Inorganic Nanostructures

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Peptide-Based Methods for the Preparation of Nanostructured Inorganic Materials

*Chun-Long Chen and Nathaniel L. Rosi**

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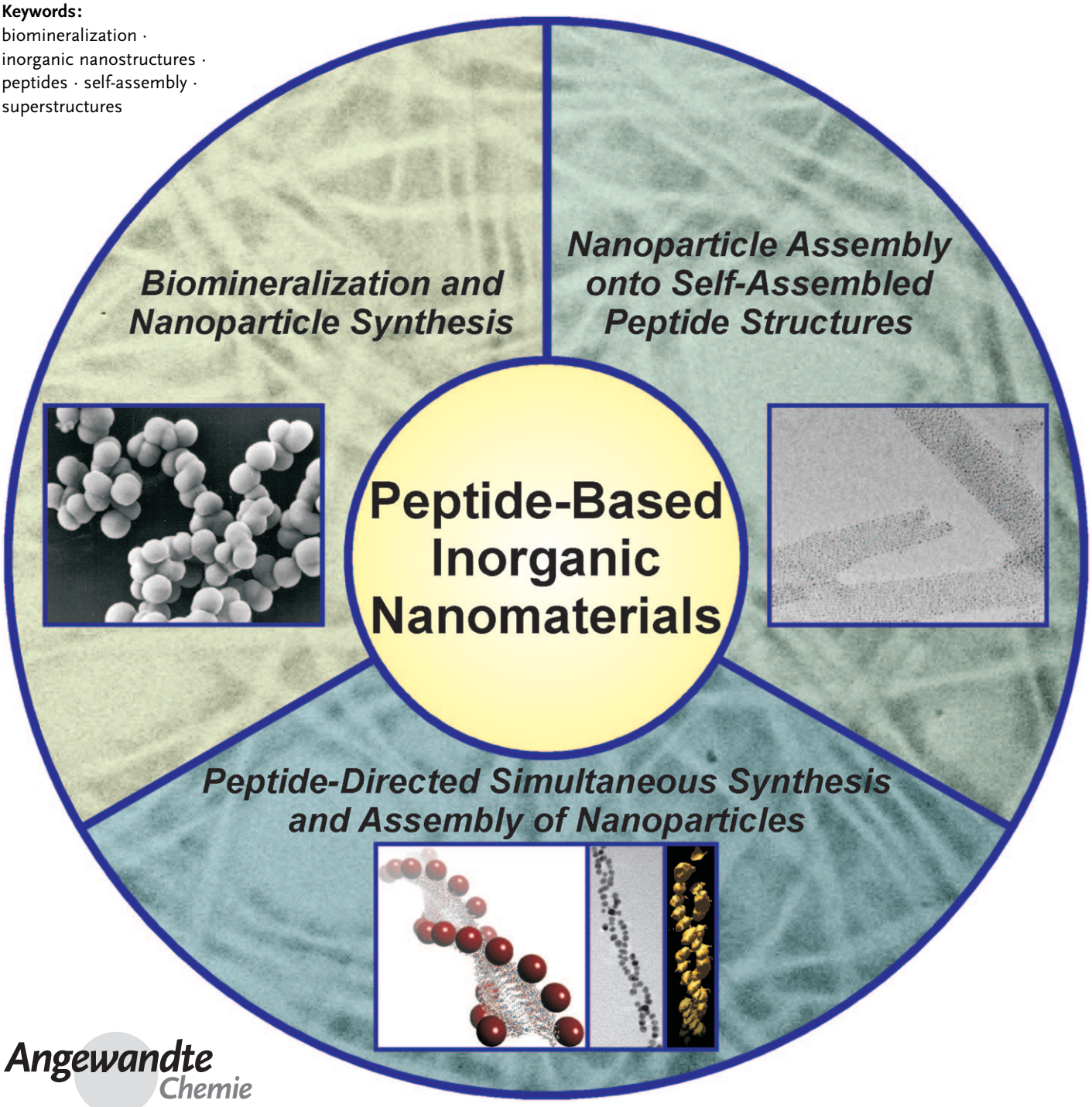


With their unique sequence-specific self-assembly and their substrate recognition properties, peptides play critical roles in controlling the biomineralization of inorganic nanostructures in natural systems and in directing the assembly of important soft matter. These attributes render them particularly useful molecules for the fabrication of new materials. Researchers from many scientific disciplines now use peptides to direct the synthesis of new inorganic nanostructures and the assembly of soft biomaterials. In this Review we describe the developments in this field and focus on the versatility of peptides and their ability to direct the composition and structure of new inorganic materials.

From the Contents

1. Introduction

Nanostructures are materials that have at least one dimension within the 1–100 nm length scale. The last 20 years have witnessed an influx of research endeavors aimed at developing synthetic methods for the preparation of new nanostructures. The excitement in this area is fueled by the unique optical,[1–3] electrical,[4–6] and catalytic[7] properties that result when at least one dimension of the material is reduced to the nanometer length scale. These physical properties are determined by the size,[8] shape,[8–10] and composition[8,11] of the nanostructure. Ensemble properties emerge when individual nanostructures aggregate together into hierarchical structures.[12–14] The individual and ensemble properties of nanostructures, collectively, make them promising candidates as building blocks for materials with enhanced functional capabilities.[12,14]

Inorganic nanostructured materials, in particular, have received much attention. For example, semiconductor nanoparticles,[15–18] metallic nanoparticles,[8,11,18,19] and metal oxide nanoparticles[17,18] have been studied and evaluated as components of next-generation electronic devices,[20] photovoltaic and fuel cells,[21,22] bio-imaging tools,[15] drug-delivery vehicles,[23] biodiagnostic sensors,[24,25] and data-storage platforms.[26] The compositions, structures, and dimensions of these materials can be tuned to optimize their performances.[8,14,19,27–29]

Inorganic nanostructured materials are typically prepared by using either of the following complementary strategies: the "top-down" approach[30,31] or the "bottom-up" approach.[28,32,33] The first approach is essentially a "whittling" method, whereby a bulk material is reduced down to nanoscale objects. This approach offers precise control over the size and shape; however, the point-by-point or layer-by-layer processing makes this approach time-consuming. In contrast, the "bottom-up" approach involves constructing nanostructures one atom or molecular unit at a time by chemical synthesis and one unit at a time through self-assembly. This approach is simple and flexible, and the building blocks can be designed precisely to facilitate the assembly of nanostructures with tailorable features.[28,32]

Self-assembly processes are critical for the "bottom-up" construction of nanostructures. Self-assembly enables the fabrication of three-dimensional structures on the nano- and micrometer scale,[27,28,32,34–36] and are commonplace in biology. For example, organisms use "bottom-up" strategies to assemble a wide variety of exquisitely complex, nano-, micro-, and macroscale functional materials,[37–43] and many of these materials are often used by the organisms for routine functions (for example, mechanical support[43] or navigation[39]). Biomineralization processes are of particular interest to biologists and biotechnologists for studying hard tissue growth and regeneration, as well as to materials scientists for developing biomimetic approaches to design and synthesize well-defined functional materials under mild, environmentally benign conditions. Inspired by natural systems, many biological molecules (for example, nucleic acids,[44] carbohydrates,[45] proteins,[46,47] and peptides[47,48]) have been studied and exploited for these purposes. In this Review, we focus exclusively on the roles peptides play as directing agents for the synthesis, growth, and assembly of nanostructured inorganic materials.

Why Peptides?

Peptides are polymeric biomolecules composed of amino acids. There are 20 naturally occurring amino acids, each with its own unique size and functionality. Peptides undergo distinctive sequence-specific self-assembly[34,48,49] and have recognition properties,[37,50] thus making them important structural and signaling molecules in biological systems. It is these same attributes, namely the self-assembly and recognition capacities of peptides, which makes them useful as building blocks for directing the growth and assembly of inorganic nanostructures.

Self-Assembly of Peptides. Depending on the conformation and stereochemical configuration of their constituent amino acids, peptides exhibit different secondary structures, such as α helices and β sheets. The β-sheet structure has been

[*] Dr. C.-L. Chen, Prof. N. L. Rosi
Department of Chemistry, The University of Pittsburgh
Pittsburgh, PA 15260 (USA)
E-mail: nrosi@pitt.edu
Homepage: http://www.pitt.edu/~nrosi/home.htm

studied intensively not only because of its important role in diseases related to peptide fibrillization,[48,51–53] but also because of its application in the design and assembly of well-defined functional materials.[35,48,49,51,54,55] For example, when β-sheet-forming peptides are combined with synthetic polymers, the resultant peptide–polymer hybrids assemble into well-organized structures.[49]

Various molecules can be attached to peptides to affect their self-assembly properties and direct their assembly into particular desired structures. Such modified peptides are often termed "peptide conjugates". Peptide conjugates can self-assemble into various well-defined nanostructures, such as micelles, vesicles, nanotubes, and nanoribbons, through ionic and hydrophobic/hydrophilic interactions, including π···π stacking and hydrogen bonding. The inclusion of specific peptide sequences with unique biological properties has resulted in a large number of biocompatible biomaterials being self-assembled by using peptide conjugates as building blocks.[48,54,56–59] These biomaterials exhibit a variety of promising applications (for example, drug delivery,[60] regenerative medicine,[56,57,61,62] hemostatic agents[63]).

Recognition Capabilities of Peptides. In addition to their interesting self-assembly properties, peptides also have highly specific recognition capabilities. For example, short peptide sequences derived from extracellular matrix (ECM) proteins can interact with cell receptors.[56] Many of these peptides are used in biological applications for surface modification of biomimetic materials. One of the most commonly used peptides for cell recognition is RGD, which is naturally found in a number of proteins including fibronectin (FN) and laminin (LN). Many materials (for example, quantum dots,[64] carbon nanotubes,[65,66] metal oxides[67,68] polymers[50]) have been modified with RGD peptides for various biological applications.

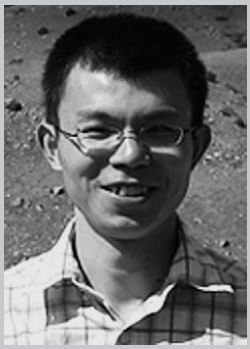
To stay within the context of this Review, however, we will focus on the ability of specific peptides to recognize, bind, and promote the nucleation and growth of specific inorganic materials. In natural systems, proteins often serve as scaffolds for controlling the nucleation, growth, and structural attributes of highly functional inorganic materials.[46,47] Compared to proteins, peptides are less complex, yet they can still encode unique recognition properties. Adapting molecular biology methods to materials science now allows for the combinatorial selection of peptides with high affinities for specific inorganic materials. By using such methods, a large number of mineral-specific inorganic binding peptides have been isolated, and many have found practical applications in biotechnology and materials science.[37,47,69] These peptides can selectively bind, interact with, and direct the assembly of inorganic solids, as well as regulate the nucleation of inorganic nanoparticles. They have played significant roles in the fabrication of various functional inorganic nanostructured materials. Some of these peptides are listed in Table 1. Compared to other biomolecules, peptides are excellent scaffolds for the nucleation and growth of inorganic materials because they can be easily processed and prepared through genetic engineering or by chemical synthesis. In addition, they can be easily modified by incorporation of unnatural amino acids or by functionalization with various chemical side chains, and they are robust, biocompatible, and biodegradable. The inorganic binding and recognition capabilities of peptides will be described in detail in Sections 2 and 3.

As peptides exhibit both unique self-assembly[34,35,48,54,93] and recognition properties,[37,47,50,94] a large number of peptide-based "bottom-up" methods have been developed for their application in the growth and assembly of inorganic nanostructures. This Review focuses primarily on some of the more seminal and recent advances in the use of peptides in the design and synthesis of inorganic nanostructured materials.

2. Peptide-Based biomineralization

2.1. Naturally Occurring Peptides

Living organisms produce nanostructured materials in an energy-efficient, high-yielding, and highly reproducible manner under mild aqueous synthetic conditions.[37–43,95] These materials often have properties that surpass those of analogous synthetically manufactured materials with similar phase compositions. For example, the formation of many natural inorganic materials, such as bone,[43,57] dental structures,[43] shells,[96,97] silica skeletons,[95] and well-ordered magnetic nanoparticle chains within magnetotactic bacteria,[39,98,99] is controlled and performed, under mild conditions. The organisms use interactions between the peptide or protein and inorganic species, whereby the biomolecules



Chun-Long Chen was born in 1979 in Jiangxi, China, and earned his PhD from Sun Yat-Sen University in 2005 with Prof. Cheng-Yong Su and Prof. Bei-Sheng Kang on the assembly and structural dynamics of metallasupramolecular species. During this time he also worked with Prof. Hans-Conrad zur Loye at the University of South Carolina. He then carried out postdoctoral research with Prof. Alicia M. Beatty at Mississippi State University (2006) and then with Prof. Nathaniel L. Rosi at the University of Pittsburgh. He is currently working at the Lawrence Berkeley National Laboratory with Dr. Ronald N. Zuckermann and Dr. James J. De Yoreo.

Nathaniel L. Rosi was born in Grayling, Michigan in 1976. He earned a BA in chemistry from Grinnell College in 1999 and a PhD in chemistry from the University of Michigan in 2003. After postdoctoral research at Northwestern University (2003–2006), he began his independent career at the University of Pittsburgh. His research group focuses on developing synthetic methods for directing the assembly of biomolecules, metal clusters, and nanoparticles into hierarchical materials, particularly with a view to environmental and biomedical applications.

Table 1: Examples of peptides known to direct the mineralization of inorganic nanomaterials.

Peptide sequences	Inorganic materials	Salt	Ref.
AYSSGAPPMPPF	Ag nanoparticles	$AgNO_3$	[70]
	Au nanoparticles	$HAuCl_4$	[71, 72]
NPSSLFRYLPSD	Ag nanoparticles	$AgNO_3$	[70, 73]
AHHAHHAAD	Au nanoparticles	$ClAuPMe_3$	[74]
HGGGHGHGGGHG	Cu nanoparticles	$CuCl_2$	[75]
	Ni nanoparticles	$NiCl_2$	[76]
HYPTLPLGSSTY	CoPt nanoparticles	$(NH_4)_2PtCl_4$ + Co-$(CH_3COO)_2$	[77]
HNKHLPSTQPLA	FePt nanoparticles	$FeCl_2$ and H_2PtCl_6	[78]
GDVHHHGRHGAEHADI	CdS nanoparticles	$CdCl_2$ + Na_2S	[79]
VCATCEQIADSQHRSHRQMV	ZnS nanoparticles	zinc 2,9,16,23-tetrakis(phenylthio)-29*H*,31*H*-phtanlocyanine + Na_2S	[80]
NNPMHQN	ZnS nanoparticles	$ZnCl_2$ + Na_2S	[81]
SLKMPHWPHLLP TGHQSPGAYAAH	GeO_2 nanoparticles	tetramethoxygermanium	[47]
SSKKSGSYSGSKGSKRRIL	TiO_2 nanoparticles	titanium bis(ammonium lactato) dihydroxide	[82]
	titanium phosphate spheres	tetramethoxysilane	[83]
	silica nanostructures	triisopropylsilane	[84–86]
EAHVMHKVAPRPGGGSC	ZnO nanostructure	$Zn(OH)_2$	[87]
HQPANDPSWYTG NTISGLRYAPHM	$BaTiO_3$ nanoparticles	$Ba(CH_3COO)_2$ + $K_2[TiO(C_2O_4)_2]$	[88]
PDFDFDFDFDFDP	calcium phosphate	$CaCl_2$ + K_2HPO_4	[89]
FDFDFDFD	$CaCO_3$	$CaCl_2$ + $(NH_4)_2CO_3$	[90]
AAPNSPWYAYEY SWSPAFFMQNMP YESIRIGVAPSQ DSYSLKSQLPRQ	$CaMoO_4$ microparticles (powellite)	calcium acetate + ammonium paramolybdate	[91]
GLRSKSKKFRRPDIQYPDATDEDITSHM	hydroxyapatite (HA)	KH_2PO_4 + $CaCl_2$	[92]

collect and transport raw materials and assemble them consistently and uniformly into ordered composites. These natural systems provide inspiration to chemists and materials scientists for the development of new bio-inspired synthetic approaches to generate inorganic nanostructured materials in a clean and energy-efficient fashion.[38,47,97,100,101] Researchers now use peptides and proteins to control the formation of inorganic nanostructures.[47] The isolation of naturally occurring biomineralization peptides and the study of their structures and functions ex vivo have led to a better understanding of some inorganic mineralization processes. In many cases, these peptides are used to synthesize new inorganic materials.

The calcification-associated peptide (CAP-1) isolated from the exoskeleton of a crayfish by Inoue et al. has the ability to bind calcium and inhibits the precipitation of calcium carbonate.[102] CAP-1 is involved in the formation of the exoskeleton (Figure 1).[103] By using this peptide, Kato and coworkers succeeded in preparing uniaxially oriented thin-film crystals of $CaCO_3$ on chitin matrices (Figure 2).[103] They further examined how varying the structure of the peptide affects the mineralization, and reported the structure–function correlation of this peptide and its related derivatives. They found that the C-terminal acidic region effected $CaCO_3$ crystallization more than did the N-terminal acidic region and that the 17th phosphoserine residue also effected the mineralization. The resultant $CaCO_3$ crystals exhibited various morphologies depending on the different chemical structures of these peptides.[104]

Several biomolecules isolated from biosilicification organisms can promote the biomineralization of silica, such as silicateins isolated from marine sponges,[105–107] and silaffins[108,109] and silacidins[110] isolated from marine diatoms. For example, Kröger et al. demonstrated that polycationic peptides (called silaffins) isolated from diatom cell walls could be used to generate silica nanostructures.[111] They showed that networks of silica nanospheres (Figure 3) formed within seconds when polycationic silaffins were added to solutions of silicic acid. The amount of precipitated silica was

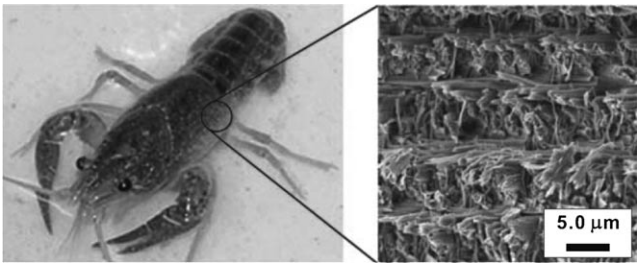


Figure 1. Crayfish and SEM image of the fractured surface of its exoskeleton.[103]

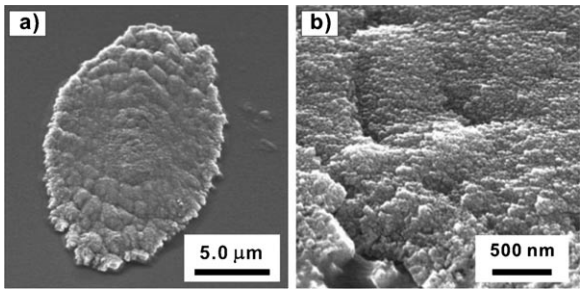


Figure 2. a) SEM image of $CaCO_3$ crystals grown on a chitin matrix in the presence of CAP-1 (3.0×10^{-3} wt%). b) Magnified image of the crystal surface in (a).[103]

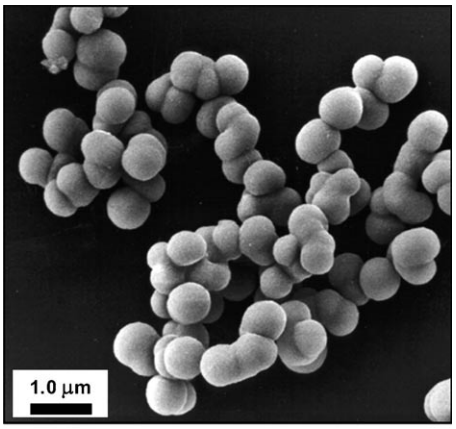


Figure 3. SEM image of silica precipitated in the presence of silaffin.[111] Reproduced with permission from the authors.

proportional to the amount of added silaffin. When silaffin-1A was used, the spherical silica particles within the networks had diameters ranging from 500 to 700 nm.

The R5 peptide is a 19 amino acid sequence derived from the silaffin-1A protein of *Cylindrotheca fusiformis*. This peptide promotes and regulates the formation of silica, titanium phosphate, and titania under mild aqueous conditions.[82–84] For example, Naik et al demonstrated that R5 catalyzes the formation of several silica nanomorphologies, with structures ranging from common spheres to highly organized and complex fibrils (Figure 4). By careful manipulation of the environment and the use of mechanical force, they were able to direct the formation of silica to produce a desired morphology.[84] By using a similar method, but instead adding titanium(IV) bis(ammonium lactate) dihydroxide to the solution of R5 peptide in phosphate buffer, Cole et al. found that the R5 peptide effectively promotes the rapid precipitation of titanium phosphate into both spherical and fused spherical morphologies with diameters ranging from 700 nm to 10.6 μm (Figure 5a).[83] Sewell and Wright demonstrated that R5 can also catalyze the formation of TiO_2 nanoparticles at room temperature (Figure 5b). In this case, the amount of precipitated TiO_2 increased linearly with added peptide until the peptide concentration reached approximately 6 mg mL^{-1}.[82] To explore the role of the R5 peptide in the mineralization of TiO_2, Sewell and Wright further examined a series of related peptides; the authors suggested

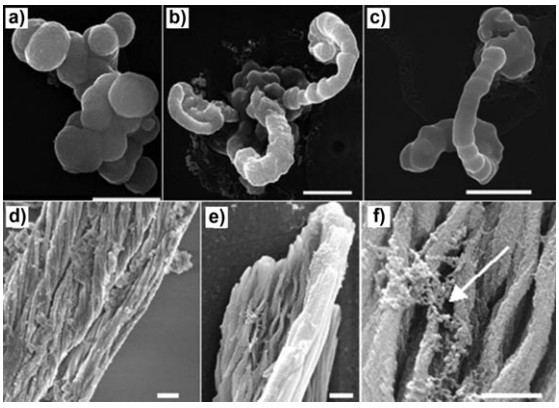


Figure 4. SEM images of biosilica structures formed using the R5 peptide: a) spherical particles; b,c) arch-shaped particles; d,e) fibrils; f) irregular agglomerates of silica spheres (arrow). Scale bar 1 μm.[84] Reproduced with permission from the Royal Society of Chemistry, copyright 2003.

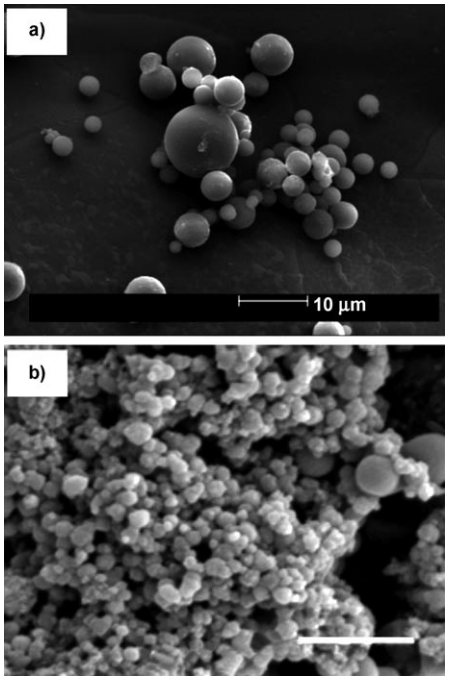


Figure 5. SEM images of a) titanium phosphate spheres[83] and b) TiO_2 nanoparticles (scale bar 1.2 μm)[82] formed using the R5 peptide. Reproduced with permission from the American Chemical Society, copyright 2005.

that self-assembled peptide structures were vital for the production of TiO_2 and, specifically, that the RRIL motif was important for the self-assembly of R5.

GLRSKSKKFRRPDIQYPDATDEDITSHM, a peptide identified and isolated from the protein osteopontin (OPN), specifically binds collagen. Researchers found that the complex of collagen and this peptide promotes the mineralization of hydroxyapatite (HA) both in vitro and in vivo. The collagen surface alone could not induce noticeable nucleation of apatite, while GLRSKSKKFRRPDIQYPDATDE-

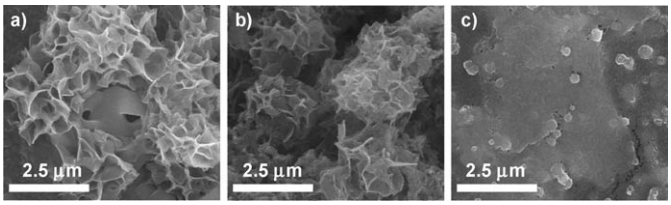


Figure 6. SEM images of hydroxyapatite nucleation a) with peptide + collagen; b) with peptide; c) with collagen without peptide.[92] Reproduced with permission from Elsevier, copyright 2007.

DITSHM alone could initiate the biomineralization of apatite (Figure 6).[92]

The peptide pelovaterin, extracted from eggshells of *pelodiscus sinensis* (Chinese soft-shelled turtle), is a glycine-rich peptide with 42 amino acid residues and 3 disulfide bonds. This peptide directs the formation of a metastable vaterite phase. As shown in Figure 7, $CaCO_3$ crystals with different morphologies were grown in the presence of pelovaterin. When the peptide concentration was 5–100 $\mu g\,mL^{-1}$, floret-shaped crystals of vaterite formed, while spherical particles (25–30 μm) of vaterite were observed exclusively at higher peptide concentrations ($\geq 0.5\ mg\,mL^{-1}$). The diameter of the sphere decreased significantly and some spheres fused together to form larger aggregates when the peptide concentration was further increased.[112]

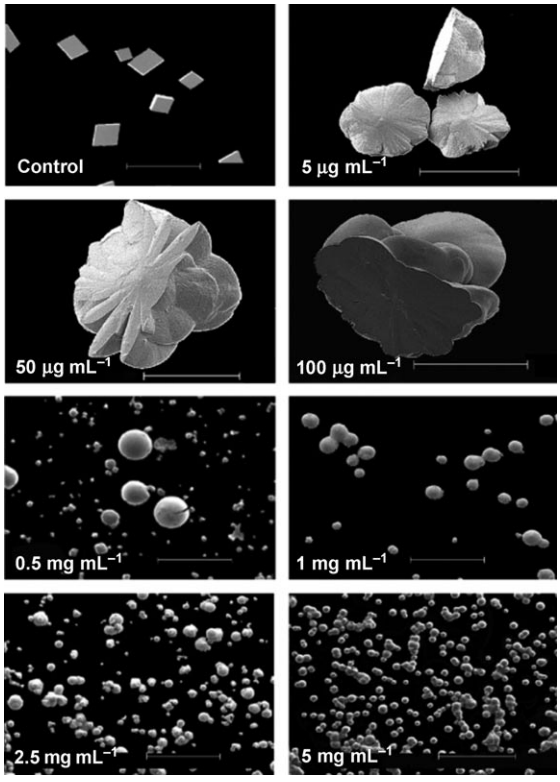


Figure 7. Representative SEM images of $CaCO_3$ crystals grown at various concentrations of the peptide pelovaterin.[112] The peptide concentration is indicated on the images. The scale bar in each case corresponds to 50 μm. Reproduced with permission from the American Chemical Society, copyright 2005.

In some cases, natural peptides can be isolated and used to promote the nucleation of unnatural inorganic materials. Wright and co-workers showed that the histidine-rich epitope (HRE) AHHAHHAAD from the histidine-rich protein II of *Plasmodium falciparum* mediates the aqueous synthesis of a variety of metal sulfide, metal oxide, and metal clusters (with the metal in the 0 oxidation state).[113,114] Their synthetic process consists of two steps: formation of metal–HRE complexes followed by nucleation of the nanocrystals. For example, the histidine-rich peptide AHHAHHAAD (HRE) efficiently mineralizes gold ions. Matsui and co-workers showed that nanotubular structures coated with HRE peptides can serve as templates to mineralize gold ions to yield monodisperse Au nanoparticles on the nanotube surfaces (Figure 8).[74]

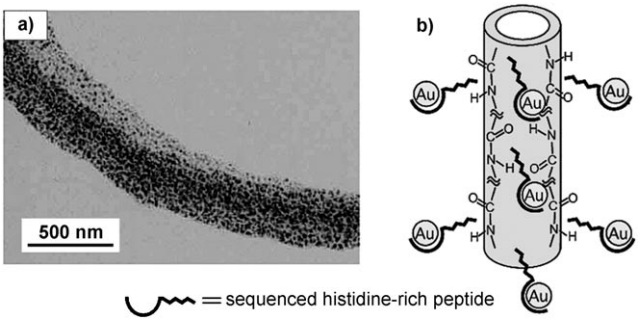


Figure 8. a) TEM (transmission electron microscopy) image of monodisperse gold nanoparticles on a nanotube coated with histidine-rich peptides; b) gold nanoparticles nucleate at the histidine sites on the nanotubes.[74] Reproduced with permission from the American Chemical Society, copyright 2002.

2.2. Genetically Engineered Peptides

The number and diversity of naturally occurring biomineralization peptides is limited. Such peptides evolved over the course of millions of years, and they are generally specific for controlling the nucleation of inorganic materials that have plenty of precursors in the environment (for example, calcium carbonate,[40,42,96] silica,[41,107] iron oxide,[39,99] etc.). There are many other useful inorganic compositions that do not exist in biological systems (for example, platinum, gold, silver, cadmium sulfide, etc.) and which, therefore, may not have a corresponding naturally occurring peptide or protein to mediate their nucleation under mild conditions. Clearly, it would be useful to have peptides which could direct the nucleation and formation of unnatural inorganic materials.

Combinatorial library approaches (for example, phage display and cell-surface display) have successfully been employed to evolve new peptides that exhibit exceptional sequence-specific affinities for unnatural inorganic materials.[37] As shown in Figure 9, these methods involve insertion of randomized nucleic acid sequences into certain genes within phage genomes or bacterial plasmids. These sequences code for the expression of particular peptide sequences on the surface of the phage or bacterium. Millions of different phages or cells, each with different peptides on their surfaces, are exposed to specific inorganic materials (for example, gold

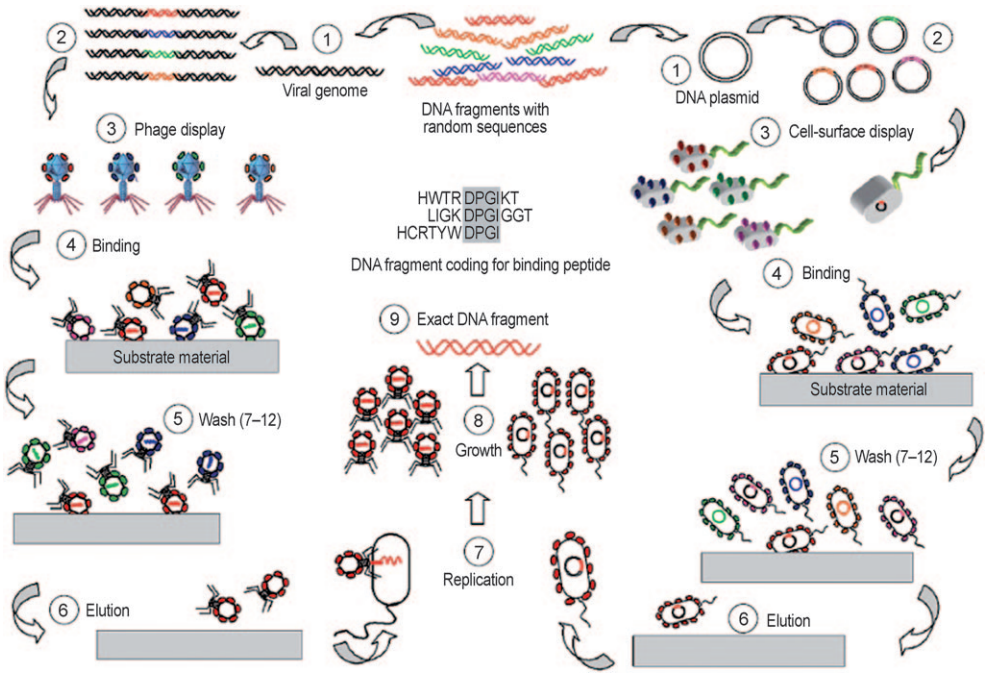


Figure 9. Phage display and cell-surface display.[37] Reproduced with permission from the Nature Publishing Group, copyright 2003.

or platinum). Stringency washes are used to remove phages or cells from the inorganic surface. Those phages or cells lacking surface peptides that strongly interact with the inorganic material are removed, while those with peptides that strongly interact with the inorganic material are collected. For phage display, the eluted phages are multiplied in a bacterial host. Similarly, the eluted cells are cultured for cell-surface display. Those phages or cells are then reexposed to the inorganic material. This cycle is repeated with successively more stringent washes until only phages or cells having surface peptides with very high affinities to the specific inorganic material remain. The peptide sequences are determined by decoding the viral or bacterial genome.

These methods have afforded numerous new peptides that exhibit high binding affinities for various inorganic materials, including ZnO,[87,115] Cu_2O,[115] GeO_2,[116] SiO_2,[117,118] TiO_2,[82,117,119] Cr_2O_3,[120] Fe_2O_3,[121] PbO_2,[120] CoO,[120] MnO_2,[120] $CaCO_3$,[122] $BaTiO_3$,[88] $CaMoO_4$,[91] hydroxyapatite (HA),[123] GaAs,[69] ZnS,[81,124] CdS,[79,124] FePt,[78] Ag,[70] Au,[125–127] Pt,[37] Pd,[37] Co,[77] and Ti.[128] Many of these peptides exhibit the unique capability of mediating the formation of specific inorganic nanoparticles at room temperature. Examples of the development and roles of these peptides in the synthesis of inorganic nanostructures are detailed below. Unless otherwise noted, the peptides discussed in the following section were isolated by using the phage-display method.

Adschiri and co-workers isolated five peptides with affinities for ZnO, with the peptide ZnO-1 (EAHVMHKVAPRP) showing the strongest affinity. After adding the GGGSC sequence to the C terminus, the resultant peptide promoted the synthesis of flowerlike ZnO nanostructures at room temperature (Figure 10).[87] In this case, conjugation of the GGGSC tag to the ZnO peptide was critical for the synthesis of ZnO from $Zn(OH)_2$. Control experiments showed that when GGGSS was attached to the ZnO peptide, the resultant peptide conjugate did not lead to the deposition of ZnO. Furthermore, the addition of GGGSC to the solution of $Zn(OH)_2$ did not cause detectable condensation of $Zn(OH)_2$ or deposition of ZnO. The addition of a non-ZnO-binding peptide conjugated to the GGGSC tag also resulted in no condensation or deposition. Therefore, the authors proposed that the ZnO-1 peptide interacted with $Zn(OH)_2$, the cysteine residue in GGGSC initiated dehydration of $Zn(OH)_2$, and the conjugation of GCGSC to the ZnO-1 peptide resulted in the mineralization activity of the ZnO-1 peptide.

Sandhage and co-workers identified several germanium-binding peptides. They found by adding these peptides to a solution of germanium alkoxide at room temperature that peptide Ge8 (SLKMPHWPHLLP) and Ge34 (TGHQSPGAYAAH) promoted rapid precipitation of networks of amorphous germania nanoparticles at room temperature (Figure 11).[116] The peptide Ge2 (TSLYTDRRSTPL) exhibited much lower germania-precipitating activities, and its ability to precipitate germania was difficult to detect by visual observation. Careful comparison of these three germania-binding peptides revealed that peptides Ge8 and Ge34 have hydroxy- and imidazole-containing amino acid residues, and Ge8 exhibits a more basic isoelectric point (pI) and a higher germania-precipitating activity than the Ge34 peptide.

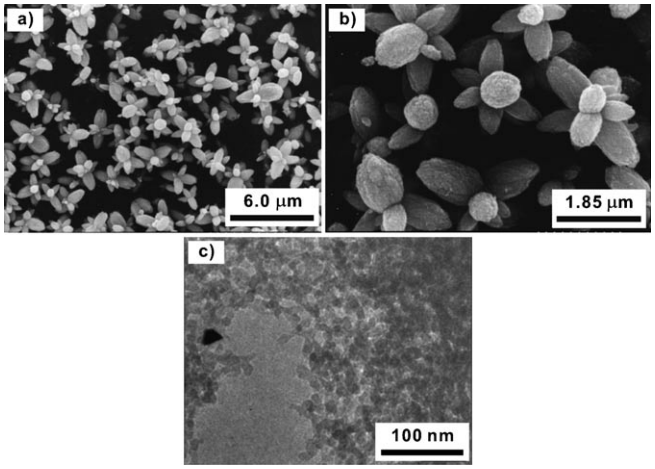


Figure 10. a, b) SEM and c) TEM images of the ZnO particles precipitated using the peptide EAHVMHKVAPRPGGGSC.[87]

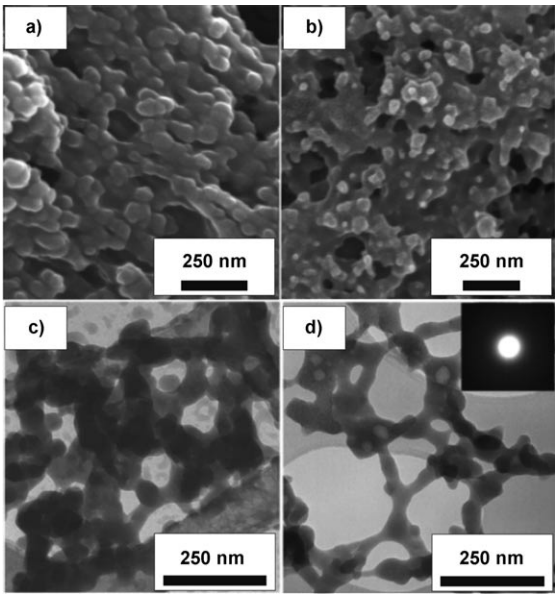


Figure 11. Nanoparticle networks of germania prepared using GeO_2-binding peptides. a, b) SEM image of particles prepared with Ge8 (a) and Ge34 (b). c, d) TEM image of particles prepared with Ge8 (c) and Ge34 (d).[116] Reproduced with permission from the Royal Society of Chemistry, copyright 2004.

The same authors also demonstrated that peptides BT1 (HQPANDPSWYTG) and BT2 (NTISGLRYAPHM) could direct the room-temperature formation of ferroelectric (tetragonal) barium metatitanate ($BaTiO_3$) within two hours from an aqueous solution of the precursor at a near neutral pH value (Figure 12). Several control experiments suggested that the combination of certain conserved amino acids (with hydroxy or amine groups, charged, and hydrophobic) in the BT1 and BT2 peptides was important for the formation of crystalline (tetragonal) $BaTiO_3$.[88]

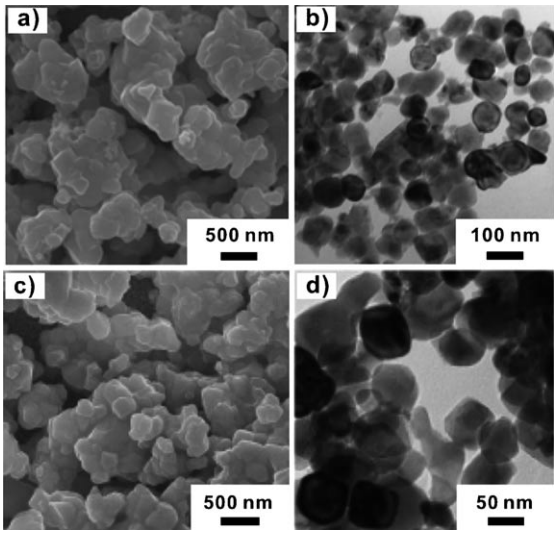


Figure 12. a, c) SEM image of $BaTiO_3$ prepared with the peptide BT1 (a) and BT2 (c); b, d) TEM image of $BaTiO_3$ prepared with peptide BT1 (b) and BT2 (d).[88] Reproduced with permission from the American Chemical Society, copyright 2008.

Peptides specific for binding metallic platinum phases have also been isolated. Naik et al. used phage-display methods coupled with the polymerase chain reaction (PCR) to discover a cobalt-binding peptide Co1-P10 (HYPTLPLGSSTY) which can control the nucleation and formation of discrete CoPt nanoparticles with an average diameter of (3.5 ± 0.5) nm (Figure 13).[77] The combination of

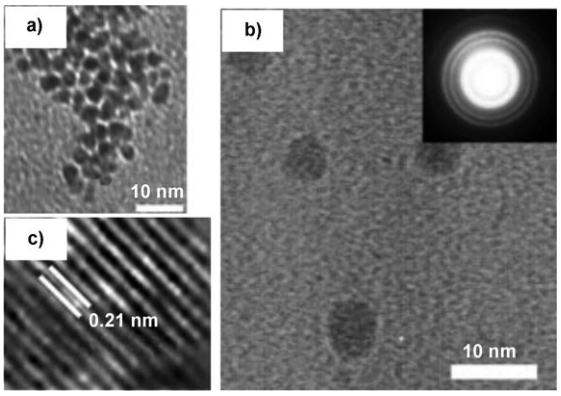


Figure 13. TEM images of CoPt nanoparticles prepared with peptide Co1-P10.[77]

PCR amplification methods with typical in vitro evolution methods allows the discovery of some peptides that may otherwise pass undetected. Belcher and co-workers isolated the FePt-specific dodecapeptide HNKHLPSTQPLA,[78] and they used this peptide to generate FePt nanoparticles with average diameters of (4.1 ± 0.6) nm (Figure 14). These nanoparticles are ferromagnetic at room temperature (Figure 14d).[78]

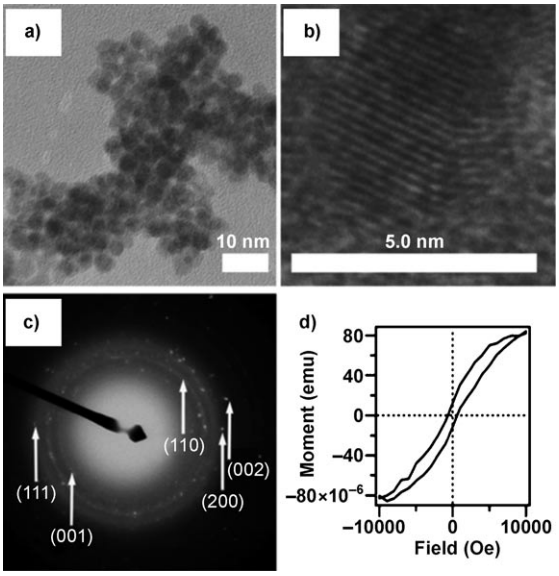


Figure 14. a, b) TEM images of FePt nanoparticles prepared with peptide HNKHLPSTQPLA. c) Electron diffraction pattern. d) Characterization of the FePt nanoparticles by SQUID magnetometery.[78] Reproduced with permission from the American Chemical Society, copyright 2004.

In some cases peptides can bind specifically to one crystalline face of an inorganic nanocrystal. Naik et al. demonstrated that the peptide NPSSLFRYLPSD (AG4) directs the fabrication of hexagonal, spherical, and triangular-shaped silver nanoparticles from an aqueous solution of silver ions (Figure 15). This peptide binds specifically to the Ag(111) surface and thus enables the synthesis of polyhedral Ag crystals with face-centered-cubic lattice structures.[70]

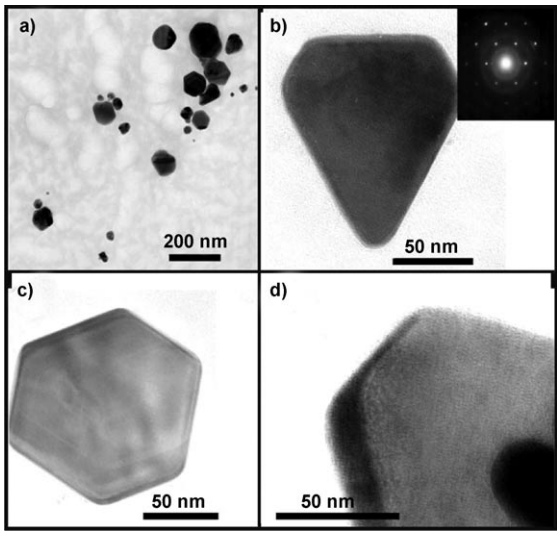


Figure 15. Silver nanoparticles prepared with peptide NPSSLFRYLPSD (AG4).[70] Reproduced with permission from the Nature Publishing Group, copyright 2002.

Hydroxyapatite (HA; $Ca_5(PO_4)_3(OH)$) is the primary inorganic component of both teeth and bone. HA and HA-derivatized composites are increasingly being utilized in tissue engineering applications as support structures for guiding stem cell differentiation toward osteogenic lineages (namely, for bone growth). Becker and co-workers isolated the peptide SVSVGMKPSPRP (HA 6-1), which has a strong affinity and specificity for binding HA.[123] Binding-specificity studies based on a fluorescence microscopy approach showed that this peptide exhibited highly specific binding to crystalline hydroxyapatite, but very little adhesion to calcium carbonate and amorphous calcium phosphate ($aCa_3(PO_4)_2$). Their observations indicate that this peptide does not merely recognize the phosphate components of the mineral; instead, its adhesion relies upon both the chemical composition of the mineral and also the defined physical arrangements of those components (that is, crystal structure) at the surface. These conclusions were further supported by their observations that HA regions within the lateral cross-section of a human tooth were successfully recognized by this HA-specific peptide.

2.3. Rationally Tailored Peptides

The peptides described in Sections 2.1 and 2.2 were all generated through evolutionary processes, and therefore little rationale or design input from the researcher was used in their discovery. However, understanding the mechanisms underlying the ability of proteins and peptides to recognize and bind with specific affinities to minerals and inorganic substrates is a central goal in many fields of biology and material science. A better understanding of these processes will be necessary for rationally tailoring these peptides.

Scientists and engineers have invested much effort to understand the relationships between peptide sequences and their binding affinities or specificities, and these studies have enabled the development of novel peptides with interesting properties.[37,94] For example, to more thoroughly understand the role of the peptide in the formation of discrete gold nanoparticles, Naik and co-workers used the peptide AYSSGAPPMPPF (identified through phage-display methods) and its derivatives, in which key amino acid residues within its sequence were substituted, deleted, rearranged, or scrambled, and tested their ability to mediate the formation of gold nanoparticles.[129] They found that an alanine-substituted peptide (AYSSGAPPAPPF) exhibited the highest affinity for gold, while a proline-substituted peptide (AYPPGAPPMPPF) showed almost no affinity. Other peptides, including ASSSGAPPMPPF, AMSSGAPPYPPF, and PSPGSAYAPFPM, all displayed moderate binding affinities. On the basis of their observations, they concluded that the hydroxy groups present on the serine and tyrosine residues were likely required for these peptides to have strong binding affinities to the surfaces of the gold nanoparticle.[129]

The role played by peptides in the actual reduction of certain metal salts and the nucleation of nanoparticles is not always clear. It is known, however, that tyrosine is redox active and has strong electron-donating properties. In some cases, it can reduce Au^{3+}/Ag^{+} ions in situ to Au^0/Ag^0 colloids. A series of oligopeptides containing tyrosine residues was used to fabricate gold/silver nanoparticles from salt precursors in situ through a simple peptide-catalyzed redox technique at room temperature. Mandal and co-workers demonstrated that oligopeptides containing tyrosine residues could act as both stabilizers and reducing agents for the synthesis of gold and silver nanoparticles.[130,131] The size of the resultant nanoparticles increases with the number of added tyrosine residues. They proposed that the dityrosine form of the peptide forms during the synthesis of the nanoparticles, and that the rate of reaction depends on the number of tyrosine moieties present in the peptide molecules. In some cases, the redox activity of tyrosine can be exploited for both the synthesis and assembly of silver or gold nanoparticles. For example, Ray et al. prepared oligopeptide gels by using tyrosine-containing peptides as building blocks.[132] The redox activity of tyrosine enabled these gels to be used successfully for the in situ synthesis of gold and silver nanoparticles. The resulting metal nanoparticles were trapped and stabilized within the supramolecular gel-phase network and aligned along the nanostructured gel fibers (Figure 16).

In many cases, structural and functional clues can be gleaned by examining the sequences of naturally occurring peptides. Inspired by the hypothesis that positively charged amino acid residues were largely responsible for facilitating biosilicification, the artificial peptide poly(L-lysine) (PLL) was evaluated for its ability to promote silicification.[85,133–136]

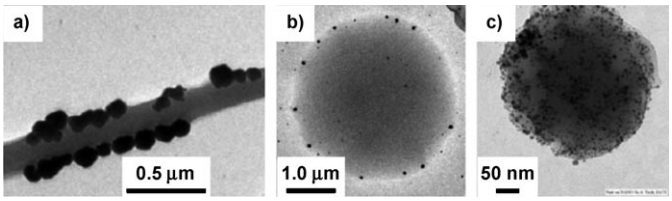


Figure 16. a) Gold nanoparticles aligned along a gel fiber. b) Gold nanoparticles formed within a gel network. c) Silver nanoparticles embedded in a spherical sponge-like gel network.[132] Reproduced with permission from the Royal Society of Chemistry, copyright 2006.

It was found that PLL induces the formation of silica within minutes by hydrolysis of silicic acid. Shantz and co-workers demonstrated that the secondary structure of the PLL could be used as a means to tune the porosity of the silica structures. When PLL adopted an α-helix conformation, the synthesized silica possessed highly uniform 1.5 nm pores. In contrast, silica synthesized with PLL in a β-sheet conformation had larger pores, and the pore size was a function of the peptide concentration.[136] Naik and co-workers found that the molecular weight of PLL could affect the morphology of the synthesized silica. High-molecular-weight PLL produced hexagonal silica platelets, whereas low-molecular-weight PLL afforded spherical silica nanoparticles (Figure 17).[133]

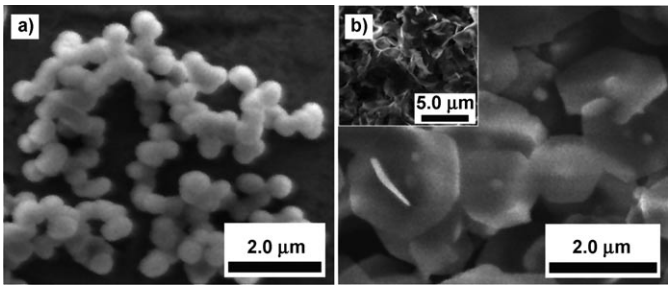


Figure 17. a) Silica network prepared with peptide PLL_{20} (with 20 amino acid residues). b) Hexagonal silica platelets prepared with peptide PLL_{222} (with 222 amino acid residues).[133] Reproduced with permission from the American Chemical Society, copyright 2005.

During the silicification processes, the high-molecular-weight PLL underwent a rapid secondary-structure transition from a random coil to a helical structure in the presence of silicic acid and phosphate ions. The formation of the helical PLL chains caused the formation of hexagonal silica platelets. In contrast, low-molecular-weight PLL could not adopt helical structures and showed no significant secondary structure transition.

In analogy to the formation of biological glass fibers, Börner and co-workers encoded structural and functional information in a fiberlike nanostructure designed to direct the silicification process.[137] They first combined polyethylene oxide (PEO) with two preorganized oligopeptides (VTVT) to yield peptide–polymer hybrid building blocks.[137,138] Driven by the formation of β sheets between these preorganized oligopeptides (VTVT), these building blocks self-assembled into nanotapes with peptide β-sheet cores and PEO shells, in which the precisely positioned hydroxy groups from threonine (T) residues were located in well-defined patches running along the center of the nanotapes (Figure 18a). After addition of prehydrolyzed tetramethoxysilane to a dilute solution of nanotapes in ethanol, the hydroxy patches directed the formation of silica and resulted in the spontaneous precipitation of macroscopic fibers within a few seconds (Figure 18b). Calcination of the composite product decomposes the organic components quantitatively to yield porous silica fibers (Figure 18c).

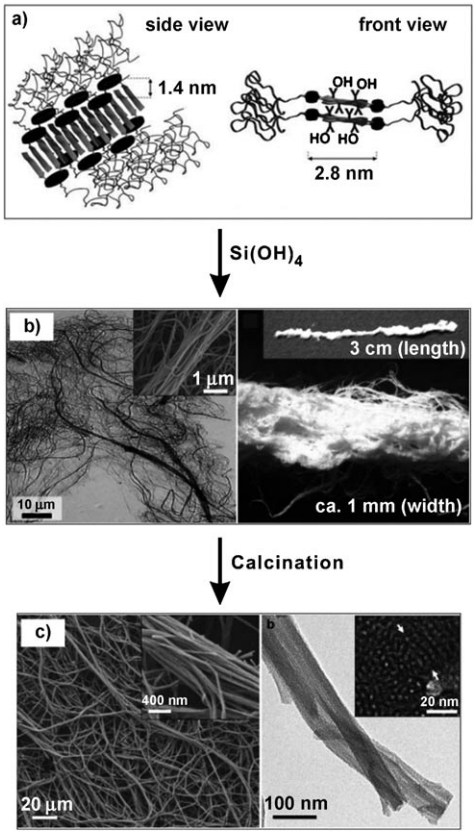


Figure 18. a) Schematic view of functional nanotapes. b) Inorganic–organic composite silica fibers. c) Porous silica fibers.[137]

Other research groups have also tailored peptides for the nucleation of inorganic materials. For example, Kelly and co-workers demonstrated that an easily synthesized amphiphilic peptidomimetic could form a 2D β-sheet monolayer spontaneously at an air–water interface and nucleate the [010] face of CdS nanocrystals, thereby controlling the CdS crystal growth and limiting the crystal width and length to around 2.5–5.0 nm.[139] Stupp and co-workers prepared nanostructured fibers using peptide amphiphile (PA) building blocks. They then used these fibers as templates for the nucleation of hydroxyapatite (HA; Figure 19). Interestingly, hydroxyapatite (HA) crystals grow with their *c* axes oriented along the long axes of the peptide fibers.[140] They reasoned that the negatively charged surfaces of the nanofibers promoted the mineralization of hydroxyapatite. The orientation of crystalline nuclei and the subsequent crystal growth were controlled by the PA micelles.

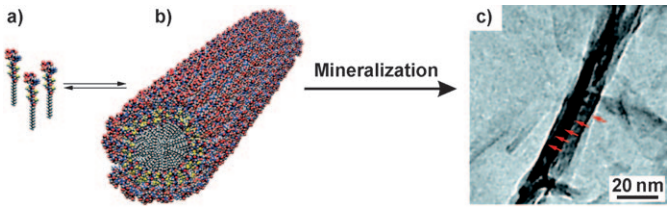


Figure 19. Mineralization of hydroxyapatite (HA) with a peptide amphiphile. a) Peptide amphiphile (PA). b) Model of the PA fiber. c) Mature hydroxyapatite crystals (red arrows) completely cover the peptide fibers.[140] Reproduced with permission from the authors.

3. Peptide-Based Scaffolds for Assembly of Inorganic Nanoparticles

Inorganic nanoparticles are often classified as "artificial atoms" and have been heralded as potential building blocks for new materials with superior properties and applications.[1,29,141–143] To harness the potential of inorganic nanoparticles as building blocks, researchers must devise methods for organizing nanoparticles and assembling them into well-defined one-, two-, and three-dimensional hierarchical architectures. Many new methods for controlling the assembly of inorganic nanoparticles have recently emerged.[26–29,69,72,141–148] For example, various polymers[146–148] and biomolecules[36,46,47,72,142,143,148,149] have been used as templates. These template species are often chosen based on their ability to bind nanoparticles, their self-assembly characteristics, and their size, which should generally be similar to the size of the nanoparticles.

Recently, peptide-based methods for the assembly inorganic nanoparticles have received increasing interest because of the unique self-assembly[34,35,48,54,93] and recognition properties of peptides.[37,47,50,94] Many inorganic nanoparticle superstructures, including nanoparticle chains,[150–152] nanoparticle sheets,[153] nanoparticle spheres,[154–156] and nanoparticle double helices,[72] have been designed and synthesized by using peptide-based methods. In the following section some representative methods and nanoparticle superstructures will be reviewed.

3.1. Peptide Scaffolds

The assembly of inorganic nanoparticles using self-assembled peptide scaffolds generally involves several independent steps. These steps may include 1) peptide assembly, 2) nanoparticle synthesis, 3) nanoparticle functionalization with surface ligands suitable for interacting with the peptide-based template, and finally 4) mixture of the template structures with the functionalized nanoparticles to effect assembly of the nanoparticles. In some cases, the nanoparticles are nucleated and grown directly onto the peptide-based template structures. In general, these methods can be categorized according to the principle driving forces that direct the assembly of the nanoparticles: electrostatic interactions, metal-coordination interactions, and peptide folding.

3.1.1. Electrostatic Interactions

Since many colloidal inorganic nanoparticles are negatively charged, positively charged peptide-based nanostructures are often designed and synthesized as scaffolds for the electrostatically driven assembly of nanoparticles. For example, Wang and co-workers demonstrated that the T1 peptide RGYFWAGDYNYF self-assembles into nanofibers with lengths of up to several micrometers and average diameters of 10 nm.[150] They reasoned that, after protonation of T1, the nanofibers with positively charged surfaces would attract and assemble negatively charged metal nanoparticles. To test this hypothesis, they mixed a solution of T1 peptide fibers with 3.6 nm gold nanoparticles at pH 6. They observed that the gold nanoparticles attach to the peptide fiber to form double-helical arrays with lengths ranging from hundreds of nanometers to several micrometers (Figure 20).[150] They found

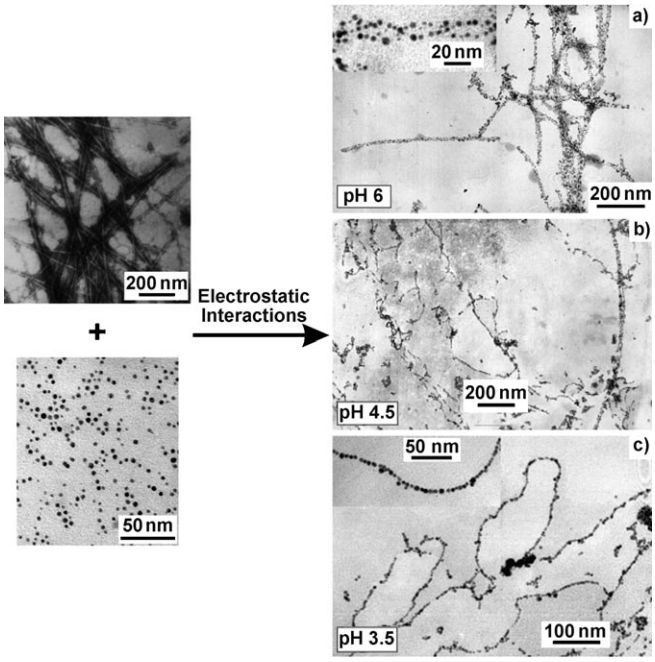


Figure 20. Assembly of gold nanoparticle arrays by mixing peptide nanofibers and gold nanoparticles at different pH values.[150]

that small gold particles led to the formation of double-helical arrays, while large particles, especially those having an average diameter larger than 10 nm, randomly attached to the peptide nanofibers. To prove that the process was driven by electrostatic forces, they demonstrated that the nanoparticle aggregates were favored under acidic conditions, while it was difficult to observe any such aggregates under basic conditions. Interestingly, when peptide fibers and gold nanoparticles were mixed at pH 3.5, the gold nanoparticles assembled only into single-chain arrays, while both single-chain and double-helical arrays formed at pH 4.5 (Figure 20). It was speculated that the T1 peptide fibers adopt a helical structure at pH 6, but the helical structure disappears at pH 3.5.[150]

By using a similar strategy, Pochan and co-workers prepared sheets of gold nanoparticles (Figure 21), in which assembled, nontwisted laminated β-sheet peptide fibrils acted as templates, and negatively charged gold nanoparticles intercalated within fibril laminates. The formation of the aggregates was induced by electrostatic interactions with the positively charged lysine side chains of the fibrils. The intercalation of gold nanoparticles increased the interfilament spacing from 2.5 nm to 3.9 nm.[153]

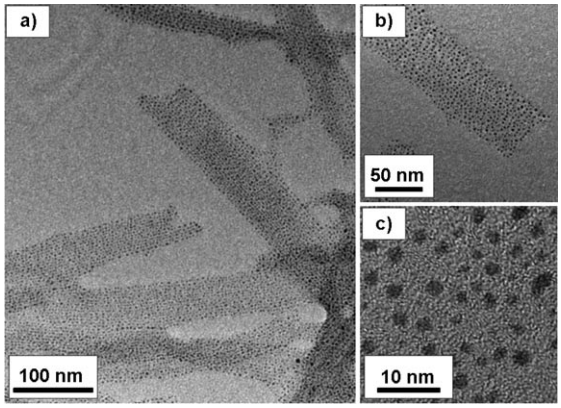


Figure 21. TEM images of sheets of gold nanoparticles templated by nontwisted laminated peptide fibrils.[153]

Very recently, Pochan and co-workers used electrostatic interactions as a driving force to construct chains of gold nanoparticles that exhibit precise axial separations (Figure 22). Specifically, they first designed and assembled peptide fibrils with regularly spaced positively charged patches along the fiber axis. After negatively charged gold nanoparticles were mixed with the peptide fibrils, they were immobilized in a regular arrangement on the fibril template through electrostatic interactions with positively charged histidine patches. Only a single nanoparticle could bind to each patch as a result of electrostatic repulsions between particles.[151]

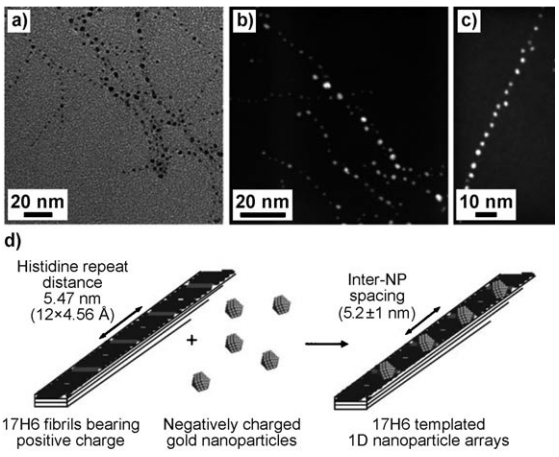


Figure 22. a–c) TEM images of chains of gold nanoparticles. d) Mechanism for the assembly of negatively charged gold nanoparticles on positively charged histidine patches in peptide fibrils.[151]

Assembly methods driven by electrostatic interactions between nanoparticles and peptide scaffolds are very effective for assembling small negatively charged nanoparticles (<6 nm).[150,151,153] However, their wide application is limited by the size of the nanoparticles, since larger nanoparticles will normally only randomly bind to the fibril surfaces.[153]

3.1.2. *Metal Coordination*

Since many peptides have coordination donor atoms (for example, N, O, and S atoms), coordination chemistry can, in some cases, be used to direct the assembly of nanoparticles. In these cases, the metal–peptide complex acts as a template.[157,158] For example, Mandal and co-workers functionalized gold nanoparticles with carboxylated peptides and demonstrated that various heavy metal ions (Pb^{2+}, Cd^{2+}, Cu^{2+}, and Zn^{2+}) could drive these functionalized gold nanoparticles to self-assemble into two- and three-dimensional nanostructures in aqueous solution. Here, the metal-ion/carboxylate coordination bonds result in the formation of a metal–peptide scaffold that supports the nanoparticle assembly.[158] The color of the solution changes from red to blue during the assembly process. The self-assembly process could be completely reversed by the addition of metal-chelating agents, such as alkaline solutions of ethylenediaminetetraacetic acid (EDTA; Figure 23).[158]

Figure 23. Metal-ion-induced reversible self-assembly of gold nanoparticles, in which the solution color changes from red to blue.[158]

3.1.3. *Peptide Folding*

JR2EC is a de novo designed glutamic acid rich helix-loop-helix polypeptide with 42 residues and a net charge of −5 at neutral pH. Below pH 6, or in the presence of selected metal ions, this peptide folds into a globule-like four-helix bundle upon dimerization. At neutral pH, JR2EC can heterodimerize with the charge-complementary, lysine-rich polypeptide JR2KC.[159–163] By using peptide JR2EC, Liedberg and co-workers demonstrated that polypeptide folding can be used to control the assembly of the nanoparticles.[159–163] Particle assembly could be controlled in a switchable manner after covalent immobilization of JR2EC onto gold nanoparticles.[161] At neutral pH, the peptide-functionalized particles gave rise to a strong absorption peak with a maximum close to 520 nm, which suggests that the particles were dispersed. When the pH value was lowered below 5, a significant red-shift of the plasmon resonance maximum

occurred, which can be attributed to particle aggregation. However, decreasing the pH value to 3.5 causes JR2EC to become positively charged, and the resulting electrostatic repulsion between the JR2EC-functionalized gold nanoparticles is sufficient to disrupt aggregation. Therefore, the position of the resonance absorption maximum shifts back close to the value observed at pH 7.

Liedberg and co-workers also showed that JR2EC could fold into a four-helix bundle consisting of two helix-loop-helix monomers upon exposure to Zn^{2+} ions. Particle aggregation occurs when Zn^{2+} ions are added to JR2EC-functionalized nanoparticles (Figure 24a); in the presence of chelating

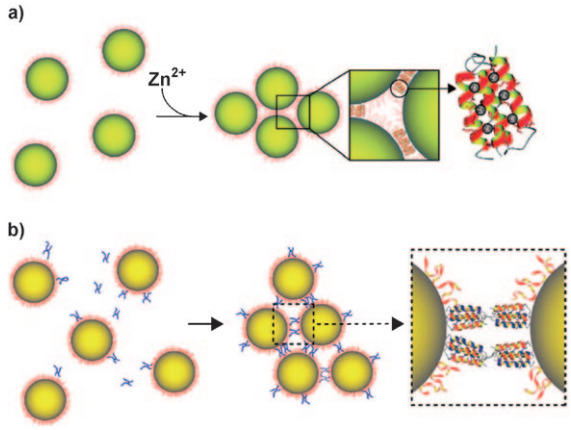


Figure 24. Assembly of gold nanoparticles induced by peptide folding.[159,160] Reproduced with permission from the American Chemical Society, copyright 2008.

agents such as EDTA, the aggregates fragment to yield dispersed nanoparticles.[159] The reversible formation of disulfide bridges was also used to effect nanoparticle assembly.[160] Specifically, the peptide JR2EC was heterodimerized with the disulfide-containing linker peptide $JR2KC_2$ and folded into two disulfide-linked four-helix bundles. This process could induce the assembly of nanoparticles when the nanoparticles were appended to JR2EC, (Figure 24b). The assembled nanoparticle superstructures could be disassembled by cleaving the disulfide bridges with tris(2-carboxyethyl)phosphine (TCEP).[160]

In some cases, peptide-based structures not only direct the assembly of nanoparticles, but they also protect the nanoparticles and improve their properties. For example, Li and co-workers demonstrated that organogels assembled from diphenylalanine peptides could serve as scaffolds to assemble one-dimensional arrays of presynthesized lipophilic quantum dots (QDs) or gold nanoparticles. The peptide gel encapsulates the nanoparticles and protects the QDs effectively from oxidation, thus resulting in improved stability of the QDs. Importantly, the gel–QD hybrids still remain photoluminescent.[164] The authors further demonstrated that gels assembled from cationic dipeptides (H-Phe-Phe-NH_2·HCl) could also be used to assemble QDs (Figure 25a).[156,164] Interestingly, spherical QD superstructures with average diameters of 150 nm formed when they transferred the nanocrystal/organogel phase into water (Figure 25b).[156]

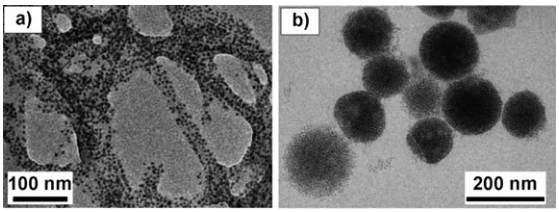


Figure 25. a) TEM image of the fibrous aggregates of quantum dots. b) TEM image of colloidal spheres assembled from QDs.[156]

3.2. Hybrid Organic–Peptide Scaffolds

Peptide conjugates can be easily prepared by appending various organic molecules to the peptide. Such molecules can dramatically influence the self-assembly of peptides[35,49,72] and nanoparticles.[152,154,155,165,166] Stupp and co-workers have studied the self-assembly of peptide amphiphiles and the applications of assembled bio-nanomaterials.[35,140,152,165,166] In regard to the assembly of inorganic nanoparticles, they demonstrated that assembled peptide amphiphiles could be used as scaffolds to direct the synthesis and assembly of nanoparticles through two different strategies.[152,165,166] The first strategy involves using the formation of complementary hydrogen bonds as a driving force to assemble presynthesized and specifically functionalized nanoparticles. For example, by mixing a small amount of peptide conjugate **2**, which contains a thymine recognition moiety, and a much larger amount of **1**, which was known to assemble into nanofibers, they were able to obtain nanofibers which express thymine residues on their surfaces.[152] They then modified gold nanoparticles with diaminopyridine (DAP) functionalized alkyl thiols (**3**). The addition of these nanoparticles to suspensions of the nanofibers resulted in them being assembled into linear arrays of nanoparticles (Figure 26).[152]

In a second strategy, Stupp and co-workers added metal salts directly to suspensions of a peptide nanofiber gel. The metal cations which bound to the peptide served as nucleation sites for the mineralization of nanoparticles onto the fibers.[165,166] For example, when a gel suspension of nanofibers assembled from a peptide amphiphile (PA) displaying $S^{(P)}$RGD sequences ($S^{(P)}$ = phosphoserine) was mixed with a solution of $Cd(NO_3)_2$ in a Cd^{2+}/PA molar ratio of 2.4:1 and then exposed to hydrogen sulfide (H_2S) gas to initiate the nucleation of CdS nanoparticles, one-dimensional nanoparticle arrays with individual CdS nanoparticles of 3–5 nm decorated the PA fibers (Figure 27a). Each particle was a single crystal with the CdS zinc blende structure. In some cases, a gap of 2–3 nm between two rows of CdS particles was observed, and this gap was the approximate dimension of the hydrophobic core of the fiber. When they increased the Cd^{2+}/PA ratio to 24:1, the PA fibers were completely encapsulated by CdS with a cubic zinc blende structure. In this case, the CdS layer appeared to be composed of a continuous polycrystalline coating with grains of 5–7 nm. The observation of a 2–3 nm wide stripe in the TEM images suggested that only the hydrophobic core of the PA fibers was unmineralized (Figure 27b).[165] In this method, the binding affinity between

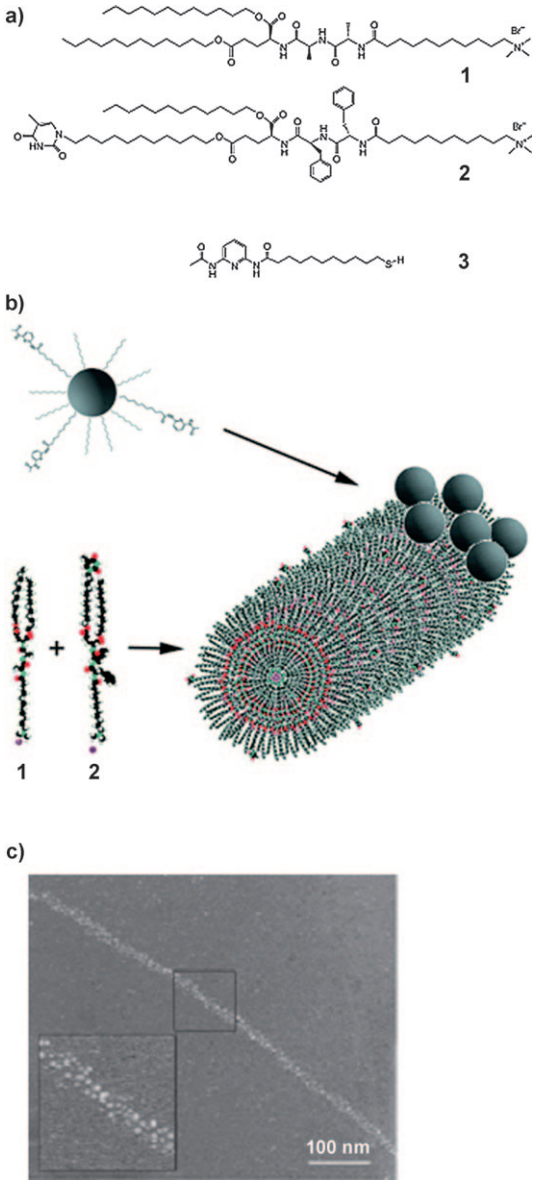


Figure 26. a) Structure of DAP-SH (**3**) and peptide amphiphiles **1** and **2**. b) Structure of the coassembled nanofibers from **2** and **3** and hydrogen-bond-directed binding of nanoparticles to nanofibers. c) TEM images of linear nanoparticle arrays templated by nanofibers.[152]

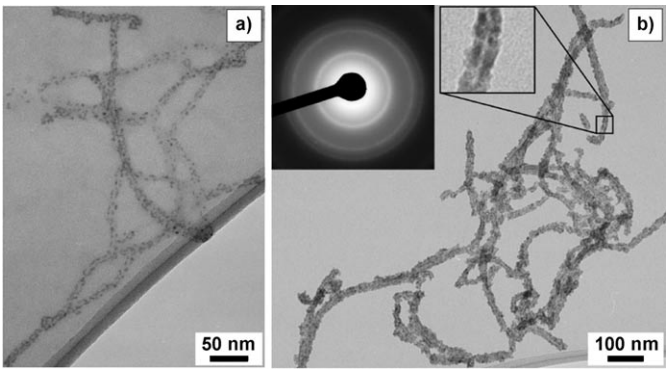


Figure 27. TEM images of 1D cadmium sulfide nanostructures templated by peptide nanofibers.[165] Reproduced with permission from the American Chemical Society, copyright 2004.

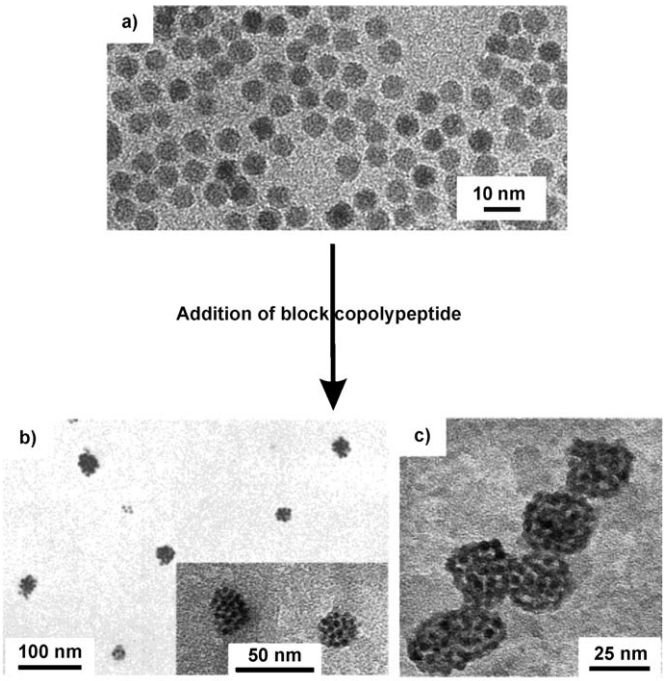


Figure 28. TEM images of: a) maghemite nanoparticles from dispersions in water; b, c) clusters of maghemite nanoparticles formed by the addition of poly(EG_2-K)$_{100}$-*b*-poly(D)$_{30}$ block copolypeptide.[154] Reproduced with permission from the American Chemical Society, copyright 2003.

the peptide and metal ion was proposed to be a key factor in promoting the synthesis and assembly of nanoparticles.[165,166]

Block copolypeptides have also been used to direct the assembly of nanoparticles. For example, Held et al. demonstrated that the block copolypeptide poly(EG_2-K)$_{100}$-*b*-poly(D)$_{30}$ could direct the assembly of aqueous 6 nm maghemite (γ-Fe_2O_3) nanoparticles into water-soluble clusters (Figure 28).[154] By using homopolymer poly(EG_2-K)$_{100}$ as a control, they found that the assembly of magnetic nanoparticles was facilitated by favorable electrostatic interactions between their positively charged surfaces and the negatively charged carboxylic acid side groups of the poly(asp)$_{30}$. They also found that the magnetic nanoparticle clusters assembled using block copolypeptide poly(EG_2-K)$_{100}$-*b*-poly(D)$_{30}$ were significantly more uniform than with homopolymer poly(D)$_{30}$.

Stucky et al. used lysine–cysteine diblock copolypeptides to coassemble silica and gold particles (ca. 10 nm) into robust and hollow spherical nanoparticle superstructures.[155] In this case, the ability of the cysteine sulfhydryl group to form inter- and intrachain disulfide bonds and thiolate bonds to the gold was the key determinant in the formation of hollow spheres. Hollow spheres were formed only when the disulfide-containing block copolypeptide was treated with gold nanoparticles prior to treatment with silica nanoparticles.

Peptide nanostructures (for example, nanotubes) assembled using peptide amphiphiles can also be coated with various biomineralization peptides. In these cases, the coated nanostructures can act as scaffolds for directing both the

synthesis and the assembly of inorganic nanoparticles. The composition of the nanoparticles can be rationally varied by changing the biomineralization peptide. Matsui and co-workers have used this strategy, in which they immobilized sequenced "mineralizing peptides" on peptide nanotubes assembled from bis(*N*-α-amidoglycylglycine)-1,7-heptane dicarboxylate, to fabricate various one-dimensional arrays of metallic nanoparticles.[73–76,167–169] In this approach, the mineralizing peptides adhere to the sidewalls of peptide tubes through hydrogen bonds and coordinate to metal ions to generate nucleation sites for nanoparticle growth. For example, the histidine-rich peptide AHHAHHAAD, which is capable of serving as a nucleation site for gold in the presence of a reducing agent, was immobilized onto peptide nanotubes for the fabrication of one-dimensional arrays of gold nanoparticles. They showed that the packing density of the gold nanoparticles could be controlled by tuning the pH value of the solution. Increasing the pH value resulted in more densely packed arrays of nanoparticles (Figure 29).[169] Immobilization of the histidine-rich peptide HGGGHGHGGGHG (HG12) onto the same peptide nanotubes enabled the mineralization of copper nanoparticles, and thus the fabrication of one-dimensional arrays of copper nanoparticles. By changing the conformation of the peptide HG12 on the nanotube surfaces, the size of the copper nanoparticles could be varied between 10 and 30 nm.[75] HG12-coated peptide nanotubes were also used as templates for preparing one-dimensional arrays of nickel nanoparticles. The size of the nickel nanoparticles could be increased by increasing the pH value of the growth solution: the diameter of the nickel nanoparticles was (30 ± 4) nm at pH 4, (50 ± 5) nm at pH 6, and (100 ± 23) nm at pH 8.[76] The use of the peptide NPSSLFRYLPSD (AG4)[70] as the mineralizing peptide led to one-dimensional nanoparticle arrays composed of isotropic hexagonal silver nanoparticles.[73] Similarly, one-dimensional arrays of platinum nanoparticles could be generated using the peptide HPGAH, which is known for its high affinity toward Pt ions.[167] Lastly, by immobilizing the M1 peptide (VCATCEQIADSQHRSHRQMV) onto the template nanotubes, the authors were able to prepare one-dimensional arrays of wurtzite ZnS nanocrystals at room temperature.[80] The M1 peptide played a significant role in regulating the size and surface coverage of the ZnS nanocrystals. At pH 5.5, the ZnS nanocrystals adopted the highly crystalline wurtzite phase, but when grown at pH 10, the nanoparticles were amorphous. The M1 peptide unfolds at elevated pH values; this results in a change of the Zn^{2+}-His coordination mode, which ultimately influences the nucleation process and, therefore, the final crystalline structure of the ZnS nanocrystals.[80]

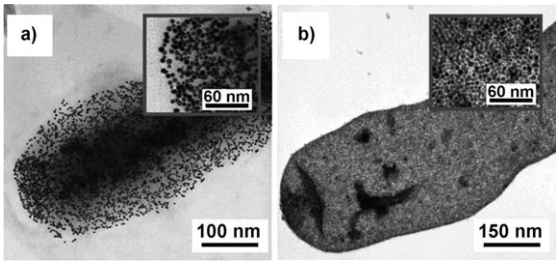


Figure 29. TEM images of gold nanoparticles grown on nanotubes decorated with histidine-rich peptides. The pH value at which the gold ions were incubated with the nanotubes prior to reduction was important in determining the density of the gold nanoparticles in the final assembly: a) pH 8; b) pH 11.5.[169] Reproduced with permission from the American Chemical Society, copyright 2003.

3.3. Simultaneous Peptide Self-Assembly and Peptide-Based Biomineralization

As detailed in Sections 2, 3.1, and 3.2, peptides can play key roles in mediating the formation of inorganic nanostructures and self-assembly to form scaffolds onto which inorganic nanostructures can be assembled. Various multistep approaches have been developed that combine these two functions. We recently demonstrated that both peptide self-assembly and peptide-based biomineralization of gold nanoparticles could be combined into one process which enables the 1) assembly of left-handed twisted peptide nanoribbons, 2) synthesis of gold nanoparticles, and 3) self-assembly of nanoparticles to all occur in a single preparative step (Figure 30).[72]

Specifically, we first selected the water-soluble peptide AYSSGAPPMPPF, which had been identified by Naik et al.[70] This peptide is known to bind to both gold and silver surfaces.[70,71] Moreover, it is able to mineralize chloroauric acid to form monodisperse spherical gold nanoparticles in the presence of HEPES buffer.[71] We then functionalized the N terminus of this peptide with a hydrophobic aliphatic C_{12} tail to obtain a peptide amphiphile termed C_{12}-

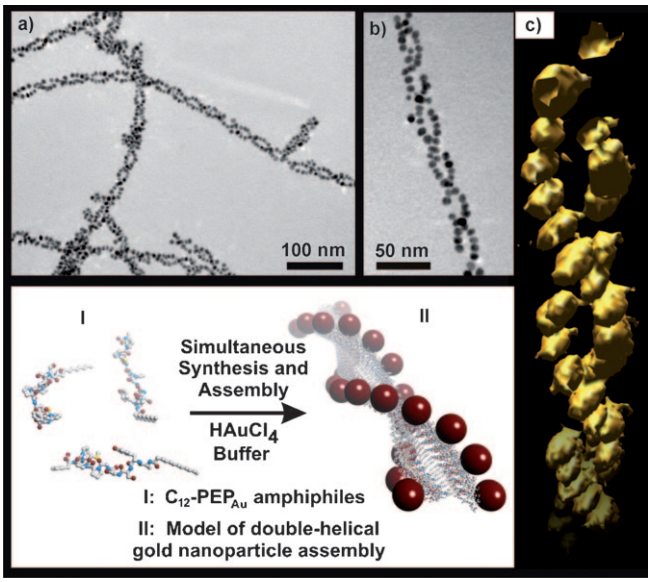


Figure 30. a, b) TEM images of left-handed gold nanoparticle double helices. c) Tomographic 3D reconstruction image of left-handed gold nanoparticle double helices. d) Schematic representation of the formation of left-handed double helices of gold nanoparticles by combining peptide self-assembly and peptide-based biomineralization.[72] Reproduced with permission from the American Chemical Society, copyright 2008.

PEP_{Au}. In the presence of HEPES buffer, C_{12}-PEP_{Au} self-assembles into a unique left-handed twisted nanoribbon structure through a process driven by hydrophobic/hydrophilic interactions and the formation of parallel β sheets.[72] The self-assembly of C_{12}-PEP_{Au} was further studied in the presence of both HEPES buffer and chloroauric acid with the aim to combine C_{12}-PEP_{Au} self-assembly and PEP_{Au}-based mineralization of gold nanoparticles. The addition of chloroauric acid was found to assist the formation of twisted nanoribbons. Moreover, we observed that the self-assembly process and the PEP_{Au}-based biomineralization of gold nanoparticles were successfully coupled into one simultaneous process to form structurally complex and highly ordered left-handed double helices of gold nanoparticles (Figure 30).[72] The spherical gold nanoparticles comprising the double helices are monodisperse, and the length of individual helices extends into the micrometer range.

The formation of these complex structures in a single preparative step exemplifies the utility and power of this method. Since many peptides are known for their abilities to direct the mineralization of inorganic nanoparticles (see Table 1), we expect that this method will be particularly attractive for generating diverse libraries of nanoparticle superstructures with different inorganic components.

4. Summary and Outlook

The ability to control the assembly and morphology of inorganic nanostructures is critically important for controlling their physical properties and, therefore, their ultimate application. The research studies detailed herein sugggest the utility of peptide-based methods for preparing nanostructured inorganic materials in a highly predictable manner. However, there are still important scientific and practical issues that need additional attention to further improve these methods and harness their full potential.

For example, we still do not fully understand why and how specific peptides direct the biomineralization of specific inorganic materials. More studies need to be carried out to determine the roles of specific amino acids and the roles that peptide secondary structure have in controlling the biomineralization processes. With more insight into these processes, a priori design of peptide sequences may be possible. Clearly, this is a daunting experimental task, and it is expected that computational studies will eventually help in the design of new peptides.[170–172]

Peptide design should allow for the preparation of multifunctional peptides with various specific amino acid domains that could each direct the nucleation of a different inorganic material. The design of such peptides would enable facile fabrication of materials with various inorganic domains that could each perform a different function. As a first step in this direction, Slocik and Naik have developed approaches to make bimetallic Au-Pd nanoparticles[173] and CdS-Pt nanoparticle systems which exhibited high catalytic activity for the reduction of nitrate to nitrite.[174] This study elegantly demonstrates the potential of peptide-based methods for preparing multicomponent and multifunctional inorganic nanostructured materials. It is also expected that more insight into peptide design should lead to new peptides or peptide conjugates that control not only the simultaneous nucleation of multiple different inorganic nanoparticles but also their assembly into superstructures.

Although nanoparticle superstructures are envisioned to have many applications, it remains to be determined which applications are best targeted with superstructures constructed by using peptide-based approaches. One must consider the scale of the application and associated costs when selecting target applications. At this stage, peptide-based approaches may be best for applications that do not require large amounts of material, such as diagnostic sensing. To target larger scale applications, methods must be developed for producing mass quantities of peptides at low cost.

With many opportunities still on the horizon, we anticipate that continued creative and collaborative research in this area by chemists, biologists, and materials scientists will lead to increasingly complex materials with increasingly complex functions and advanced applications.

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