Perspective

Modular Materials by Self-Assembly

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Self-assembly is a promising route to producing materials and other chemical products with unprecedented functionality for biomedical, electronic, catalytic and separation process technologies. However, self-assembly will not achieve its full potential unless it is taken seriously as a manufacturing process, as opposed to a laboratory technique, and the obstacles to large-scale implementation are tackled and surmounted. This article, which is an extension of an earlier AIChE Journal Perspectives *article, defines and suggests important research directions for chemical engineers in an effort to develop self-assembly into a practical process technology.* © 2005 American Institute of Chemical Engineers *AIChE J,* 51: 2386–2390, 2005

Introduction

Self-assembly is an approach being explored for materials creation and manufacture that draws inspiration from biology. The principle of materials synthesis by self-assembly is to build into constituent parts of a materials system (molecules, particles, objects, etc.) sufficient information content so that the desired structure forms spontaneously, moving to a minimum free-energy state by sampling an ensemble of possible configurations. The ability to sample many configurations implies that noncovalent bonding, with energies of relatively small multiples of kT, is the general mode of interaction and bonding among constituents, although assembled systems maybe toughened after assembly by polymerization or other means. The role of self-assembly in biology, in creating intricate, highly functional materials structures and systems, gives rise to the many efforts attempting to exploit self-assembly for the manufacture of synthetic structures and systems.

Although self-assembly occurs frequently in biology, translating that bioinspiration to efficient and controllable chemical processing presents many significant and interesting problems. Complexity, in the sense of development of emergent properties of an assembly that cannot readily be envisioned from the constituents (Ottino, 2003), can arise spontaneously during self-assembly and often does, especially in biological systems. The potential advantages of self-assembly for the manufacture of synthetic materials are many, including:

1. Simultaneous parallel processing of multiple components for multiple products in the same reaction;
2. Access to length scales in structured products that are not achievable by other means (photolithography, laser machining and other such "top-down" methods);
3. Utility for many classes of materials;
4. Defect resistance in the sense that defects raise the free energy of the system and self-assemblers by definition seek the optimum configuration;
5. Inexpensive processing equipment.

The modularity inherent in this approach to synthesis of functional materials systems and devices also mimics biology (Hartwell et al., 1999), which places a high degree of importance on the precision synthesis of the assembling components. Limitations on using self-assembly as a manufacturing method are not inherent but rather have to do with the development of practical implementation. A challenge for chemical engineers is to develop the practical routes to technologically important self-assembly processes. Applications will be to biomaterials (Silva et al., 2004), porous materials for catalysis and separation (Cha et al., 2000), electronic (Whitesides and Grzybowski, 2002) and photonic devices (Bocksteller and Thomas, 2004; Manoharan and Pine, 2004), and many other areas.

A previous article (Texter and Tirrell, 2001) posed the question, "What are the barriers to development of self-assembly and its widespread implementation in the commercial sector?" and focused on a set of challenges to the practical realization of self-assembly processing, including precision synthesis of self-assembly precursors, scaleup, kinetics and mechanisms, and characterization and control. In this article, precision synthesis is explored in more detail, along with a set of other important issues, including expanding the idea of the molecule, bonding and interactions, and introduction of programmability and addressability, which represent new frontiers in self-assembly processing and products.

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Precision synthesis of precursors. The ability to form a desired state of organization spontaneously depends on the internal structure of the assemblers. Information (internal guidance for assembly) must be built into the assembling objects with some degree of fidelity. There are various avenues for achieving this. Size, shape (in rigid objects), conformation (in flexible objects), sequence (in multicomponent macromolecules), spatial relationships among subunits all can be "read" in molecular recognition interactions. Impurity in assembling molecular structure creates disorder or other degradation in quality in the self-assembled product.

Only biological systems currently achieve precise syntheses of molecules of more than a few hundred daltons. There are two broadly thought-provoking points in this realization for current self-assembly research. One is that *precision synthesis* and fidelity of information content *is essential* for effective self-assembly of intricate, functional systems. It will be fruitful to understand, in much more detail than we currently do, the sensitivity of various synthetic self-assembly processes to the lack of precision in the architecture of the assemblers. A second lesson that may be extracted arising from consideration of biological self-assembly is understanding of how nature achieves precision synthesis. *Biological systems do not synthesize perfectly*; rather, considerable effort is expended in detecting and correcting errors en route to a pure product. The chemical processing analogs of this are on-line measurement, control and post-reaction separation processes. To achieve the necessary control over molecular architecture, it will be necessary to explore both chemical and biological synthesis routes with a realistic eye toward process efficiency.

The future of self-assembly processing, if it is to fulfill its potential in modular assembly over a hierarchy of length scales from molecular to macroscopic, will perforce encompass the organization of components or modules that are very much larger than even the typical polymer molecules weighing hundreds of kilo-daltons. Since we know, for example, from studies of protein folding after site-directed mutagenesis (Smith, 1994), that very minor modifications of structure of the assemblers (primary structure of the protein, in this example) can lead to significant differences in structure and function of the assembled object (folded protein with tertiary structure, in this example), the precision and fidelity with which we can synthesize, and ultimately manufacture, assembling components is a key issue in the future of self-assembly processing.

With molecular objects, such as polymer molecules, precision syntheses via some variety of controlled chain-growth polymerization reactions, such as anionic (Cha et al., 2000), and controlled free-radical mechanisms, such as ARTP (Matyjaszewski and Xia, 2001), and RAFT (Pyun et al., 2003), are being employed. In practice, controlled radical reactions are increasingly being used owing to their broader versatility and comparative insensitivity to reaction conditions and impurities.

For larger objects designed for assembly, to which we will apply the generic term "nanoparticle", a variety of new synthetic routes are being developed, including micelle-templated synthesis (André et al., 2000), membrane-templated synthesis (Natan et al., 2001; Wu et al., 2004), kinetically controlled growth (Alivisatos et al., 2000), and a variety of deposition methods (Van Duyne et al., 2002, Jin et al., 2003). Figure 1 shows an example of nanoscale tetrahedral prisms made from silver. There is approximately a 20% variation in size among these prisms which is generally speaking a reasonably high degree of control, but is by no means monodisperse. This raises two interesting points. The first is that evidently these nanoparticle synthesis methods are becoming capable of significant levels of precision. The second is the open matter of whether or not this level of precision is sufficient to yield assembled structures with low levels of defects and high degrees of reproducibility. These are same sorts of questions as have been raised earlier with respect to molecular assembly (Barron and Zuckermann, 1999). Whether with macromolecules or with nanoparticles, we are only beginning to develop sufficiently sophisticated synthetic assemblers to mimic biology in this way, as illustrated in Figure 2, from Simon et al. (2001).

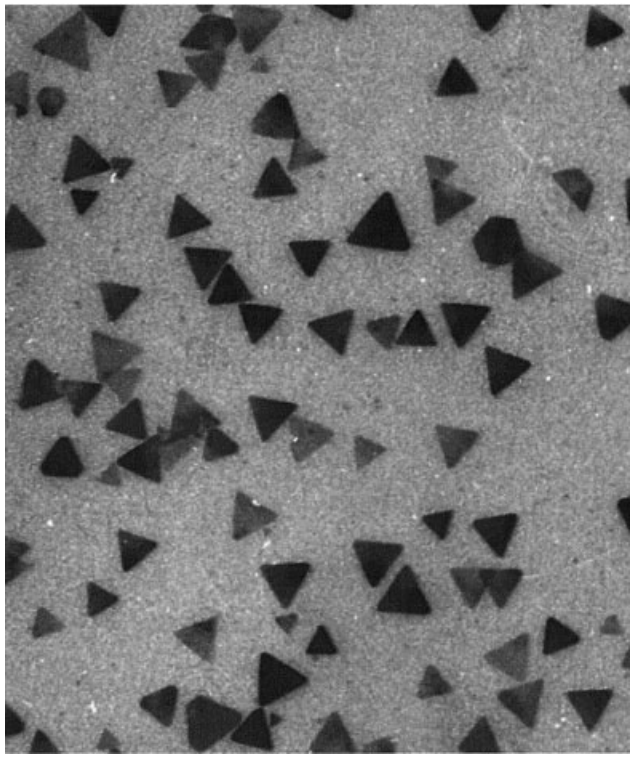

Figure 1. Unimodal growth of silver nanoprisms through the photoinduced transformation of a colloidal suspension (courtesy of C. A. Mirkin).

Prism edge lengths in this image are 120 ± 14 nm.

Expanding the idea of the molecule. The implication of the greater control of nanoparticle synthesis discussed in the preceeding paragraph is that self-assembly will increasingly involve the spontaneous organization of objects considerably larger than molecules. It is, therefore, useful to begin to think about larger assembling objects in self-assembly processes as we do about molecules in chemical reactions. The atomic and molecular notions of valence, bond strength, bond order, etc., have inexact but pragmatic counterparts when applied to interactions among structured macromolecules, nanotubes, particles and other important self-assembly constituents. Figure 3 (from Manoharan et al., 2003) shows that composite, or structured, collodial nanoparticles can be formed by the controlled consolidation of primary particles. The symmetry of these structured particles endows them with the potential for directional

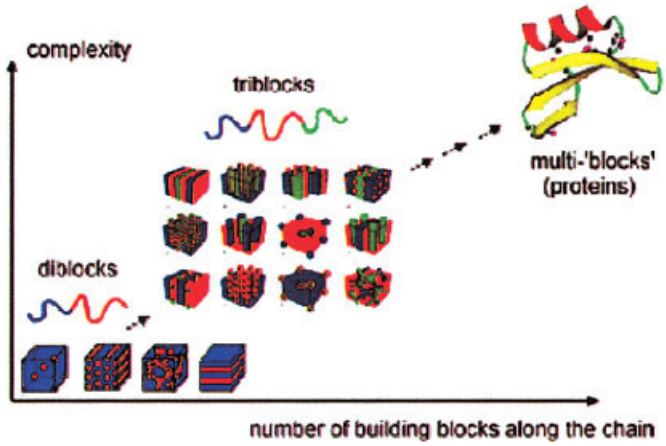

Figure 2. Increasing complexity possible in macromolecules as the numbers of types and sequences of monomeric units increase (adapted from Simon et al., 2001).

bonding, the molecular analog of the symmetry of electronic wavefunctions.

Another relevant example of an enlarged definition of the molecule is shown in Figure 4. In our group, we have been exploring the properties and applications of synthetic peptide-lipid conjugate molecules (Tirrell et al., 2003).

The idea of these molecules is to confer on unstructured, short, potentially biologically active peptide chains, some self-assembly character that will organize and present the functional peptide in an effective way. We have found that micelles formed from these peptide amphiphiles resemble proteins in several significant, and possible useful, ways, enumerated in Figure 4. We now know (Yu et al., 1999) how to use this self-assembly character to drive the peptide into ordered secondary structures as they are found in intact protein macromolecules.

Peptide amphiphiles typify the modular approach to materials construction by self-assembly. The peptide portions display biological activity; the lipid portions confer a self-assembly character to the molecule from which the protein-like structure results. Protein analogous micelles are objects that can mimic protein molecules and, in this way, expand the notion of how to use protein functionality in self-assembly.

Programmability and addressability in self-assembly. Specific, reversible, noncovalent interactions among molecular building blocks are the basis for development of functional biological structures in nature (Klug, 1983). Recent decades have seen exciting results of the exploration of the introduction of noncovalent interactions into synthetic materials science, both nonspecific interactions, such as those leading to hydrophobic self-assembly and, more recently, specific, reversible interactions. (for example: Lehn, *Supramolecular Chemistry*, 1994, Brunsveld et al., 2001). For macromolecular materials, specific, reversible, noncovalent interactions are (1) a means of creating chain connectivity and topology that differs from covalent bonding, and (2) a means of developing energetically favorable, attractive interactions among segments that differ from the generally energetically unfavorable, nonspecific van der Waals interactions that govern polymer phase behavior.

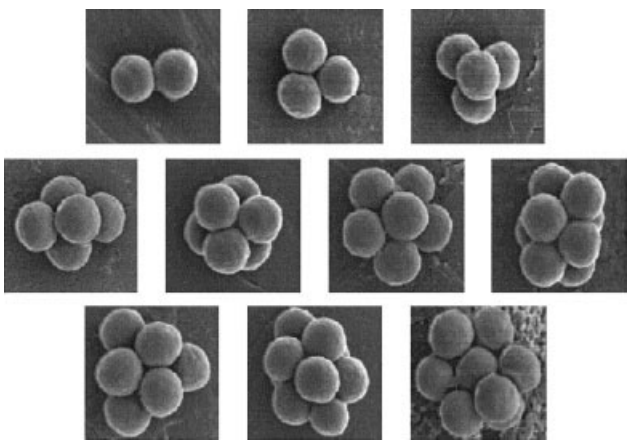

Figure 3. Geometrically precise aggregates of polystyrene latex spheres created by evaporation of toluene from a microemulsion (courtesy of D. J. Pine).

These aggregates are minimum moment structures (see Manoharan et al., 2003).

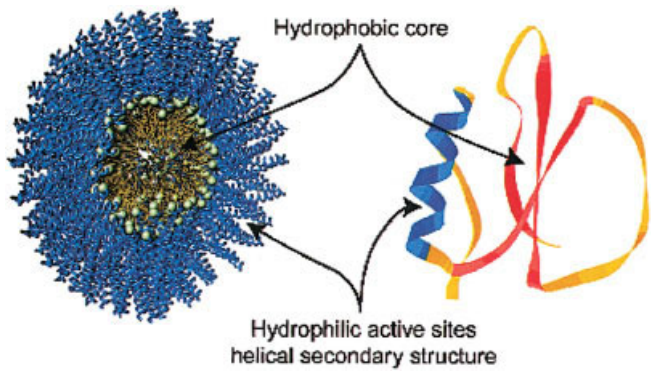

Figure 4. Analogy between a micelle of peptide amphiphiles (protein analogous micelle) and a protein macromolecule.

The micelle, as in the protein, has a hydrophobic core with biologically modules oriented outward. The two objects, both organized by a form of self-assembly, are similar in size. The micelle can be converted into a unimolecular object by photopolymerization of the lipid tails.

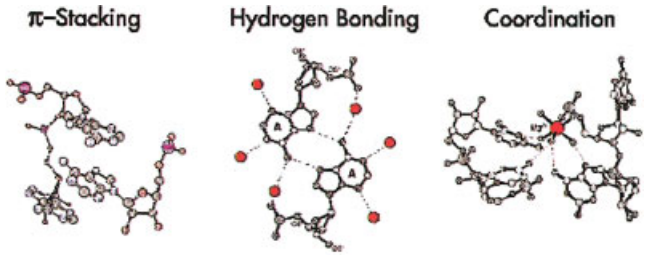

Figure 5. The three principal types of reversible, specific, noncovalent interactions, which enabling the incorporation of addressable and programmable elements into self-assembling structures.

"Specific" is a key word here, which we use to differentiate interactions, such as those exemplified in Figure 5, from nonspecific, but still useful reversible, interactions, such as hydrophobic interactions or χ parameters, based on van der Waals forces. Specific implies more than simply attractive and reversible; it implies molecular recognition, directionality, tunability of interaction strength, addressability and programmability of the self-assembly character built into molecules via these interactions. These are powerful characteristics to build into the development of new materials.

Nucleic acids, owing to the crucial role they have in storing and transcribing genetic information, have employed these types of interactions in a particularly highly developed form of self-assembly, namely nucleotide base-pairing. In the context of looking at the future of self-assembly, it is interesting to consider the possibilities for self-assembly processing that could result from the degree of specific assembly that could be achieved either by incorporating nucleic acids into products or by developing synthetic mimics of the specific, reversible, noncovalent interactions that enable nucleic acid assembly.

The pioneering work of Seeman, and more recently Mirkin and others, has shown that it is possible to direct the precise assembly and organization of materials relying on nucleic acid base pairings (Yan, 2004; Seeman, 2003; Mirkin, 2000, Alivisatos, 1996, Batey et al., 1999). Nucleic acids can be programmed at the level of their sequence to assemble with exquisite precision, and to specify functional 3-D shapes with predefined topologies. Although most scrutiny has been given to DNA, RNA may offer a richer repertoire of functional and rigid structural and motifs that can be used in supra-molecular engineering (Westhof et al., 1996; Jaeger et al., 2000, 2001, 2004) Despite the crucial importance of base pairing specificity to the central dogma of biology, and a few demonstrations of the possibilities for materials science, the power of nucleic acid programming of material structures remains largely unexplored and unexploited. There are many opportunities to explore integration of nucleic acid based materials with the elements of more traditional macromolecular science including using nucleic acids to template the synthesis of other materials, and conjugating and coupling nucleic acid elements to peptides, lipids and other entities. (Gore et al., 2001; Vernille et al., 2004; Vernille and Schneider, 2004).

Multiple specific, reversible interactions built into the same assembling system give rise to the possibility to assemble multiple, different components in parallel. Parallel processing is one of the great processing advantages of self-assembly. Programmability refers to this parallel assembly guidance capability. An additional capacity that multiple, specific interactions enables is addressability, which is the ability to recognize or differentiate specific sites in the assembled product. This in turn allows subsequent stages of assembly to build on the template formed by programmable self-assembly.

Conclusions

Self-assembly has unique capabilities as a chemical processing method. Thus far it has penetrated little from the laboratory to manufacturing. The limitations on its employment as a manufacturing route appear to be practical rather than fundamental. The principal aim of this article is to give a glimpse of areas of important research opportunities, experimental, theoretical and computational, which we expect will lead to the development of commercially significant processing efforts.

Acknowledgments

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