Nanominerals

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From Metal Complexes to Nanominerals: The Formation of Inorganic Nanoparticles on Fibrils of Transferrin

*Matthias Epple**

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The controlled deposition of inorganic minerals (i.e. of solids) by biological systems is called biomineralization.[1–3] According to Lowenstam/Weiner[1] and Mann,[2] we distinguish between a biologically induced and a biologically controlled mineralization. In the first case, the crystallization of the inorganic solid from an oversaturated solution is induced by suitable nucleation (similar to a seed crystal). The local oversaturation is released by suitable functional groups, for example, on the surface of a cell or of a bacterium, whereupon the crystallization occurs in an unspecific manner.[4] In the case of biologically controlled mineralization, an organism actively influences the crystallization process, for example, by creating a local oversaturation in a confined compartment by using ion pumps. A classical example is the iron transport protein ferritin that carries about 4500 iron atoms as ferrihydrite ($5\,Fe_2O_3{\cdot}9\,H_2O$) inside its protein cage.[2] In the seminal papers by Mann et al. it was shown how the iron mineral in ferritin can be exchanged by other minerals, that is, how this biological "container" can be used as a nanoreactor for the deposition of iron oxide, manganese oxide hydroxide, iron sulfide, or cadmium sulfide.[5,6]

Transferrin is an iron transport protein with a molecular weight of about 80 kDa that occurs in human blood serum and in related form also in bacteria.[7] It binds two Fe^{III} ions in an octahedral configuration, in which two coordination sites are occupied by a bidentate carbonate anion. Ghosh et al. have deposited human transferrin (hTf) on surfaces and found a formation of fibrils of this protein. The holo-form was used, that is, the protein loaded with iron.[8] During the study of these fibrillar superstructures with various methods, they surprisingly detected a local accumulation of iron instead of a more or less continuous distribution. These iron accumulations turned out to consist of crystals of lepidocrocite, γ-FeO(OH), as shown by electron diffraction (Figure 1). Because no other iron source was present during the deposition process (which involved simply drying near ambient temperature), the originally individually complexed iron must have been mobilized to crystallize as iron oxide hydroxide.

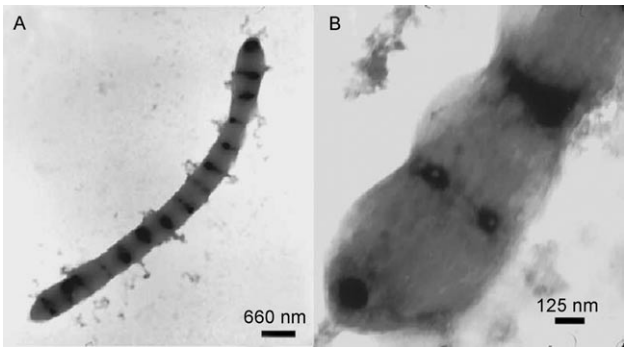

Figure 1. A fibril of holo-hTf (1 μM) deposited from a 1 mM $NaHCO_3$ solution at pH 7.22. A) The periodically localized mineral deposits of Fe(O)(OH) are visible as dark contrast in the TEM image. B) The magnified view shows that the deposits can occur as bands or in highly localized forms (taken from reference [8], Supporting Information).

In further experiments, the authors used the apo-form of transferrin, that is, the iron-free protein. This was remineralized with iron(III) nitrolotriacetate and showed the same structures of iron oxide hydroxide. In similar experiments, the authors succeeded in depositing manganese and bismuth compounds by adding manganese citrate and bismuth nitrilotriacetate, respectively, and sodium bicarbonate. Unfortunately, in these cases no crystallographic analysis by electron diffraction was carried out. Therefore, we can only speculate on the nature of the deposited solids. In the case of manganese, it is probably a mixture of manganese carbonate and manganese(III/IV) oxide/hydroxide (oxidation by oxygen from air).[9] In the case of bismuth, it is probably bismuth(III) oxide, possibly in a hydrated form (Figure 2).[10] The removal of the sugar moieties of the protein (deglycosylation) had no influence on the mineralization or the fibril formation, as shown by the authors in control experiments.

In conclusion, the authors report an interesting possibility for the structuring of metal oxides by this protein. However, the degree of loading is rather low (a few metal ions per protein unit, for example, 2.2 manganese atoms, which represents about 0.2 wt% of metal oxide relative to the protein mass). Similar structures are known for magnetite (Fe_3O_4) in magnetotactic bacteria, in which, however, the

[*] Prof. Dr. M. Epple
Inorganic Chemistry and
Center for Nanointegration Duisburg-Essen (CeNIDE)
University of Duisburg-Essen
Universitätsstrasse 5–7, 45117 Essen (Germany)
Fax: (+49) 201-183-2621
E-mail: matthias.epple@uni-due.de

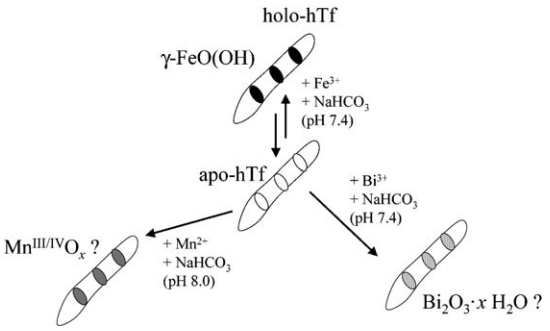

Figure 2. Schematic summary of the mineralization processes on transferrin fibrils. The holo-form of the protein (holo-hTf) shows periodic depositions of γ-Fe(O)OH, as identified by electron diffraction. If the iron is removed (apo-hTf), a deposition of other ions can occur, which leads either back to the iron-containing protein or to bismuth- or manganese-containing compounds, whose structure and composition were not investigated in detail.

mineralization of nanocrystals occurs under strict biological control.[11] In the case of transferrin, the mineralization occurs in a structurally directed manner (in distinct sections of the fibrils). So far, it is not known whether the observed periodicity is due to periodic structures in the fibril or to nucleation/oversaturation effects like in Liesegang's rings. The reason for the mobilization of iron out of its coordination sphere is also unknown. The authors speculate that the carbonate ligand is released as carbon dioxide upon drying, thereby weakening the binding of iron (including a conformational change of the whole protein). It was not reported whether the mineralization is reversible upon redissolution of the deposited fibrils.

The work by Ghosh et al. shows that "simple" biological systems are able to crystallize inorganic nanoparticles in defined form and in defined distance. In the field of geomicrobiology such results are of high interest for the better understanding of the interaction of bacteria with mineral deposits.[12] A fundamental medical interest comes from the fact that a number of neurodegenerative diseases (Parkinson's, Huntington's, and Alzheimer's) could be related to iron accumulations in the brain.[13,14] The herein reported "reorganization" of iron during drying or possibly as a general effect during fibril formation could well play a role in the development of these diseases.

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