

1.4: Iron Biomineralization

Many structures formed by living organisms are minerals. Examples include apatite [$\text{Ca}_2(\text{OH})\text{PO}_4$] in bone and teeth, calcite or aragonite (CaCO_3) in the shells of marine organisms and in the otoconia (gravity device) of the mammalian ear, silica (SiO_2) in grasses and in the shells of small invertebrates such as radiolaria, and iron oxides, such as magnetite (Fe_3O_4) in birds and bacteria (navigational devices) and ferrihydrite $\text{FeO}(\text{OH})$ in ferritin of mammals, plants, and bacteria. Biomineralization is the formation of such minerals by the influence of organic macromolecules, e.g., proteins, carbohydrates, and lipids, on the precipitation of amorphous phases, on the initiation of nucleation, on the growth of crystalline phases, and on the volume of the inorganic material.

Iron oxides, as one of the best-studied classes of biominerals containing transition metals, provide good examples for discussion. One of the most remarkable recent characterizations of such processes is the continual deposition of single-crystal ferric oxide in the teeth of chiton.⁴⁸ Teeth of chiton form on what is essentially a continually moving belt, in which new teeth are being grown and moved forward to replace mature teeth that have been abraded. However, the study of the mechanisms of biomineralization in general is relatively recent; a great deal of the information currently available, whether about iron in ferritin or about calcium in bone, is somewhat descriptive.

Three different forms of biological iron oxides appear to have distinct relationships to the proteins, lipids, or carbohydrates associated with their formation and with the degree of crystallinity.⁴⁹ Magnetite, on the one hand, often forms almost perfect crystals inside lipid vesicles of magneto-bacteria.⁵⁰ Ferrihydrite, on the other hand, exists as large single crystals, or collections of small crystals, inside the protein coat of ferritin; however, iron oxides in some ferritins that have large amounts of phosphate are very disordered. Finally, goethite [$\alpha\text{-FeO}(\text{OH})$] and lepidocrocite [$\gamma\text{-FeO}(\text{OH})$] form as small single crystals in a complex matrix of carbohydrate and protein in the teeth of some shellfish (limpets and chitons); magnetite is also found in the lepidocrocite-containing teeth. The differences in the iron-oxide structures reflect differences in some or all of the following conditions during formation of the mineral: nature of co-precipitating ions, organic substrates or organic boundaries, surface defects, inhibitors, pH, and temperature. Magnetite can form in both lipid and protein/carbohydrate environments, and can sometimes be derived from amorphous or semicrystalline ferrihydrite-like material (ferritin). However, the precise relationship between the structure of the organic phase and that of the inorganic phase has yet to be discovered. When the goal of understanding how the shape and structure of biominerals is achieved, both intellectual satisfaction and practical commercial and medical information will be provided.

Synthetic iron complexes have provided models for two stages of ferritin iron storage and biomineralization:⁵¹⁻⁵⁹

1. the early stages, when small numbers of clustered iron atoms are bound to the ferritin protein coat, and
2. the final stages, where the bulk iron is a mineral with relatively few contacts to the protein coat. In addition, models have begun to be examined for the microenvironment inside the protein coat.⁵⁴

Among the models for the early or nucleation stage of iron-core formation are the binuclear $\text{Fe}(\text{III})$ complexes with [$\text{Fe}_2\text{O}(\text{O}_2\text{CR}_2)$]²⁺ cores;^{55,56} the three other $\text{Fe}(\text{III})$ ligands are N. The μ -oxo complexes, which are particularly accurate models for the binuclear iron centers in hemerythrin, purple acid phosphatases, and, possibly, ribonucleotide reductases, may also serve as models for ferritin, since an apparently transient $\text{Fe}(\text{II})\text{-O-Fe}(\text{III})$ complex was detected during the reconstitution of ferritin from protein coats and $\text{Fe}(\text{II})$. The facile exchange of (O_2CR) for (O_2PR) in the binuclear complex is particularly significant as a model for ferritin, because the structure of ferritin cores varies with the phosphate content. An asymmetric trinuclear (Fe_3O)⁷⁺ complex⁵⁷ and an (FeO)₁₁ complex (Figure 1.21) have been prepared; these appear to serve as models for later stages of core nucleation (or growth).⁵⁹

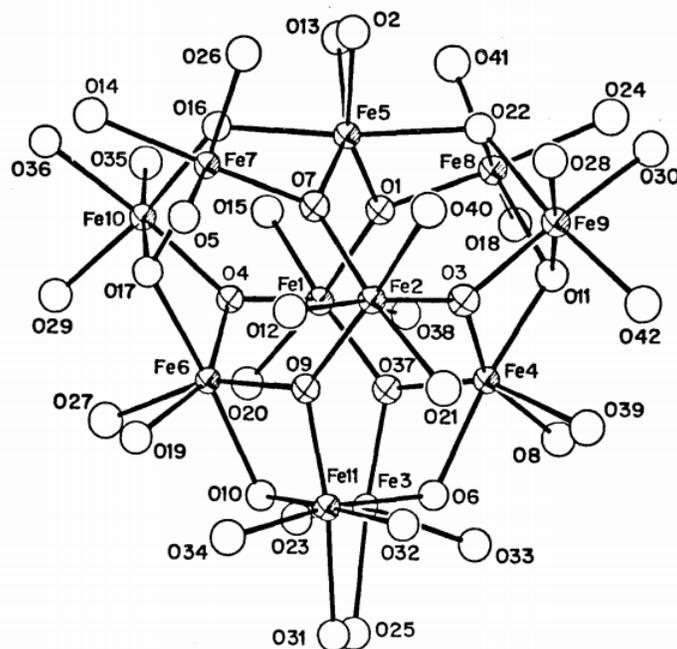


Figure 1.21 - The structure of a model for a possible intermediate in the formation of the ferritin iron core. The complex consists of 11 Fe(III) atoms with internal oxo-bridges and a coat of benzoate ligands; the Fe atoms define a twisted, pentacapped trigonal prism. See Reference 53.

Models for the full iron core of ferritin include ferrihydrite, which matches the ordered regions of ferritin cores that have little phosphate; however, the site vacancies in the lattice structure of ferrihydrite [FeO(OH)] appear to be more regular than in crystalline regions of ferritin cores. A polynuclear complex of iron and microbial dextran (α -1,4-D-glucose)_n has spectroscopic (Mössbauer, EXAFS) properties very similar to those of mammalian ferritin, presumably because the organic ligands are similar to those of the protein (-OH, -COOH). In contrast, a polynuclear complex of iron and mammalian chondroitin sulfate (α -1,4-[α -1,3-D-glucuronic acid-N-acetyl-D-galactosamine-4-sulfate]_n) contains two types of domains: one like mammalian ferritin [FeO(OH)] and one like hematite (α -Fe₂O₃), which was apparently nucleated by the sulfate, emphasizing the importance of anions in the structure of iron cores.⁶⁰ Finally, a model for iron cores high in phosphate, such as those from bacteria, is Fe-ATP (4:1), in which the phosphate is distributed throughout the polynuclear iron complex, providing an average of 1 or 2 of the 6 oxygen ligands for iron.⁶¹

The microenvironment inside the protein coat of ferritin has recently been modeled by encapsulating ferrous ion inside phosphatidylcholine vesicles and studying the oxidation of iron as the pH is raised. The efficacy of such a model is indicated by the observation of relatively stable mixtures of Fe(II)/Fe(III) inside the vesicles, as have also been observed in ferritin reconstituted experimentally from protein coats and ferrous ion.^{43,54}

Models for iron in ferritin must address both the features of traditional metalprotein interactions and the bulk properties of materials. Although such modeling may be more difficult than other types of bioinorganic modeling, the difficulties are balanced by the availability of vast amounts of information on Fe-protein interactions, corrosion, and mineralization. Furthermore, powerful tools such as x-ray absorption, Mössbauer and solid state NMR spectroscopy, scanning electron and proton microscopy, and transmission electron microscopy reduce the number of problems encountered in modeling the ferritin ion core.

Construction of models for biomineralization is clearly an extension of modeling for the bulk phase of iron in ferritin, since the major differences between the iron core of ferritin and that of other iron-biominerals are the size of the final structure, the generally higher degree of crystallinity, and, at this time, the more poorly defined organic phases. A model for magnetite formation has been provided by studying the coulometric reduction of half the Fe³⁺ atoms in the iron core of ferritin itself. Although the conditions for producing magnetite have yet to be discovered, the unexpected observation of retention of the Fe²⁺ by the protein coat has provided lessons for understanding the iron core of ferritin. Phosphatidyl choline vesicles encapsulating Fe²⁺ appear to serve as models for both ferritin and magnetite; only further investigation will allow us to understand the unique features that convert Fe²⁺ to [FeO(OH)], on the one hand, and Fe₃O₄, on the other.

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