Innovative Materials Processing Strategies: A Biomimetic Approach

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Many organisms construct structural ceramic (biomineral) composites from seemingly mundane materials; cell-mediated processes control both the nucleation and growth of mineral and the development of composite microarchitecture. Living systems fabricate biocomposites by: (i) confining biomineralization within specific subunit compartments; (ii) producing a specific mineral with defined crystal size and orientation; and (iii) packaging many incremental units together in a moving front process to form fully densified, macroscopic structures. By adapting biological principles, materials scientists are attempting to produce novel materials. To date, neither the elegance of the biomineral assembly mechanisms nor the intricate composite microarchitectures have been duplicated by nonbiological processing. However, substantial progress has been made in the understanding of how biomineralization occurs, and the first steps are now being taken to exploit the basic principles involved.

PLANTS AND ANIMALS HAVE EVOLVED A VAST DIVERSITY OF structures through strategies that often are very different from those used by the materials engineer. These naturally fabricated bioceramics are invariably composites and are assembled from readily available materials, usually in aqueous media, at ambient conditions, and to net shape. Bioceramics often exhibit a fine-scale microstructure with an absence of porosity or other flaws and with unusual crystal habits and morphologies. Materials like nacre (mother-of-pearl) from mollusk shells have an esthetic decoration, smooth surface finish, high strength, and remarkable fracture toughness. Bioceramics are normally produced very slowly and present a limited portfolio of compositions, dominated by calcium carbonate, calcium phosphate, silica, and iron oxide; nevertheless, more than 60 biominerals are now known and more are being discovered at a surprising rate (*1, 2*).

Most synthetic ceramics find application either as high-temperature structural materials (such as SiC and Si_3N_4 in engine applications or Al_2O_3 for refractory applications), as corrosion- or wear-resistant materials (such as traditional porcelain, cement, and high-performance Si_3N_4, Al_2O_3, or ZrO_2 bearings and guides), or as functional materials (such as electronic, optical, magnetic, and chemical sensors).

The need for improved materials processing is a constant refrain in materials science and engineering, and a small group of materials scientists have been analyzing natural materials and their methods of production, with the anticipation that novel biomimetic strategies may be identified (*3*). Biomimetic strategies for processing such materials would provide low-temperature, aqueous syntheses of oxides, sulfides, and other useful ceramics by adapting biological principles for controlling bioceramic production, microstructural design, and composite processing.

Bioceramic Fabrication

Mineralized tissues are bioceramic-biopolymer composites made by cell-mediated processes. Their production involves an exquisite level of control both of the spatial regulation of the nucleation and growth of mineral and of the development of microarchitecture during formation of these structures. These biofabrication processes are so complex at the molecular level that the details of the process are not completely known for even the simplest hard tissue.

Biomineralization is not a single process. Every organism has adapted certain strategic principles to optimize the specific function of its hard tissue to the specific environment in which it lives (Fig. 1). Analysis of a variety of mineralizing biosystems leads to the following general principles that have significant implications for both biology and materials science:

1) Biomineralization occurs within specific subunit compartments or microenvironments, which implies stimulation of crystal production at certain functional sites and inhibition or prevention of the process at all other sites;

2) A specific mineral is produced with a defined crystal size and orientation; or

3) Macroscopic growth is accomplished by packaging many incremental units together, which results in a unique composite and accommodates later stages of organism growth and repair.

In contrast to colloidal or solution processing techniques commonly used for production of ceramic powders or their precursors, biomineral production occurs under moderate conditions of super-

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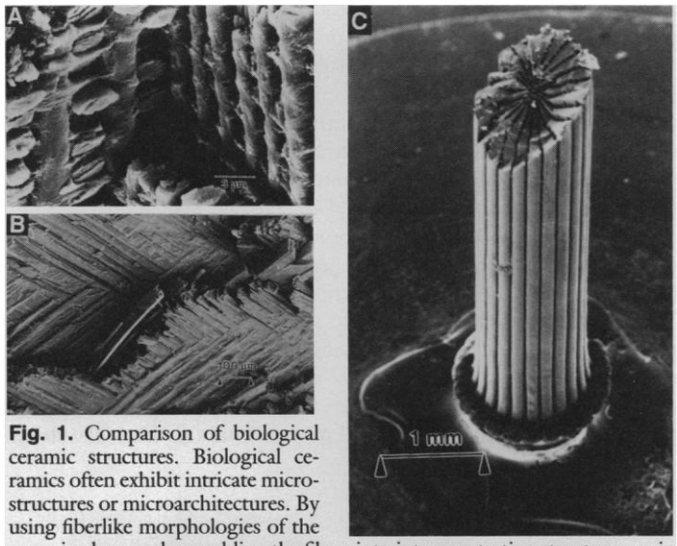

Fig. 1. Comparison of biological ceramic structures. Biological ceramics often exhibit intricate microstructures or microarchitectures. By using fiberlike morphologies of the ceramic phase and assembling the fibers into interpenetrating structures, as in rat tooth enamel (**A**), or into cross-ply laminated structures, as in crossed lamellar mollusk shell (**B**), these materials obtain useful mechanical properties, including high hardness and fracture resistance. The spines of echinoderms (**C**) represent a remarkable case in which fully dense load-bearing elements of the structure are separated by highly porous regions reminiscent of so-called "cellular materials." Nevertheless, the entire structure is essentially a single crystal of calcite.

saturation. Heterogeneous nucleation at the appropriate "functional sites" is initiated, whereas nucleation at other sites or in solution is inhibited. The effectiveness of the crystal growth and inhibition processes depends on the structure and chemistry of the interfaces between organic substrate, mineral, and medium. The highly specific control of morphology, location, orientation, and crystallographic phase all indicate the existence of an optimized or "engineered" substrate surface.

The key characteristics of these optimized interfaces are elusive at present because of the complexity of most biological model systems. However, investigations of representative systems, such as nacre (*4*), dentin (*5*), enamel (*6*), cartilage (7), bone (*8*), and avian eggshells (*9–11*), suggest a few basic principles of the biomineralization process. Box 1 summarizes the key sequence of events known to operate in biomineralization processes and highlights the importance of coupled dynamics, microenvironments, and orientation between the organic matrix (*12*) and the inorganic precursors.

The basic principles of the biomineralization paradigm are illustrated in Figs. 2 and 3 for two extreme cases, mollusk shells and avian eggshells, respectively. The rates at which these calcium carbonate structures are deposited differ dramatically—nacre production is very slow (a few grams per year) (*13*), whereas eggshell deposition is about 100 to 1000 times faster (5 grams per day) (*14*). These materials processing rates are achieved through contrasting assembly strategies that are instructive to the materials scientist. In the cases presented, when bioceramics like nacre are slowly synthesized (the most common case), lamellar composites are produced in which thin ceramic plates embedded in an organic matrix are stacked parallel to the surface of the structure. When bioceramic synthesis is rapid (eggshell), columnar structures composed of mineral and matrix grow perpendicular to the surface. Other structures often are assembled with more complex microarchitectures (Fig. 1). Understanding the inherent complexity of the molecular systems controlling the biological synthesis is the major challenge to materials scientists, who want to copy the structure, property, and performance (function) relations of these elegant structures.

Molecular Control of Biomineralization

In the biomineralized structures analyzed to date, the process of mineral deposition might be called matrix-regulated. In this process, acidic biopolymers, typically bound to a cell-secreted

Box 1. Strategic elements of biomineralization.

Biomineralization occurs within specific subunit compartments.

1) The dimensions of the compartment are established by the spatial distribution of a cell-derived biopolymer matrix, which (i) self-assembles into arrays of oriented fibers or sheets and (ii) incorporates intrinsic domains that control the crystal formation process.

2) Outside of the "active" compartment, mineralization is actively inhibited by a variety of molecular processes.

3) The processes of crystal nucleation and growth are separated temporally and regulated by complementary and redundant feedback control loops, which are crucial for countering the thermodynamic driving force leading to unrestricted mineralization from a supersaturated environment.

4) Nucleation of mineral within the matrix is actively controlled at the macromolecular level by specific initiation domains—genetically controlled initiation steps are required for normal mineral development.

5) Supersaturation of the compartment is effected by any of a potentially wide array of ion delivery vehicles or pumps, which currently are poorly understood. These may include one or more of the following: (i) microencapsulated ions (matrix vesicles); (ii) polyelectrolytes; (iii) phosphoproteins or other Ca^{2+}-binding proteins; (iv) phospholipids; and (v) enzyme catalysts to liberate nascent ions.

6) The density of the developing biomineral may be increased by removing organic templates or protecting groups or both—these regions may be backfilled with additional inorganic crystal at a later time.

A specific mineral is produced with defined crystal size and orientation.

1) Because of the matrix architecture and chemistry, a specific crystal habit is achieved and its growth is highly directional relative to the organic phase.

2) Crystal selectivity is often accomplished by tailored initiation sites that may include, alone or in combination: (i) periodic, negatively charged surfaces; (ii) bifunctional scaffolding molecules; and (iii) epitaxial elements containing a critical number of sites for nucleation.

3) Most of the crystals grow within the matrix structure.

4) Some matrix molecules may be incorporated within the crystal lattice.

5) In some cases, the mineral phase can be resorbed or remodeled, generally by cell-mediated processes different from the original mineralization steps.

Macroscopic growth is accomplished by packaging many incremental units together.

1) Matrix-secreting cells create a compartment (unit) or single layer forming one side of compartments.

2) Each compartment is processed to full density and shape.

3) The compartment secretion process is repeated for the next unit or layer of units, thereby producing a "moving front" of mineral deposition.

4) In most cases (for example, bone and nacre), biomineralization occurs very slowly, forming thin crystals or matrix lamellae perpendicular to the direction of growth. When rapid biomineralization occurs (avian eggshell), columnar crystals surrounded by matrix form parallel to the direction of growth.

organic surface, interact with ions to initiate the nucleation and growth of the inorganic phase. The mineral crystals grow within the organic phase, and their pattern of growth follows that of the matrix—the mineral adopts some particular crystal habit dictated by the organic matrix and assumes an orientation specified by the matrix architecture. The crystal morphology and size distribution are not necessarily those that would occur in spontaneous precipitation of the ions from supersaturated solutions.

Any biomineralized system might be idealized as a three-component system composed of: (i) an organic matrix, (ii) one or more "interactive proteins," and (iii) a system for transporting ions to the growing mineral phase. It is characteristic of most biological systems that the assembly of the matrix and the interaction of the various soluble components are controlled by highly specific protein catalysts (enzymes). Examples of these molecular constituents are provided below and illustrated in Fig. 4 for bone development, which is possibly the most complex case.

The organic matrix is the crucial structural component that either spatially or temporally defines the space that is to be mineralized and, by the way it is organized, the space available to the mineral grains. In bone, for example, the primary regions of mineralization are discrete—the space within collagen fibrils—thereby limiting the possible primary growth of the mineral crystals and forcing the crystals to be discrete and discontinuous. In nacre and tooth enamel, on the other hand, the organic matrix forms the boundaries of large compartments within which the mineral phase is continuous, thereby forming accretions of elongated crystal aggregates.

Certain interactive proteins appear to be most important in the initiation of biomineralization and seem to be developmentally regulated to perform two critical functions for mineral formation (*15*). These proteins must bind to some specific region of the structural matrix and, at the same time, provide the capacity to sequester large amounts of one of the mineral-phase constituents. In the usual case, it appears that the interactive protein is anionic, rich in specific arrays of carboxyl or phosphate groups, and may present a β-sheet–like struc-

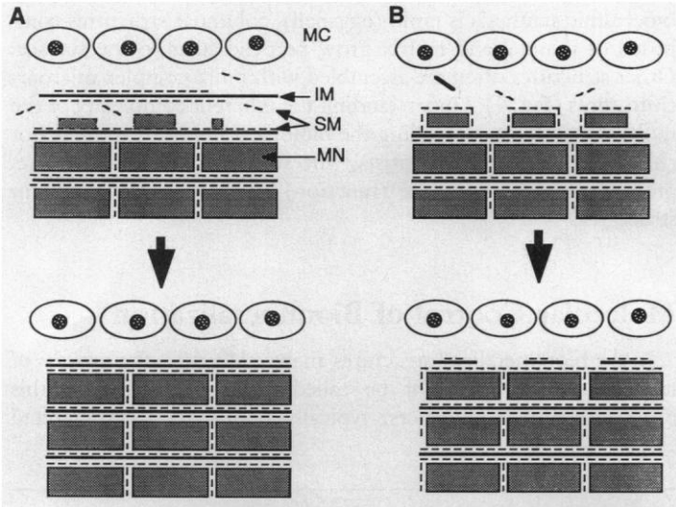

Fig. 2. Laminated biological ceramics: nacreous shell formation. Possible mechanisms of formation of nacreous shell, following Wada (*66*) (**A**) and Erben (*67*) (**B**), are illustrated. Mantle cells (MC) secrete insoluble (IM) and soluble (SM) matrix components into the extrapallial space, as well as ions necessary for mineral (MN) formation. In (A), a compartment or envelope is defined by the formation of new matrix above the previous shell layer, after which nucleation and growth of mineral commences in the compartment. Growth continues normal to the shell until impingement upon the new matrix layer, and it continues laterally until terminated by impinging with other mineral grains. In (B), new grains of mineral nucleate on the most recent layer, with soluble matrix components adsorbed on the crystal defining an expanding envelope. Growth is terminated upon impingement of neighboring crystals, and then secreted insoluble and soluble matrix components coalesce to form the next matrix layer. (**C**) A scanning electron micrograph of a cross section of nacreous shell in the vicinity of a propagating crack. [Reprinted from (*68*) with permission © Royal Society]

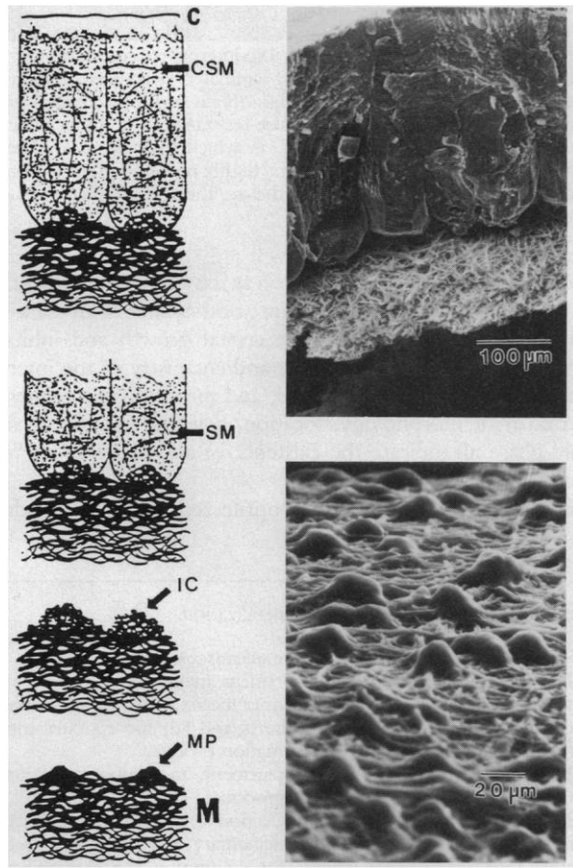

Fig. 3. Diagram of an eggshell cross section illustrating the main steps in eggshell formation. The oviduct is a cellular tube with five main regions: (i) the infundibulum, which receives the ovum; (ii) the magnum, which produces egg white; (iii) the isthmus, which forms the shell membranes; (iv) the uterus, in which deposition of calcium carbonate takes place; and (v) the vagina, from which the egg is extruded. When the egg reaches the uterus, proteinaceous mammillary protrusions (MP) are sparsely built on the fibrillar shell membranes (M). Randomly oriented spherulites of aragonite (IC) are then nucleated on the mammillary knobs, which are shown on the micrograph at lower right. Together with the secretion of shell matrix (SM), the more oriented calcite crystals start building the crystalline columns of the shell proper, shown with the shell membrane on the micrograph at upper right. The shell matrix deposition continues to the cessation of the shell matrix (CSM) and is related to the development of a crystallographic texture. The glycoproteinaceous cuticle (C) finishes the shell formation.

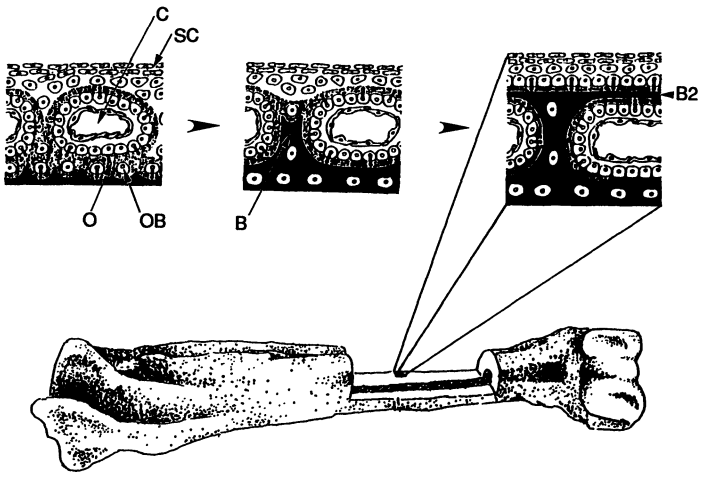

Fig. 4. Sequence of progressive bone development in the developing chick tibia. Osteoblasts (OB), oriented with their backs toward the capillary vasculature (C), secrete osteoid (O) away from the vasculature, causing the formation of a bony strut (B), and eventually forming a second layer of bone (B2). The stacked cell layer (SC), which provides osteoprogenitor cells for the process, continues to expand in the direction of bone growth.

ture (*16*) that, in the case of apatite, matches the *c*-axis of the apatite crystallites, thereby orienting the crystalline long axis relative to the fibrillar matrix. The two known macromolecules in this category are bone sialoprotein (*17*) in bone and phosphophoryn (*18*) in dentin. Phosphophoryn, for example, is known to have a high capacity for binding calcium ions and a strong affinity for collagen monomers.

Other interactive proteins in bone, such as osteopontin (*19*) and osteocalcin (*20*), have cell attachment properties or chemically mediated cell attraction properties or both that are specific for osteoblasts (bone-producing cells) and osteoclasts (bone-digesting cells), which suggest that they play a role in bone turnover (*21*).

The final part of the mineralizing system delivers the mineral-phase ions to sustain crystal growth. These ion transport systems are only poorly understood. In less complex systems, it may be that the ions accumulate in the region of the mineralization front by simple diffusion. However, considering the exquisite control of all other aspects of the formation of mineralized tissues such as bone, it is likely that the movement of mineral ions is also a regulated, energy-requiring process.

If, as suspected, phosphorylated proteins are particularly important in the process of crystal induction, then it may also be important to identify the roles of the various kinase and phosphatase enzymes present in the extracellular matrix that may represent an integral feature of the ion transport system (or systems).

A separate, also not completely understood, group of molecular complexes are the matrix vesicles (*22*), which appear as small, membrane-bounded aqueous containers within the extracellular matrix. These complexes may function as part of the ion transport system by either enzymatically or physically regulating the formation of microcrystalline nuclei.

As illustrated in Figs. 2 and 3, mineralized biostructures less complex than bone, such as mollusk shells and avian eggshells (which experience only limited turnover), may involve less sophisticated control mechanisms. In these cases, soluble matrix biopolymers may play a more significant role in spatial or temporal definition of the crystal compartment, and passive ion transport systems may be involved.

Biomimetic Ceramic Engineering

Current investigations involve many of the important features of the biomineralization process discussed above, as well as studies of novel processing strategies.

The biopolymer matrix: Lessons from cement. In some (perhaps surprising) features, hydraulic cements such as calcium sulfate, calcium silicate, and calcium aluminate resemble biological hard tissues. Cements are made from available raw materials (often from dead mollusks in the case of Portland cement), harden in moist environments at room temperature to net shape, and sometimes contain low concentrations of active species (typically 40 μM for silicon in a siliceous cement). Cement grains are approximately the same size (1 to 50 μm) as cells, so the scales of microstructure in both cements and biominerals are similar. Further, cement grains act as ion pumps and force ions into solution where reprecipitation occurs as cementitious hydrated phases. The hydrates may form large, well-developed crystals at modest supersaturations, as in calcium sulfate, or fine colloidal species at high supersaturation, as in calcium aluminate.

It has long been recognized that polymer additions could change the hardening reactions, microstructure, and properties of cement products in the same way that extracellular biopolymers contribute to the properties of bone and nacre. For example, an ordinary mixture of premixed cement and water is prone to freeze damage when stored under freezing conditions. Strength after thawing is much reduced because of flaws introduced by the growth of large ice crystals. The addition of a water-soluble polymer to the cement mix allows freezing to occur without damage by inhibiting the growth of large ice crystals (*23*). After thawing, the cement again becomes fluid and reacts to give the same mechanical properties as unfrozen controls.

Addition of polymers to cements also improves their rheological properties. For example, when 2 to 10% by volume of polyvinyl alcohol–acetate or of hydroxypropylmethyl cellulose is added to calcium silicate or aluminate cements, the water content can be substantially reduced, the cement mixes can be readily extruded, and the material can be rolled and laminated (*24*). By adding 3% by weight of polyvinyl alcohol to a calcium aluminate cement mix with 10% water by weight, porosity can be reduced to below 1%—comparable to biominerals—to produce a very smooth hard surface (*25*). Perhaps more significant is the absence of macropores in cements that incorporate water-soluble polymers. Addition of the polymer permits fabrication of the cement into thin sheets with surprisingly high bend strengths, from 100 to 300 MPa, comparable to nacre (*26*); these structures do not contain the millimeter-scale flaws found in conventional cement products, which lead to low fracture strengths.

The examples above illustrate one of the most important principles engineered into biomineralized tissues—the dramatic effect of the polymer addition on the resulting ceramic composite. Even with the addition of relatively unoptimized polymers and without the development of microarchitecture, cement properties are considerably enhanced.

Crystal nucleation control. Attempts to create synthetic surfaces that would initiate mineral nucleation and growth have embraced a variety of chemical approaches, including supramolecular templates and templates made from inorganic polymers, organic polymers, or biomolecules.

Monolayer films, self-assembling monolayer films, and self-assembling amphiphilic structures in aqueous solution form periodic

organic interfaces, or supramolecular templates, suitable for influencing mineral deposition. For example, Langmuir film techniques have been used to prepare amphiphilic monolayers with well-defined and variable charge densities, molecular packing states, and microstructural features (*27*). Variation of these parameters have provided some control over nucleation site densities, crystalline morphologies, stereochemistry, and sizes of particles grown at the film-solution interface.

Self-assembling monolayer films anchored at solid surfaces and that present a range of functional groups remote from the anchoring sites have been used to vary the interfacial chemistry as a means of immobilizing metal ion–organic multilayers (*28*) (Fig. 5A).

Precipitation of a wide range of metal-oxide particles within bilayer vesicles tends to stabilize the particles sterically, but control of the resulting crystal habit and polydispersity is difficult to achieve in this format (*29*). Microemulsions and reversed micelles formed by surfactant-water mixtures have also been used to form inorganic catalysts with precisely controlled sizes and shapes (Fig. 5B), including "quantum" particles and nanoparticles (*30*).

Cast films of bilayer vesicles formed by either double-chain or azobenzene-ammonium amphiphiles have recently been used as a matrix for producing lamellar glasses with individual lamellae thicknesses on the submicrometer scale (*31*) (Fig. 5C).

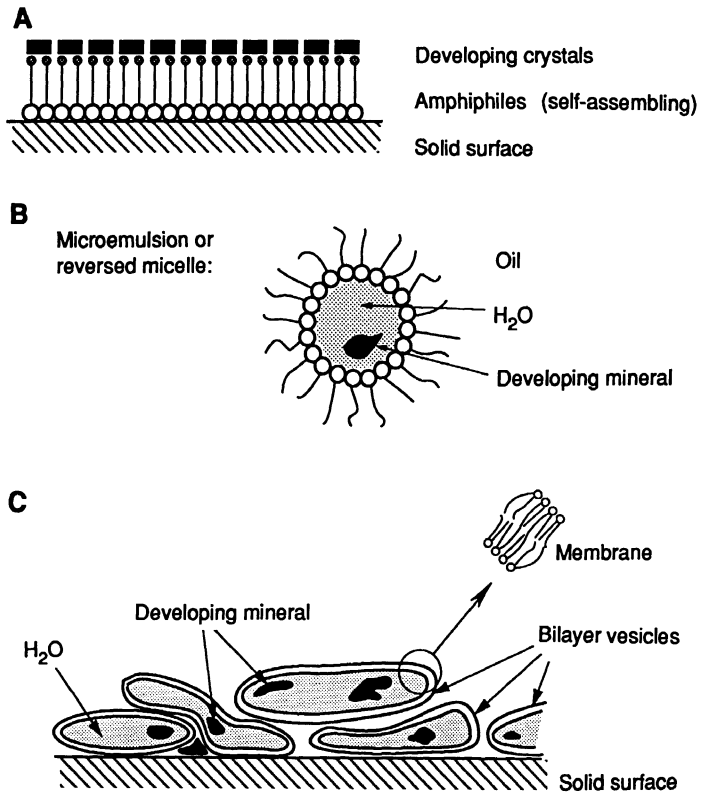

Fig. 5. Supramolecular templates can control ceramic growth. (**A**) Self-assembled monolayers formed by covalent attachment of bifunctional surfactants to inorganic or organic substrates (*69*) offer the possibility of constructing ordered surfaces with charged polar groups, which may be used as substrates for growth of ceramic thin films. (**B**) Crystallization of CdSe in AOT-water-heptane microemulsions or iron oxyhydroxides in AOT-reversed micelles offers precise control of crystal size and shape (spherical to needle-like), depending on the nature of the organic microphase (*30*). (**C**) Lamellar glasses were grown by introducing the sol-gel precursor, $CH_3Si(OCH_3)_3$, between the organic lamellae (*31*). Interlayer diffusion of ammonia then induced hydrolysis of the silicon reagent with subsequent polymerization of the resulting inorganic monomer.

The advantage of the supramolecular approach to controlling crystallization is the ease of modification of the interface properties to achieve initiation of crystal growth. However, low film stability, lack of control over local ordering, and the inability to direct crystal growth in three dimensions may cause some limitations.

Rigid inorganic polymer networks, such as zeolites, also offer templating capacity for mineralization (*32*). Advantages of these materials include their mechanical and thermal stability and their availability at low cost. In addition, because there is some size and shape selectivity with respect to host cavity dimensions, it may be possible to induce different crystal habits or morphologies or both through the use of varying zeolite types and blocking agents. Possible disadvantages of these materials for crystal growth are the limited range of compositions available within the host lattice and the inherent difficulty of retrieving deposited mineral from the three-dimensional matrix for further processing.

Synthetic organic polymers offer a greater range of physicochemical properties than inorganic media, and their availability, stability, ease of modification, and processability into a wide variety of shapes make them well suited for mineral deposition substrates. Three procedures for CdS crystallization illustrate these advantages.

1) Stabilized CdS colloids with average diameters of 38 Å (aqueous solutions) or 28 Å (acetonitrile) were produced with styrene–maleic anhydride copolymers (*33*). Electron microscopy revealed a low-contrast copolymer zone surrounding the CdS crystallites, suggesting that the polymer binds Cd^{2+} and serves as a template during precipitation.

2) CdS was synthesized from dip-coated polyethylene oxide/$CdCl_2$ films cured with a "hydrophobized" sulfide source [$S(Si(CH_3)_3)$] (*34*). Amorphous CdS was formed that was evenly distributed throughout the film, and micrometer-sized cubic CdS crystals were reconstructed after heat treatment for 1 hour under an inert atmosphere.

3) CdS particles with sizes in the 40 to 60 Å range were grown when Cd-exchanged Nafion films were exposed to hydrogen sulfide gas (*35*).

Perhaps the greatest selectivity for directing crystal growth could be provided by purified biomolecules (or their synthetic analogs) that are known to display this property in vivo. For example, calcium phosphate crystals have been grown in purified collagen matrices by both cell-mediated and acellular processes (*36*), and bivalve organic matrix proteins have been used to mediate the nucleation and growth of calcium carbonate (*37*). Eggshell membranes have also been used to test cellular or acellular mineralization processes (*10*). These systems serve as useful models for understanding biological mineralization events, but their selectivity may be so great that they may not be useful for growing other crystals with these templates. To our knowledge, no studies have been conducted to modify the ion- or crystal-binding sites of these biopolymers. It is likely that use of synthetic analogs would help in the identification of peptide sequences that are important for regulation of biomineralization.

Control of crystal growth. It is well accepted that the interaction of a soluble organic component with growing bioceramic crystals strongly influences both the kinetics and morphology of crystal growth (*38*). Most bioceramics contain components that are rendered soluble upon demineralization, which are excellent candidates for mineral growth regulators. The "soluble matrix" is typically highly anionic. In the case of mollusk shell, the soluble matrix contains sulfated or phosphorylated (glyco-) proteins that are also rich in aspartic or glutamic acid, whereas polyanionic keratan sulfate

and γ-carboxyglutamate–rich proteins have been found in eggshell matrix (*39*). Polyanions are known to inhibit in vitro crystal growth of phosphate and carbonate minerals by adsorbing onto the surfaces of growing crystals and controlling crystal habit through the selectivity of this adsorption. It appears that the secondary structure of the interacting organic molecule is important, as indicated by the identification of β-sheet structure in adsorbed soluble matrix proteins (*40*). If the primary and secondary structures of matrix proteins are tailored for adsorption to specific crystal faces, or if the secondary structure upon adsorption favors certain sites, then the kinetics and morphology of crystal growth can be modulated by genetically controlled protein synthesis. In an in vitro system in which ordered synthetic co- and terpolymers modeled after molluscan matrix primary structure were used, the number of active growth sites on growing calcite crystal was highly correlated to the primary protein structure (*41, 42*).

Although most effects of organic matrices on crystal growth are viewed as exclusively surface phenomena, evidence for intracrystalline matrix has long been cited (*38*), especially in reference to mollusk shells or carbonate grown in vitro. Recently it has been established that crystals grown in vitro have different cleavage faces, and thus different physical properties, depending on the type of soluble matrix protein incorporated within (*43*). Further, it appears that the incorporation of proteins can be accomplished in vitro with little disruption of the crystal lattice.

Macroscopic processing. Conventional ceramic processing can be quite varied, but in general the body is first formed approximately to net shape while the material is in a formable state and then processed into a different state to fix the geometry (*44*). Molten silicate glasses are cast to shape and then cooled to harden. Other bulk ceramics are formed as aqueous slurries or slips and then hardened by drying and firing. Similarly, when sol-gel chemistry is used to make ceramic materials, either in powder or "near net-shape" forms, the gel is often a precursor that requires further treatment (drying, densification, or crystallization) to produce the desired material.

In contrast to conventional ceramic processing, in biomineralized tissues large dense parts are formed in a "moving front" in which incremental matrix-defined units are sequentially mineralized. This processing approach facilitates the production of fully dense materials to net shape and permits an unequaled level of control of microstructural organization. In this sense, many of the distinctive features of bioceramics—their high volume fractions of mineral, their high toughness, strength, and fracture resistance, and their anisotropic properties—appear to result from this approach to fabricating ceramic materials.

One fundamental problem confronting the materials scientist is controlling the crystallization of the desired mineral within a polymer-defined space at high maximum crystal density. Without some form of facilitated ion transport, it seems unlikely that a large ceramic body can be produced by any process that depends on diffusion of mineral precursors into the bulk polymer matrix—the final loading of mineral is generally too low because of resistance to diffusion produced by the growing crystal phase itself.

Perhaps a more realistic approach to composite ceramic processing is to cast successive layers of polymer plus mineral precursor at high concentration and then to initiate the precipitation of each layer by cyclic manipulation of an external field (thermal, electrical, chemical, photo, and so forth). In this process, mineral density would be established by the limit of precursor solubility in the polymer matrix—that is, the ultimate ceramic density would not depend upon diffusion of one or more of the reactants into the matrix compartment.

This processing strategy is well established in the field of laminate composites, which developed quite independently of current interest in biomimetic processing, where the preparation of "highly filled" materials (greater than 50% ceramic) has recently been actively investigated. Examples of this class of "biologically inspired" materials include:

1) Silicon carbide–graphite laminates produced by laminating rolled layers of SiC mixed with polyvinyl alcohol and water, coating the layers with graphite, and sintering at elevated temperature (*45*).

2) Calcium aluminate–polymer composites produced by laminating rolled layers of calcium aluminate mixed with polyvinyl alcohol and water and then separating the layers with a thin film of fibrous polymer (*46*).

3) Boron carbide–aluminum composites produced by metal infiltration of laminate preforms. In this case, boron carbide tapes (100 to 200 μm thick) were cast and further processed by a combination of stacking, partial sintering, infiltration, and densification steps. Similar approaches are currently being used to fabricate B_4C-polymer composites (*47, 48*).

In these examples, enhanced fracture resistance resulted from crack deflection or arrest in the hardened laminate at the weak interlamellar surfaces or both effects.

Other processing schemes imitate the incremental character of bioceramic production but use established solution synthesis methods such as sol-gel processing. In the broadest sense, the formation of thin films [for example, by cyclic dipping of substrates into stable solutions of metal alkoxides and firing (*49*) or by the base-catalyzed hydrolysis of metal alkoxides to form amorphous oxide thin films (*50*)] can be considered to be "biologically inspired."

The microstructure of avian eggshell is morphologically similar to that of many columnar coatings, which can be produced in a variety of ceramic systems, including plasma sputtering of zinc oxide films on silicon (*51*), physical vapor deposition of zirconia (*52*) or anodic deposition of alumina on aluminum alloys (*53*), or electrodeposition of manganese dioxide from acidic aqueous solutions (*54*). Electrodeposition of MnO_2 can produce macroscopic, electrically conducting ceramic materials in only a few hours. Adaptation of this technology to include an organic component analogous to the shell matrix might enhance the mechanical properties of these materials.

Current investigations of molecular template surfaces as substrates for ceramic deposition may lead to truly biomimetic thin film and multilayer devices. Sequentially deposited metallic multilayers and compound semiconductor multilayers often exhibit remarkable mechanical, electronic, and optical properties, and are already technologically important nanocomposites (*55*). Biomimetic production of ceramic-polymer multilayers would require not only a deeper understanding of inorganic crystal growth on molecular templates but also of epitaxial deposition and polymerization of such templates on inorganic surfaces. An inverse approach to multilayer formation makes use of an inorganic template (such as synthetic smectite minerals—layered aluminosilicate structures) for monomer intercalation followed by solid-state polymerization (*56*).

Approaches to making three-dimensional ceramic parts in sequential layers are also being developed in the new field of technology now referred to as "rapid prototyping" or "free-form manufacturing." For example, a device for "three-dimensional printing" (Fig. 6) has been described for the rapid production, directly from computer models, of three-dimensional parts to serve as ceramic shells and cores for investment casting (*57*). Another process makes use of selective laser sintering of ceramic powders (*58*). These processes demonstrate the growing sophisti-

cation of technology for making net-shape ceramic parts by an incremental, "moving front" process. At present, ceramic-polymer composites cannot be prepared by any of the available rapid prototyping devices but the potential for the manufacture of intricate composite structures by these techniques is clear.

Biologically assisted processing. A variation on the biomimetic theme might be realized by using "hybrid" strategies that couple the distinctive properties of biologically derived materials with more conventional ceramic processing techniques. Opportunities for such systems might be found in the use of cell-derived particles to serve as preformed nucleation seeds and of cell-derived biopolymers to control crystal growth processes.

Although well known in solution precipitation (*59*), seeding has received little attention for ceramic transformation control (*60*). However, substantial control over reaction temperatures and rates and over microstructure and phase development can be anticipated if seeding strategies could be successfully implemented. The properties of ceramics are very sensitive to the distribution of flaw sizes within the final part. Smaller and more narrowly distributed grain sizes (perhaps down to about 100 nm or smaller) can be anticipated to increase material strength and improve product reliability.

The major limitation of the seeding approach is the need for extremely reproducible and fine particles (for example, much smaller than the final mineral grain size) to use for the direct control of subsequent crystal growth stages, or perhaps for use without expanding the crystal size. This is one case where cell-produced particles may become strategically important.

More than 60 distinct minerals are known to be produced by living cells—as illustrated by those produced by unicellular organisms (*1*). For example, magnetotactic bacteria such as *Aquaspirillum magnetotacticum*, first discovered in 1979 (*61*), produce magnetic minerals (iron oxides and sulfides) that are believed to align anaerobic bacteria along the earth's magnetic field, thereby directing the cell down into the anaerobic zone. These bacteria might prove to be a source of particles that could be used directly in the production of iron oxide magnetic coatings, widely used in motors and loudspeakers, and as coatings for magnetic tape.

In the yeasts *Candida glabrata* and *Schizosaccaromyces pombe*, CdS is deposited in intracellular particles, apparently as a detoxification mechanism in Cd-containing solutions (*62*). Small CdS particles displaying nonlinear optical properties are being investigated as semiconductor "quantum dots" for optical switching devices.

The iron oxide and CdS particles produced in these organisms have sizes in the 10- to 100-nm range, where it is very difficult to prepare synthetic particles without extensive aggregation. In addition, the iron oxide particles are each surrounded by a membrane, which, if the membrane survives, would greatly ease their dispersion after removal from the cells.

Cell-derived polymers are being investigated for their ability to control a variety of commercially important ceramic processes. The polysaccharides from *Azotobacter vinelandii* are being compared to alginates and synthetic polyelectrolytes for use as dispersants in ceramics processing (*63*). Similarly, lipid envelopes such as those surrounding the magnetite particles in *Aquaspirillum* may also find applications as particle stabilizers (*64*).

Genetic manipulation of single-celled organisms is now widely practiced, which presents the opportunity for the production of naturally occurring biopolymers in commercial quantities. In a broader sense, the potential exists for designing biopolymers to control specific crystal growth processes, synthesizing appropriate gene fragments to code for these molecules, and then producing the polymers by in vitro fermentation techniques (*65*).

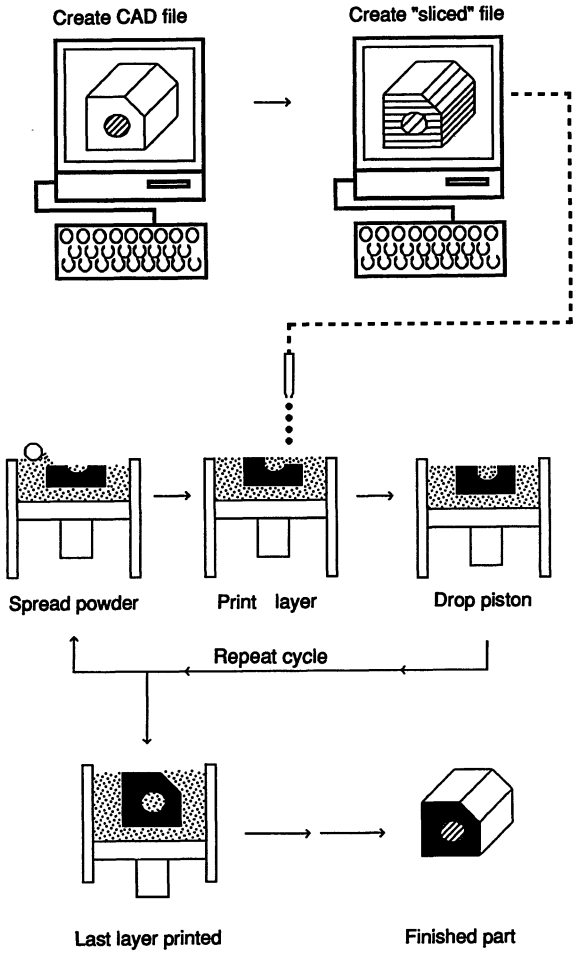

Fig. 6. Schematic description of a three-dimensional printing process. The process (*56*) begins by spreading a thin layer of powder (for example, alumina, with nominal particle size of 45 μm) over the surface of a powder bed. A computer model of the final part is numerically "sliced" into thin layers, and then the description for each slice is used to drive a device similar to an ink jet printer, which selectively applies a binder material (such as colloidal silica), thereby joining the particles to be included in that specific layer. This layer-by-layer process is repeated until the part is completed. The formed part is then heat-treated and unbound (no binder) powder is removed to reveal the final part.

But Is It Biomimetic?

If the basic strategies by which living organisms produce mineralized tissues are understood, and the operative molecular mechanisms are appreciated, how then might these principles be exploited for new ceramic processes? If biomimetic is interpreted as the reproduction of the entire sequence of biomineralization steps, then it is clear that current fabrication technology is inadequate for this purpose. In any event, the materials that can be produced by these processes are not of sufficient commercial potential to merit this exercise.

A less literal use of the term biomimetic should be applied, at least when ceramic processing is contemplated. If a materials scientist can be inspired by a biological prototype to investigate novel processing schemes incorporating one of the fundamental principles from the

bioceramic paradigm (Box 1), then a biomimetic result has been realized.

Perhaps the most fundamental principle to be gleaned from an analysis of bioceramics is that living systems construct functional ceramic-polymer composite structures from seemingly mundane materials. Tough, durable materials are generally produced by slow, carefully engineered, repetitive processing. In these biological systems, the control of composite microstructure—arising from wonderfully complex, genetically controlled, cell-mediated procedures operating at the molecular level—appears to exert greater influence on ceramic functional properties than the chemistry of the starting materials involved. We believe that research should be focused on new techniques for controlling microarchitecture of ceramic composites—as opposed to the development of new materials—so that the portfolio of important ceramic materials can be expanded to a significant extent. The processing strategies used by biological systems should be mimicked to fabricate composite materials that could provide physical, electrical, and mechanical properties not currently available by conventional technologies.

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3. The idea for this article originated at a workshop designed to explore possible new strategies for producing ceramic-polymer composites biomimetically, taking inspiration from the diversity of mineralized hard tissue in the animal kingdom. Biological systems fabricate complex multicomponent, multiphase materials using assembly and processing strategies that are unique. The use of these or derivative strategies for the fabrication of synthetic materials is referred to as mimetic because they mimic the basic biological processing schemes but are practiced outside of the natural biological context. [This workshop was held 25 and 26 January 1991 in San Diego, CA; it was supported by the Office of Basic Energy Sciences of the U.S. Department of Energy, and organized by A. I. Caplan and A. H. Heuer of Case Western Reserve University in Cleveland, OH.] This workshop brought together a group of ceramists, polymer scientists, cell biologists, and microbiologists to discuss these issues. It is difficult to imagine a more interdisciplinary group than the participants in this workshop. The existence of quite different logics and language jargons in each group was very apparent. Sufficient goodwill was exercised, however, to allow these cultural problems to be overcome and some concensus generated.
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70. A.H.H. and A.I.C. thank the Department of Energy, through Battelle's Pacific Northwest Laboratories, and the National Institutes of Health for providing major funding for aspects of the studies reported here.