Molecular Self-Assembly and Nanochemistry: A Chemical Strategy for the Synthesis of Nanostructures

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Molecular self-assembly is the spontaneous association of molecules under equilibrium conditions into stable, structurally well-defined aggregates joined by noncovalent bonds. Molecular self-assembly is ubiquitous in biological systems and underlies the formation of a wide variety of complex biological structures. Understanding self-assembly and the associated noncovalent interactions that connect complementary interacting molecular surfaces in biological aggregates is a central concern in structural biochemistry. Self-assembly is also emerging as a new strategy in chemical synthesis, with the potential of generating nonbiological structures with dimensions of 1 to 10^2 nanometers (with molecular weights of 10^4 to 10^{10} daltons). Structures in the upper part of this range of sizes are presently inaccessible through chemical synthesis, and the ability to prepare them would open a route to structures comparable in size (and perhaps complementary in function) to those that can be prepared by microlithography and other techniques of microfabrication.

NANOSTRUCTURES ARE ASSEMBLIES OF BONDED ATOMS that have dimensions in the range of 1 to 10^2 nanometers (1 nm = 10^{-9} M = 10 Å) (*1*). Structures in this range of sizes can be considered as exceptionally large, unexceptional, or exceptionally small, depending on one's viewpoint, synthetic and analytical technologies, and interests (Fig. 1). To solid-state physicists, materials scientists, and electrical engineers, nanostructures are small. The techniques, such as microlithography and deposition from the vapor, that are used in these fields to fabricate microstructures and devices require increasingly substantial effort as they are extended to the range below 10^2 nm. To biologists, nanostructures are familiar objects. A range of biological structures—from proteins through viruses to cellular organelles—have dimensions of 1 to 10^2 nm. To chemists, nanostructures are large. Considered as molecules, nanostructures require the assembly of groups of atoms numbering from 10^3 to 10^9 and having molecular weights of 10^4 to 10^{10} daltons. Synthetic techniques that generate well-defined structures at the lower ends of these ranges are only now being developed and the upper ends remain largely unexplored.

Developing techniques for synthesizing and characterizing ultralarge molecules and molecular assemblies—nanostructures—is one of the grand challenges now facing chemistry. How can one make structures of the size and complexity of biological structures, but without using biological catalysts or the information coded in genes? Nanostructures provide major unsolved problems in complexity and require new strategies and technologies for their synthesis and characterization. The solutions to these problems would be both interesting in themselves and essential elements in extending chemistry toward problems in materials science and biology.

The stimuli for development of new strategies for synthesis applicable to nanostructures have so far come primarily from biology (*2*). One major focus of nanochemistry to date has therefore been to attempt to understand and use the astonishing variety of sophisticated strategies and processes encountered in living systems. Increasingly, however, nanochemistry is being appreciated as a subject with very broad implications, and as one that would ultimately involve many areas (*3*): interface (*4*) and colloid science (*5*), molecular recognition (*6*), electronics microfabrication (*7*), polymer science (*8*), electrochemistry (*9*), zeolites and clay chemistry (*10*), scanning probe microscopy (*11*), and others. At present, approaches to nanostructures based on chemical synthesis are less highly developed than approaches through microfabrication (*12*). Chemical synthesis offers, however, the appeal of a level of control over the selection and placement of individual atoms that is ultimately much higher than that achievable by other methods of fabrication. (This increased control over individual nanostructures is purchased at the cost of increased difficulty in building regular arrays of nanostructures of the type required in microelectronic systems.) Molecular self-assembly has the additional attraction that it generates structures that occupy thermodynamic minima. These structures can be both robust and intrinsically very resistant to the incorporation of impurities.

In this article we first sketch four strategies now followed in the synthesis of large molecules and assemblies: (i) controlled formation of covalent bonds, (ii) covalent polymerization, (iii) self-organization, and (iv) molecular self-assembly. We point out the characteristics of molecular self-assembly that make it especially suitable as a method for preparing nanostructures. We then give examples of self-assembly of nanostructures drawn from biological systems to illustrate the characteristics of this type of process. We touch very briefly on the important matter of the entropy of self-assembly, to highlight the fact that understanding and controlling the entropy of reaction is substantially more important in this synthetic strategy than in others. We then list the types of interactions available for use in self-assembly, and outline their characteristics. We close with examples of nonbiological nanostructures prepared by self-assembly and with speculation concerning the future directions of the field.

Four Strategies Used in Chemical Synthesis

The central focus of synthetic chemistry has been the molecule (*13*). Chemists (organic chemists in particular) have developed extraordinarily sophisticated procedures for assembling molecules,

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based on a general strategy of sequential formation of covalent bonds, usually one or a few at a time. This first strategy for synthesis, sequential covalent synthesis, has culminated (at least for the present) in syntheses of the very complex molecules vitamin B_{12} (*14*) and palytoxin (molecular weight 2680) (*15*).

Sequential covalent synthesis can be used to generate arrays of covalently linked atoms with well-defined composition, connectivity, and shape. It can generate structures that are far from the thermodynamic minimum for that collection of atoms. It also requires enormous effort when applied to molecules as large and complex as palytoxin. Although its underlying strategy, individually controlled formation of covalent bonds, can in principle be extended to yet larger structures, in practice, at this time, it does not seem to offer a practical route to true macromolecules (substances with molecular weights of 10^4 to 10^7 daltons) or to nanostructures (although it would be indispensable in preparing the molecular components to be used in syntheses of these structures based on molecular self-assembly).

The second synthetic strategy now used, covalent polymerization, is the most important for preparing molecules with high molecular weights (*16*). A relatively simple, reactive low molecular weight substance (a monomer) is caused to react with itself in a process that produces a molecule (a polymer) comprising many covalently connected monomers. The prototype of this synthetic strategy is the conversion of ethylene to polyethylene. The molecular weight of polyethylene can be high ($>10^6$ daltons), and it is easily prepared, but the molecular structure is simple and repetitive and the process by which it is formed offers only limited opportunity for controlled variation in this structure or for control of its three-dimensional shape. Polymerization does indirectly provide synthetic routes to stable nanostructures [for example, phase-separated polymers (*8, 17*) and polymer lattices (*18*)], but until the rules defining noncovalent interactions in these systems are better defined it is limited in the control it can provide over the positions and covalent connectivity of individual atoms and in the shapes of the final nanostructures.

The third synthetic strategy widely used abandons the covalent bond as a required connection between atoms and relies instead on weaker and less directional bonds, such as ionic bonds, hydrogen bonds, and van der Waals interactions, to organize atoms, ions, or molecules into structures. For lack of any generally accepted name to describe this class of methods, we refer to them collectively as "self-organizing syntheses." Molecular crystals (*19*), liquid crystals (*20*), colloids (*21*), micelles (*22*), emulsions (*23*), phase-separated polymers (*8, 17*), Langmuir-Blodgett films (*24*), and self-assembled monolayers (*25*) represent examples of types of structures prepared with these techniques. The distinguishing feature of these methods is self-organization. The molecules or ions adjust their own positions to reach a thermodynamic minimum; the chemist does not specify these positions.

Certain of the structures prepared by self-organization are, in fact, true nanostructures, and these structures could eventually be incorporated into nanostructure technology. For example, the degree of control and technological sophistication necessary to prepare crystals of silver halide appropriate for use in silver halide–based photography (*26*) is qualitatively comparable to that required to prepare gallium arsenide quantum dots by microlithography (*27*), and colloid chemistry (*21*) is one of several increasingly interesting routes to quantum structures (*28*).

The fourth strategy used in synthesis, and the one most relevant to nanostructures, is molecular self-assembly: that is, the spontaneous assembly of molecules into structured, stable, noncovalently joined aggregates (*29*). Molecular self-assembly combines features of each of the preceding strategies to make large, structurally well-defined assemblies of atoms: (i) formation of well-defined molecules of intermediate structural complexity through sequential covalent synthesis; (ii) formation of large, stable structurally defined aggregates of these molecules through hydrogen bonds, van der Waals interactions, or other noncovalent links; and (iii) use of multiple copies of one or several of the constituent molecules, or of a polymer, to simplify the synthetic task. The key to this type of synthesis is to understand and control the noncovalent connections between molecules and to understand and overcome the intrinsically unfavorable entropy involved in bringing many molecules together in a single aggregate.

For the final assembly to be stable and to have well-defined shape, the noncovalent connections between molecules must collectively be stable. The strengths (*30*) of individual van der Waals interactions and hydrogen bonds are weak (0.1 to 5 kcal/mol) relative to typical covalent bonds (40 to 100 kcal/mol)

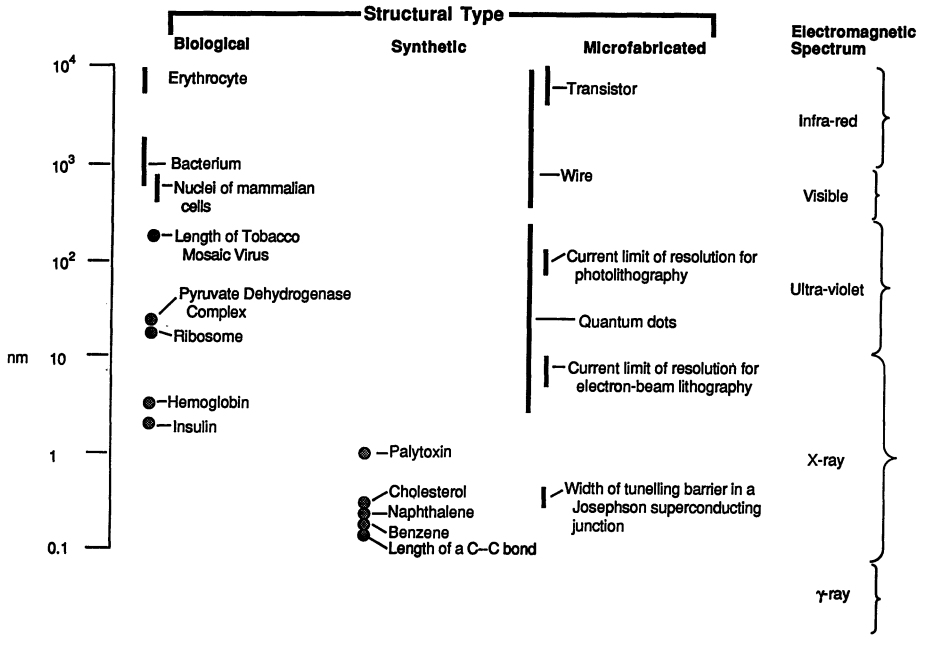

Fig. 1. A comparison of the relative sizes of structures generated in biology, synthetic chemistry, and microfabrication. The scale (left) is logarithmic and the electromagnetic spectrum (right) is included as a reference. Both biology and microfabriction provide examples of structures with dimensions ranging from 1 to 10^4 nm. Structures prepared by chemical synthesis are concentrated in the 0.1- to 2-nm range. The application of self-assembly in chemical synthesis may make it possible to obtain structures that have sizes of 10 to 10^3 nm.

and comparable to thermal energies ($RT \simeq 0.6$ kcal/mol at 300 K). Thus, to achieve acceptable stability, molecules in self-assembled aggregates must be joined by many of these weak noncovalent interactions (that is, large complementary areas of molecular surface in interacting pairs of molecules must be in van der Waals contact) or by multiple hydrogen bonds, or both. Moreover, these interactions between molecules or parts of molecules must be more favorable energetically than competing interactions with solvent and must be able to overwhelm the entropic advantages of disintegration of the ordered aggregate into a disordered or dissociated state. Biology is replete with examples of complex, nanoscale structures formed by self-assembly (*31*), and living systems have mastered the art of summing many weak interactions between chemical entities to make large ones. Chemists are just beginning to learn this art.

Biological Precedent for Modular, Noncovalent Molecular Self-Assembly

Protein folding. This ubiquitous process in biology illustrates many of the noncovalent interactions involved in self-assembly in aqueous solution (*30–32*). A polypeptide is synthesized as a linear polymer derived from the 20 amino acids by translation of a sequence present in a messenger RNA. The mature protein often has a compact, well-defined three-dimensional structure (Fig. 2). Proteins are believed to be thermodynamically stable structures (*32*). Thus, the "information" necessary to specify the final three-dimensional protein structure must be present in the amino acid sequence of the protein backbone. Analysis of the thermodynamics of protein folding (*33*) (and of many related association processes occurring in biology) are usually phrased in terms of a limited number of types of interactions: electrostatic interactions involving charged groups and electrical dipoles; hydrogen bonds; van der Waals interactions; and interactions of charged and uncharged groups with water. The interaction of nonpolar groups with water and with one another is a particularly important combination that is given the name "hydrophobic effect" (*34, 35*).

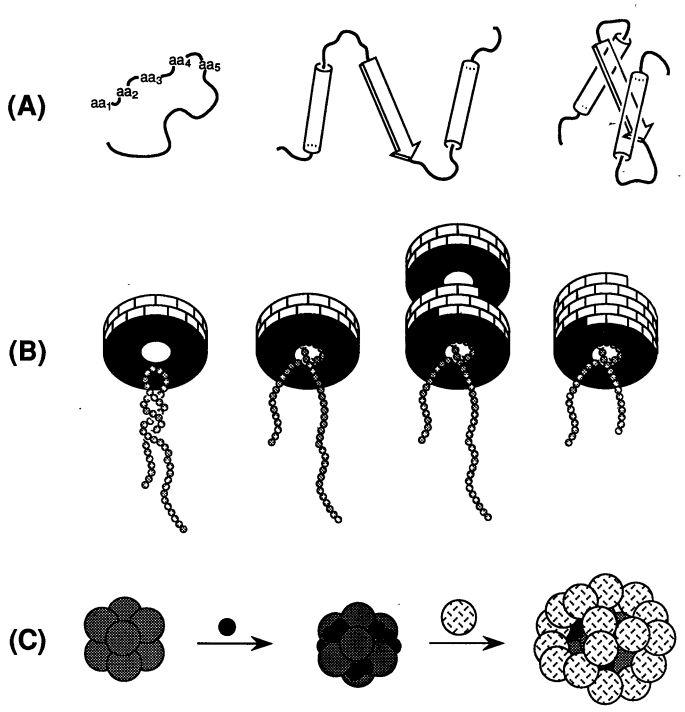

Fig. 2. Three biological examples of self-assembling nanoscale structures. (**A**) A schematic representation of the process of protein folding. This process is shown schematically in three stages: the unfolded primary amino acid sequence; with the formation of structural motifs (domains); and the folding of these structures into the final protein conformation. (**B**) Self-assembly of the tobacco mosaic virus. (**C**) Formation of the pyruvate dehydrogenase complex.

Although the amount of "information" that could be coded in a protein sequence is very large (a polypeptide containing 200 amino acids could have $20^{200} \simeq 10^{260}$ different sequences, each, in principle, having a different structure), the broad principles (although not the crucial local details) of protein folding seem relatively simple (*32*). Particular sequences of amino acids (or types of amino acids) tend to reoccur, and to form a relatively small number of local structural "motifs" (*36*) (helix and sheet structures associated through networks of hydrogen bonds); these motifs tend to aggregate in the protein in ways that associate hydrophobic regions with one another and out of contact with water and to place hydrophilic regions in contact with water. Thus, self-assembly in proteins (that is, folding) can be considered to involve two types of processes: formation of relatively simple local structures (helices, sheets) from an unfolded polypeptide chain; and more complex, structure-specific association of these local structures. Understanding and controlling the structures and processes that form the local structures is well advanced (*37*). Understanding both the much more complex associations between the arrays of side-chain groups presented on the surfaces of these local structures and the other important local interactions (including the interactions with solvent) is only just beginning (*38*).

Formation of protein aggregates. The association of proteins into functional aggregates is a theme that recurs throughout biology, from relatively simple examples [the association of four hemoglobin molecules into a tetramer or six insulin molecules into a hexamer (*39*)] to extremely complex ones [formation of the ribosome (*40*)]. Formation of this latter structure (which is responsible for the translation of mRNA to protein) has been examined in detail and demonstrated to involve the ordered self-assembly of 55 proteins and three strands of RNA. The pyruvate dehydrogenase complex is a particularly good example of the self-assembly of protein aggregates (*31*). Three types of protein are involved in this process: 8 trimeric units (24 protein molecules) of dihydrolipoyl transacylase; 12 molecules of dihydrolipoyl dehydrogenase; and 24 molecules of pyruvate decarboxylase aggregate and generate a structure with a diameter of ~30 nm.

An important feature that seems to characterize these self-assemblies in biology is cooperativity: that is, the modification of the conformation of individual particles on binding in a way that increases their affinity for the other components. Most of these systems exist in "all-or-none" complexes: either the fully formed aggregate is present, or the completely dissociated components, but not an equilibrium mixture of intermediate aggregates. Although it has been possible to rationalize this type of cooperativity after the fact by associating it with conformational changes and intermolecular contacts observed in crystal structures, predicting cooperativity and designing self-assembling aggregates is only now beginning to be possible in nonbiological systems.

An example of a complex self-assembling biological nanostructure that has been examined in great detail is tobacco mosaic virus (TMV) (*41*). Indeed, many of the concepts of biological self-assembly are derived from studies of TMV. TMV itself is a helical virus particle with dimension 300 nm by 18 nm. This virus is composed of 2130 identical protein units, each with 158 amino acid residues, that form the viral protein coat around a single

stretch of RNA that comprises ~6400 nucleotides. Since it was demonstrated that TMV could be dissociated into its component parts and these parts reconstituted successfully in vitro to reform an intact, fully infectious virus particle—that is, a structure that is indistinguishable from the original virus—the actual mechanism of this assembly process has been studied extensively (*41–43*). The picture that has emerged (*41*) is one in which, under physiological conditions, the coat proteins first self-assemble into a stable disk subunit. This disk corresponds to two turns of the final helix structure. These stable self-assembled disks then associate with the viral RNA to form the intact virus. This association process is entropically driven (*41, 43*).

The use of a single protein in the coat necessitates only a single set of binding interactions—between proteins in the individual disks and subsequently between the disks themselves—to anchor the structure together. This feature reduces greatly the molecular information that is required in molecular recognition and self-assembly. The association of the protein into a disk subassembly through reversible, noncovalent interactions allows the process of assembly and disassembly to be dynamic: each stage is at or close to equilibrium. This mechanism is therefore capable of undoing occasional errors that may occur during the assembly process: that is, the process is intrinsically error-checking and error-correcting. The disk subunits assemble around the viral RNA in a manner more efficient than the stepwise growth of the helix by addition of single protein units.

Pairing of nucleotides. A particularly important example of self-assembly, and one that, by virtue of its simplicity, has provided the greatest stimulus to efforts to design nonbiological self-assembling structures, is that provided by nucleic acids (*44*). Familiar examples are the formation of double-stranded DNA by association of two complementary chains of DNA (*45*) and the intramolecular folding of tRNA (*46*). These structures rely in part on complementary patterns in hydrogen-bond donation and acceptance for their form. Because these patterns can be easily replicated synthetically, and because hydrogen bonds are substantially better defined in their directionality than are van der Waals interactions, molecules capable of formation of networks of hydrogen bonds have become the foundation for much of the current work in chemistry in molecular recognition and self-assembly.

Some principles of biological self-assembly. The single feature common to all of these biological structures is the reliance upon noncovalent self-assembly of preformed and well-defined subassemblies to obtain the final structure, rather than the creation of a single, large, covalently linked structure. Biological self-assembly can thus be described by a series of principles that are often (but not always) obeyed:

1) Self-assembly involves association by many weak, reversible interactions to obtain a final structure that represents a thermodynamic minimum. Incorrect structural units are rejected in the dynamic, equilibrium assembly. This equilibration allows high fidelity in the process.

2) Self-assembly occurs by a modular process. The formation of stable subassemblies by sequential covalent processes precedes their assembly into the final structure. This mechanism allows for efficient assembly from the preformed units [a "convergent synthesis," in the terms of organic chemistry (*47*)].

3) Only a small number of types of molecules are normally involved in modular self-assembly. Consequently, a limited set of binding interactions is required to cause the final structure to form. This principle minimizes the amount of information required for a particular structure.

4) Self-assembly often displays positive cooperativity.

5) Complementarity in molecular shape provides the foundation for the association between components. Shape-dependent association based on van der Waals and hydrophobic interactions can be made more specific and stronger by hydrogen bonding and electrostatic interactions.

To summarize these observations, biological self-assembly requires only the information embodied in the shape, surface properties, and deformability of a limited number of molecular precursors. The association between these precursor molecules involves noncovalent interactions and generates a structure that is a thermodynamic minimum. This aggregate of molecules is stabilized by contacts between molecular surfaces of complementary shape; the stabilizing interactions are distributed over a large number of individually weak interactions, rather than concentrated in a small number of strong covalent bonds.

Thermodynamic Issues in Molecular Self-Assembly

Because self-assembled structures represent thermodynamic minima, because they are formed by reversible association of a number of individual molecules, and because the enthalpies of the interactions holding these molecules together are relatively weak, the interplay of enthalpy and entropy (ΔH and ΔS) in their formation is more important than in syntheses based on formation of covalent bonds (Fig. 3). The values of ΔH for the interactions that hold together self-assembled structures vary widely, but representative values are on the order of 2 to 20 kcal/nm^2 of complementary molecular surface (*35*). What are the contributions of the entropy of formation ($T\Delta S$) of self-assembled aggregates to the free energy ΔG?

Entropy of reaction is usually secondary in importance in reactions that form a covalent bond irreversibly. It can be much more important in equilibrium reactions. As rule-of-thumb approximations, the loss in translational entropy on bringing together two particles originally at millimolar concentration contributes approximately $-T\Delta S \simeq +5.5$ kcal/mol to ΔG, and the loss in conformational entropy in freezing a freely rotating bond with three equally populated conformations in one conformation contributes approximately $-T\Delta S \simeq +0.7$ kcal/mol. If there are a number of particles associating, and if a number of conformationally mobile sections of the participating molecules are frozen on aggregation, the sum of these unfavorable entropic terms can be significant. These considerations suggest that molecules designed for self-assembly should be as rigid as is consistent with achieving good intermolecular contact between the interacting surfaces (*48*) and that the area of contacting molecular surface be made large. The criteria of rigidity and multipoint contact are also relatively easily met by using networks of hydrogen bonds in nonaqueous solvents, and these systems have, in consequence, been extensively examined as models for self-assembly.

In biological systems, understanding the thermodynamics of self-assembly is made difficult by several factors. First, water is a complicated solvent, and the thermodynamic origins of the hydrophobic effect remain a matter of discussion (*34, 35*). The entropically favorable release of structured water on association of hydrophobic regions of aggregating molecules is an important contribution to overcoming the unfavorable loss of translational entropy in this aggregation. Second, many intermolecular interfaces in aggregated biological systems involve macromolecules and can be large (1 to 5 nm^2). It is difficult to disentangle the contributions of individual organic groups (with areas of 0.05 to 0.5 nm^2) to these interfaces. Finally, changes in conformation on self-assembly are common but may be distributed as small changes

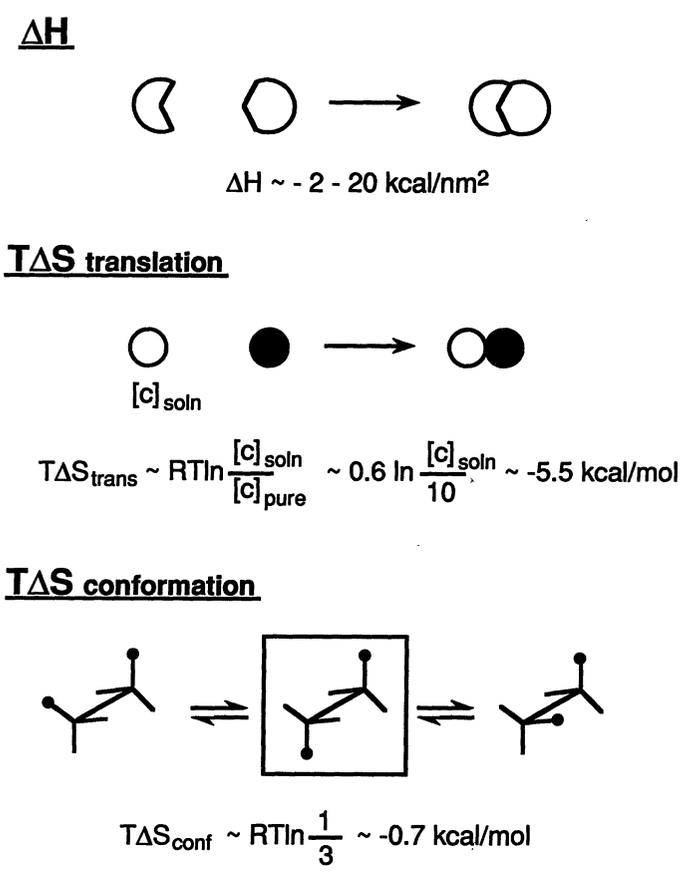

Fig. 3. Types of thermodynamic issues that are involved in molecular self-assembly. The values of ΔH vary widely depending on the type of molecular interactions that are involved. The value for $T\Delta S_{translation}$ is based exclusively on considerations of concentration and is provided only as an approximation. The value for $T\Delta S_{conformation}$ is of smaller magnitude than $T\Delta S_{translation}$ but the sum of many contributions, resulting from freezing conformations around many bonds in a large, flexible molecule, can make loss of conformational entropy significant in the thermodynamics of self-assembly processes.

in a large number of bonds. The enthalpic sum of these changes is again difficult to estimate. Computational systems capable of estimating enthalpies in biological association are developing rapidly (*49*), but approaches to estimations of entropies are at an early stage.

Types of Noncovalent Bonds or Interactions Available for Synthesis

The biological examples discussed display many, but not all, of the types of bonds or interactions that are plausible candidates for use in the formation of nanostructures. A number of nonbiological systems, especially those already showing self-organizing behavior, also offer examples of potentially useful interactions.

Molecular crystals are self-organizing (and, in the case of co-crystals, self-assembling) structures, and the interactions determining the relation between molecular structure and crystal structure are beginning to be disentangled (*50*). Liquid crystals are self-organized phases intermediate in order between crystals and liquids (*20*). Micelles (*22*), emulsions (*23*), and bilayers of detergents and lipids display a rich variety of self-organizing behaviors. Inorganic coordination chemistry and organometallic chemistry have categorized large numbers of distinct interactions between metal ions and ligands; many of these are reversible and selective

Table 1. Types of bonds and interactions applicable to molecular self-assembly. Boldfaced entries in the column headed "Examples" are important in (or taken from) biochemistry.

Bond type	Examples
Covalent bonds that can be formed and broken reversibly	Disulfides (RSSR, **ribonuclease**); vanadate and borate esters
Inorganic metal-ligand bonds	Metal salts; organometallic complexes; **zinc fingers** (*65*)
Hydrogen bonds	Crystalline urea; melamine cyanurate; **nucleotide base pairs; amide hydrogen bonds in proteins**
Electrostatic interactions involving charges	**Salt bridges in proteins**; cadmium arachidate bilayers
Electrostatic interactions involving dipoles	Crystalline IC_6H_4CN
Hydrophobic interactions	Micelles; Langmuir-Blodgett monolayers on water; **lipid bilayers, hydrophobic "cores" of proteins**, inclusion complexes with cyclodextrins (*66*)
Aromatic π-stacking and charge transfer	**Nucleic acids**; J-aggregates (*67*)
Van der Waals interactions	*n*-Alkane crystals; urea inclusion complexes

and thus are candidates for use in self-assembly (*51*). (Systems of inorganic reactions that are stable and reversible at high temperatures are particularly relevant to applications in materials science.) Molecular recognition and supramolecular chemistry are active fields of research concerned with noncovalent association (*52*). Colloid chemistry is able to precipitate small uniform crystals of inorganic solids with astonishing regularity in size and properties (*53*). Surface chemistry has already provided a number of successful applications of self-assembly (such as self-assembled monolayers and epitaxy) (*25*). Structures such as micelles and zeolites provide templates within which nanostructures can be formed (*54*).

The types of bonds and interactions that have the potential to be used in the design of self-assembling nanostructures are summarized in Table 1. Not all of these different labels represent completely different phenomena, but several are combinations that occur sufficiently frequently that they are often discussed as separate types of bonds. For example, the hydrophobic interaction combines van der Waals interactions with the enthalpic and entropic consequences of restricting the hydrogen bonding of water near a nonpolar interface (*34, 35*).

The success with which nanostructures can be prepared by self-assembly will depend on the success with which these interactions can be used to bind molecules into stable, structurally well-defined aggregates. The entries in Table 1 are arranged very qualitatively in terms of decreasing values of their free energy per unit of molecular surface area. The stronger the interaction, the smaller the area of molecular surface that must be designed to achieve a given strength of interaction, and the easier the synthetic task. Most work has so far focused on assemblies held together by hydrogen bonds in non–hydrogen bonding organic solvents (used to minimize competition of the solvent for the hydrogen bonds used in the self-assembly) (*55*). Van der Waals, π-stacking (*56*), and hydrophobic interactions are weak and nondirectional, and thus difficult to use in designing and synthesizing molecular surfaces of truly complementary shape. Interactions between charged groups have also been difficult to use because of strong interactions of these groups with solvents and counter ions and because they also are nondirectional.

Nanostructure Design and Synthesis

An example based on melamine cyanurate. An example of the application of the principles of self-assembly to the synthesis of a nanostructure carried out in our laboratory starts with the solid 1:1 complex formed on mixing melamine (M) and cyanuric acid (CA) in aqueous solution (*57*) (Fig. 4). This structure is very stable (it can be heated to 450°C without change) as a result of the network of hydrogen bonds that holds it together (*58*). It is the most symmetrical prototype for the arrays of hydrogen bonds found between base pairs in nucleic acids.

Our approach to the construction of a molecular aggregate with nanometer dimensions based on the CA·M lattice is sketched in Fig. 4 (*59*). We chose to use as our core structure two parallel planes of the CA·M lattice, each containing one hexagonal array of three CA units and three M units. To bring together 12 molecules into one is an unfavorable process entropically; moreover, even if the hydrogen-bond array were strong enough to permit assembly, there was every reason to expect them to assemble as one sheet, not two parallel sheets. Thus, both to minimize the entropic cost of self-assembly and to control the shape of the assembled nanostructure, we preorganized the CA and M units by connecting them with a benzene ring as a central "hub," with "spokes" designed to position the CA and M units in approximately the correct positions. (The delicate balance between entropy and enthalpy in these systems is underlined by the observation that if the spokes are made completely flexible, the desired structure does not self-assemble: the entropic cost of freezing conformational degrees of freedom in a long, flexible arm is larger than the enthalpic return of forming a network of hydrogen bonds.) The final aggregate forms quantitatively on mixing the components **1** and **2** in chloroform solution. It is roughly a sphere with diameter 2.5 nm.

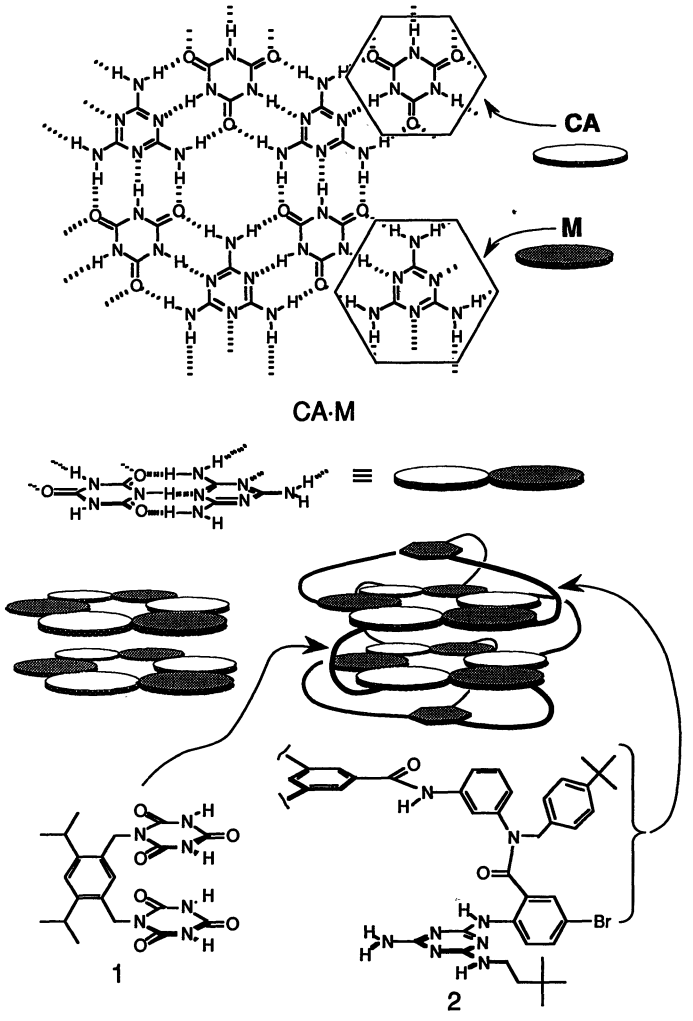

Fig. 4. The CA·M lattice is shown at the top of the figure. Cyanuric acid (CA) is represented by the nonshaded disks and melamine (M) by the shaded disks. The structure of the aggregate that forms upon self-assembly of three equivalents of **1** and two equivalents of **2** is shown schematically in the middle of the figure. The arrows indicate the correspondence between the chemical and the schematic representations.

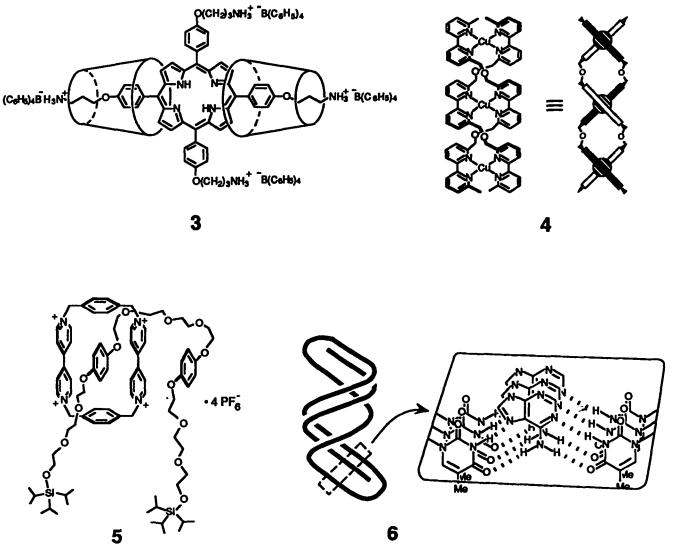

Fig. 5. Four examples of synthetic nanostructures based on self-assembly. The double helix **4** is presented both in chemical and schematic structures. A portion of the triple helix **6** is shown as a chemical structure to indicate the pattern of hydrogen bonds that hold the single strand of DNA within the circular polynucleotide loop.

This structure is a modest start along a pathway leading to functional nanostructures. It is relatively small (molecular weight 5519) and it has no function. It nonetheless illustrates the basic strategy of this type of synthesis: the use of reversible interactions (in this case, hydrogen bonds) to bind the participating molecules in the aggregate; preorganization of the interacting groups through networks of covalent bonds to control the entropy of association and to determine the shape of the aggregate; choice of the components so that they recognize each other with high selectivity; and design of the system to show positive cooperativity.

Other examples and approaches to nanostructures based on self-assembly. An important theme in current chemistry is the study of molecular recognition: that is, the specific, noncovalent association of one molecule with another. Specificity in association is also the hallmark of biological systems. Pairs of specifically interacting groups, properly positioned on different molecules, provide the basis for self-assembly. A number of examples drawn from recent studies are shown in Fig. 5. Complex **3** is based on hydrophobic association of β-cyclodextrin (*60*) (a toroid molecule that is a cyclic heptamer of glucose) with aromatic rings; the tetraphenyl borate anions seem also to be at least loosely associated with the ammonium center in this complex. The oligomer **4** is based on coordination of bipyridyl units to copper(II) ion, and is interesting for its helical structure (*61*). The toroidal bis-bipyridinium cyclophane in **5** is able to move back and forth along the backbone, a fact that has suggested its use in a fanciful "molecular abacus" (*62*). The triple helix **6** is a hydrogen-bonded complex that is formed between a circular polynucleotide and a complementary single strand of DNA (*63*). We

note that two of these four structures incorporate biologically derived components.

Chemical Synthesis and Molecular Self-Assembly Routes

The strategy outlined here—the use of reversible, noncovalent interactions to assemble relatively small molecules into aggregates of nanometer size—is a successful one. Biology provides countless examples; the essential principles are understood (although the details essential for applications are still murky). The study of molecular recognition is generating a range of specifically interacting pairs of molecules; the first purely chemical examples of nanostructures are appearing (*58–62*). There is little doubt that it should be possible to generate a broad range of types of nanostructures by using synthetic chemical approaches: that is, working "from atoms up" rather than by writing ever-smaller features with microlithography.

There remain of course a number of very important problems to resolve in this type of synthesis. How can van der Waals and hydrophobic interactions be used? They are ubiquitous in biological systems, but have been difficult to use by design in synthetic systems. How should hydrogen bonds be used in aqueous systems? Again, biological systems rely heavily on hydrogen bonding, but most synthetic systems based on hydrogen bonds disintegrate in the presence of solvents able to compete for the hydrogen bonds. How can cooperativity be built into systems? Broadly, how can one design and synthesize large areas of complementary molecular surface, since this type of complementarity is the basis for molecular recognition and self-assembly?

Beyond these questions, there is the broader issue: "Nanostructures for what purpose?" One drive for nanostructures in electronic systems has been that toward small, fast devices and high-density information storage. Even with microlithographically fabricated systems of semiconductors there are serious uncertainties about what types of structures to make to address these needs; with chemically synthesized systems, these uncertainties are even greater. Electronic device fabrication must generate arrays of interconnected nanostructures. Chemical synthesis would certainly be able to make nanostructures and may (by inclusion of appropriate electrically or optically functional groups) even be able to make nanostructures useful in electronic systems, but positioning these systems in arrays appropriately connected for use in information processing would require a new technology. The problem is not conceptually insoluble: self-assembly of these nanostructures by adsorption onto a grid written by x-ray or electron beam methods is one approach; active positioning of them with a scanning probe device (a derivative of an atomic force microscope) is a second (*64*); and approaches based largely on local connectivities (that is, cellular automata) might allow the nanostructures to self-assemble into an appropriate array, and would be a third.

A range of other, possible nonelectronic uses for nanostructures can be imagined: as components in microsensors; as the basis for new classes of micelles and colloids; as functional components in polymers; and as catalysts or recognition elements (analogous to enzymes and receptors).

The development of nanochemistry is just beginning, and current work is focused on strategies and tactics for synthesis of nanostructures. New ways of assembling molecules should lead to new ideas for their uses.

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Atomic and Molecular Manipulation with the Scanning Tunneling Microscope

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The prospect of manipulating matter on the atomic scale has fascinated scientists for decades. This fascination may be motivated by scientific and technological opportunities, or from a curiosity about the consequences of being able to place atoms in a particular location. Advances in scanning tunneling microscopy have made this prospect a reality; single atoms can be placed at selected positions and structures can be built to a particular design atom-by-atom. Atoms and molecules may be manipulated in a variety of ways by using the interactions present in the tunnel junction of a scanning tunneling microscope. Some of these recent developments and some of the possible uses of atomic and molecular manipulation as a tool for science are discussed.

THE SCANNING TUNNELING MICROSCOPE (STM) CAN IMAGE the surface of conducting materials with atomic-scale detail. As with other microscopes, we use the STM to extend our vision to a realm where our eyes cannot see. In tunneling microscopy we conventionally record an image that is a map of the trajectory of a probe tip over a surface while the height of the probe tip is constantly adjusted to maintain a constant tunneling current between the tip and the surface. Such images reflect both the topography and the electronic structure of the surface (*1*). The STM may also be used to locally modify surfaces (*2*). In the last few years efforts along these lines have culminated in the ability to manipulate individual atoms and molecules with atomic-scale precision, a goal that has intrigued scientists for decades (*3*). In a sense, we may use the STM to extend our touch to a realm where our hands are simply too big. In this article we review how the STM may be used to manipulate matter on the atomic scale and discuss the physical mechanisms involved.

A variety of different atomic manipulation processes have been demonstrated with the STM. We may divide these processes into two classes: parallel processes and perpendicular processes. In parallel processes an adsorbed atom or molecule is induced to move along the surface. In perpendicular processes the atom or molecule is transferred from the surface to the tip of the STM or vice versa. In both processes the goal is the purposeful rearrangement of matter on the atomic scale. We may view the act of rearrangement as a series of steps that results in the selective making and breaking of chemical bonds between atoms, or, equivalently, as a procedure that causes a configuration of atoms to evolve along some time-dependent potential energy hypersurface from an initial to a final configuration. Both points of view should prove useful in understanding the physical mechanisms by which atoms may be manipulated with the STM.

Parallel Processes

The first class of atomic manipulation processes that we discuss is parallel processes, that is, processes in which the motion of the manipulated adsorbate atom or molecule is parallel to the surface. We discuss two parallel processes, field-assisted diffusion and the sliding process. In this class of processes the bond between the manipulated atom and the underlying surface is never broken, by

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