coordination number (CN) is always higher than that of an  $\text{Mg}^{2+}$  or  $\text{Cd}^{2+}$  ion with the same CN. At CN = 6, the ionic radii of  $\text{Ca}^{2+}$ ,  $\text{Cd}^{2+}$ , and  $\text{Mg}^{2+}$  are 1.00, 0.95, and 0.72 Å, respectively, whereas at CN = 8 they are 1.12, 1.10, and 0.89 Å, respectively.<sup>4</sup>

Ligand preferences of  $\text{Ca}^{2+}$  depend on the fact that it is a hard metal ion. Thus  $\text{Ca}^{2+}$  strongly prefers oxygen ligands over nitrogen or sulfur ligands;  $\text{Ca}^{2+}\cdots\text{N}$  bonds are about 0.25–0.3 Å longer than  $\text{Ca}^{2+}\cdots\text{O}$  bonds.<sup>5,6,10</sup> Large differences in coordination number and geometry have been observed for  $\text{Ca}^{2+}$  complexes. In a study of 170 x-ray structures of  $\text{Ca}^{2+}$  complexes involving carboxylate groups,<sup>11</sup> binding was found to be either (i) unidentate, in which the  $\text{Ca}^{2+}$  ion interacts with only one of the two carboxylate oxygens, (ii) bidentate, in which the  $\text{Ca}^{2+}$  ion is chelated by both carboxylate oxygens, or (iii) mixed ("α-mode") in which the  $\text{Ca}^{2+}$  ion is chelated by one of the carboxylate oxygens and another ligand attached to the α-carbon (see Figure 3.1). The  $\text{Ca}^{2+}$ -oxygen distances span a range from 2.30 to 2.50 Å, with the average distance being 2.38 Å in the unidentate and 2.53 Å in the bidentate mode, respectively.<sup>11</sup> Observed coordination numbers follow the order  $8 > 7 > 6 > 9$ . By contrast,  $\text{Mg}^{2+}$  nearly always occupies the center of an octahedron of oxygen atoms (CN = 6) at a fixed  $\text{Mg}^{2+}$ -oxygen distance of  $2.05 \pm 0.05$  Å.

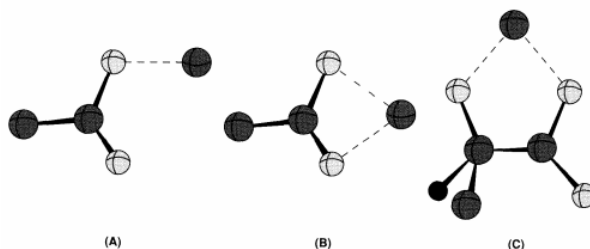


Figure 3.1 - The three commonly observed modes of calcium carboxylate ligation. (A) The unidentate mode, in which the calcium ion interacts with only one of the two carboxylate oxygens. (B) The bidentate mode, in which the calcium ion is chelated by both oxygen atoms. (C) The α-mode, in which the calcium ion is chelated by one carboxylate oxygen, and another ligand is attached to the α-carbon. Adapted from Reference II.

In Table 3.2, stability constants for the binding of  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  to various ligands are collected. We may note that selectivity of  $\text{Ca}^{2+}$  over  $\text{Mg}^{2+}$  is not very great for simple carboxylate ligands, but that it tends to increase for large multidentate ligands, such as EDTA and in particular EGTA. The  $\text{Ca}^{2+}$  sites in many intracellular proteins with "EF-hand" binding sites (see Section V. C) bind  $\text{Ca}^{2+}$  about  $10^4$  times more strongly than  $\text{Mg}^{2+}$ .

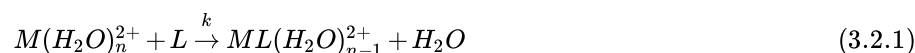
Table 3.2 -  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  (where available) stability constants (log K) for different organic and biochemical ligands. Most values are at ionic strength 0.1 and 25 °C.<sup>5,6,12-15</sup>

- a) EGTA: ethylenedis(oxyethylenenitrilo)tetraacetate  
b) EDTA: ethylenedinitrilotetraacetate

Ligand	$\text{Ca}^{2+}$	$\text{Mg}^{2+}$
Acetate	0.5	0.5
Lactate	1.1	0.9
Malonate	1.5	2.1
Aspartate	1.6	2.4
Citrate	3.5	3.4
Nitrilotriacetate	6.4	5.5
EGTA <sup>a</sup>	10.9	5.3
EDTA <sup>b</sup>	10.6	8.8
Glycine (Gly)	1.4	3.4
γ-Carboxyglutamic acid (Gla)	1.3	
Gly-Gly dipeptide	1.2	
Gla-Gla dipeptide	3.2	

Ligand	Ca <sup>2+</sup>	Mg <sup>2+</sup>
Macrobicyclic amino cryptate [2.2.2]	4.5	
Fluo-3	6.2	2.0
Fura-2	6.9	2.0
BAPTA	7.0	1.8
Quin-2	7.1	2.7
Phospholipase A2	3.6	
Thrombin fragment 1	3.7	3.0
Trypsinogen	3.8	
Chymotrypsinogen	3.9	
Chymotrypsin	4.1	
Calmodulin, N-terminal	4.5	3.3
Trypsin	4.6	
Calmodulin, C-terminal	5.3	
Protein kinase C	~7	
α-Lactalbumin	~7	
Rabbit skeletal muscle		
Troponin C, Ca <sup>2+</sup> /Mg <sup>2+</sup> sites	7.3	3.6
Carp parvalbumin	~8.5	4.2
Bovine calbindin D <sub>9K</sub>	8.8	~4.3

Another difference in ligand-binding properties of Mg<sup>2+</sup> and Ca<sup>2+</sup> can be seen by comparing the rates of substitution of water molecules in the inner hydration sphere by simple ligands, according to



This rate (log k, with k in s<sup>-1</sup>) has been determined to be 8.4 for Ca<sup>2+</sup> and 5.2 for Mg<sup>2+</sup>.<sup>16</sup>

The formation of biominerals is a complex phenomenon. In order to obtain a feeling for the conditions under which inorganic solid phases in biological systems are stable, it is of some interest to look at solubility products. Solubility products,  $K_{sp}^o$ , have a meaning only if the composition of the solid phase is specified. For a solid compound with the general composition (A)<sub>k</sub>(B)<sub>l</sub>(C)<sub>m</sub> the solubility product is defined as

$$K_{sp}^o = [A]^k [B]^l [C]^m \quad (3.1)$$

where [A], [B], etc., denote activities of the respective species, usually ionic, in equilibrium with the solid. Activities are concentrations multiplied by an activity coefficient,  $\gamma$ , nearly always less than unity. Activity coefficients for ions in real solutions can be estimated from Debye-Hückel theory<sup>17</sup> if the ionic strength of the solution is known. In human blood plasma, the ionic strength, I, is about 0.16, and the activity coefficient for Ca<sup>2+</sup> at 37 °C is 0.34. In many discussions it may be sufficient to equate concentrations with activities.

The solid phase involved is essentially assumed to be an infinitely large, defect- and impurity-free crystal with a well-defined structure. Microscopic crystals have higher solubilities than large crystals, a well-known phenomenon that leads to "aging" of precipitates, in which larger crystals grow at the expense of smaller ones.

Many anionic species appearing in the solubility products may also be involved in protonation equilibria in solution, such as those of phosphoric acid:  $\text{H}_2\text{PO}_4^- \rightleftharpoons \text{H}^+ + \text{HPO}_4^{2-}$ ;  $\text{HPO}_4^{2-} \rightleftharpoons \text{PO}_4^{3-} + \text{H}^+$ ; etc. When the prospects for the formation of a solid phase under certain solution conditions are investigated, the activity, or concentration, of the particular anionic species specified in the solubility product must be known, not only "total phosphate" or "total calcium," etc. The data in Table 3.3 show that, at  $\text{pH} > 5$ , the most stable (i.e., insoluble) solid calcium phosphate is hydroxyapatite.

Table 3.3 - Solubility products, at pH 5 and 25 °C, for solid calcium phosphates

Solid Phase	$-\log K_{\text{sp}}^0$	$-\log K_{\text{sp}}^0$ of corresponding $\text{Mg}^{2+}$ compound where applicable
$\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ (sulfate, "gypsum")	5.1	$< 1.0$
$\text{Ca}(\text{OH})_2$ (hydroxide)	5.3	10.7
$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ (hydrogen phosphate)	6.6	—
$\text{CaCO}_3$ (carbonate, "calcite," "aragonite")	8.5	7.5
$\text{CaC}_2\text{O}_4 \cdot \text{H}_2\text{O}$ (oxalate, "whewellite")	10.5	5.0
$\beta\text{-Ca}_3(\text{PO}_4)_2$ ( $\beta$ -phosphate)	29	—
$\text{Ca}_5(\text{PO}_4)_3\text{OH}$ (hydroxyapatite)	58	—

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