Molecule-Mimetic Chemistry and Mesoscale Self-Assembly

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ABSTRACT

Molecules are structured aggregates of atoms joined by chemical bonds; crystals are aggregates of molecules, interacting covalently or noncovalently. The work described in this Account uses molecules, crystals, and other forms of atomic/molecular matter to suggest principles that can be used in generating structured aggregates of millimeter-scale components, interacting through capillary interactions. The properties of these aggregates—that is, their "chemistry"—mimic aspects of the chemistry of molecules.

Molecule-Mimetic Chemistry

The study of atoms and molecules is the heart of chemistry. Scientists' understanding of molecules, and of associated subjects—from covalent bonding to molecular recognition—is profound. The research we sketch here is designed to test the proposition that *principles* learned in studying molecules—principles with which we, as chemists, are often so familiar that we take them for granted—are also useful in the design and "synthesis" of *nonmolecular* systems. We suggest that it will be possible to develop complex structures composed of "objects" that self-assemble in processes that mimic (at least to some extent) those by which molecules and molecular aggregates form, and that it will be possible to extend concepts abstracted from the synthesis of molecules to methods for the assembly of objects.

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Chemistry is accustomed to mimicry as a strategy, and often uses nature as a source of ideas: "biomimetic", "peptidomimetic", "membrane-mimetic", and related phrases suggest that we accept the idea that understanding biology leads to abstract principles that can be used to design nonbiological molecules.[1,2] Chemists routinely mimic principles of biological design—hydrogen bonds for directionality,[3] hydrophobic effects to segregate molecular surfaces from water,[4] and shape complementarity to select interacting partners[5]—for other purposes.

Our program redirects the mimicry: instead of using molecules to mimic other molecules, we use objects to mimic molecules. Ideas such as phase segregation, chirality, hydrophobicity, shape recognition, and size exclusion can be used to guide the self-assembly of these objects, as they are used to guide the aggregation of molecules. The structures that we wish to manipulate are built of components that are larger than molecules, but too small to be assembled conveniently by conventional means—sizes of a few nanometers to a few hundred micrometers cover the range of interest. We have initially studied components—millimeter- to centimeter-sized polymeric polyhedra interacting with one another through capillary forces—with sizes a little above the upper end of this range, because they embody most of the issues we wish to explore, and because they are relatively easy to fabricate and observe. This Account sketches our work in self-assembly of two- and three-dimensional arrays of small objects through capillary forces, the chemical principles that inspire this work, the molecular details that make it possible, and possible uses for these processes and assemblies.[6–22]

Mesoscale Self-Assembly (MESA)

Mesoscale Self-Assembly: The Self-Assembly of Objects into Ordered Arrays through Noncovalent Forces. "Meso" is a word that is used in two ways. It commonly means "the middle". For example, a *mesomorph* is a person of medium stature, neither fat nor thin; the mesozoic era was the time between the paleozoic and the cenozoic era. More technically, and especially in physics, a mesoscale object is one whose dimensions are comparable to the scale of the phenomenon being investigated or the probe being used to investigate it. For example, a quantum dot—a mesoscale object in electronics materials—has dimensions of the order of the ballistic mean free path of an electron (10–40 nm in a semiconductor at room temperature);[23] a photonic band gap material—a material that is meso on the optical scale—has periodic variations in index of refraction that occur at scales comparable to the wavelength of light (0.1–10 μm).[24]

Millimeter-scale objects interacting through capillary interactions extending over millimeter ranges also constitute a mesoscale system. This system, and self-assembly, allow us to generate aggregates in ways that mimic some molecular processes.[6]

The Capillary Bond. A "bond" is an interaction between two objects that holds them together. In principle, many different types of interactions—electromagnetic, hydrophobic, fluidic, photonic, capillary, and gravitational—could be used to form bonds. In most of our work, we have used capillary interactions to cause self-assembly.[6]

We suggest that the capillary interactions between objects in our systems can be viewed as bonds that are loosely analogous to chemical bonds. This analogy is not an exact mapping from the molecular to the macroscopic, but rather an aid to the imagination. There are at least three similarities between capillary and chemical bonds. (i) Both are reversible at some level of agitation or temperature. (ii) Both interact through overlaps: of menisci for capillary bonds, and of orbitals for chemical bonds. (iii) Both are directional. There are, of course, fundamental differences between capillary and chemical bonds. (i) Capillary forces are described by classical mechanics; chemical bonds require quantum mechanics. (ii) Capillary and chemical bonds are described by potential curves with different forms. (iii) Capillary forces can act over distances up to a millimeter; chemical bonds act over distances of less than 1 nm.

The Opportunity: To Extend the Principles of Molecular Self-Assembly to Mesoscale (Micrometer- to Millimeter-Scale) Self-Assembly

We wished to use ideas taken from molecular self-assembly—especially shape-selective interactions between hydrophobic surfaces—to assemble objects larger than molecules.[1] There are a number of molecular processes that are based on directional interactions and mating of hydrophobic surfaces: examples include DNA/DNA duplex formation,[25] receptor/ligand association,[26] $\pi-\pi$ stacking,[27] formation of self-assembled monolayers (SAMs),[28] molecular recognition,[29] formation of molecular crystals,[30] and folding of proteins.[31] All are processes that might be mimicked using MESA. By studying experimentally well-defined, nonmolecular, self-assembling systems, we also hope to learn principles that might be useful in understanding self-assembling molecular systems.

Previous Work in MESA

In most previous examples of MESA, spherical objects (from nanometer-sized proteins and colloids to micrometer-sized latex spheres) have formed close-packed arrays; the interactions involved have included chemical,[32−34] electrohydrodynamic,[35] capillary,[36−41] shear,[42] dipolar,[43] electrostatic,[42,44] light-based,[45] entropic,[46] magnetic,[44,47] and gravitational.[43] These systems are interesting for their ability to show self-assembly, but they are limited in the range of structures they can generate. One goal of our work, as with organic synthesis, is to develop flexible strategies leading to a range of structures. Our strategy is to design and fabricate nonspherical objects with patterned surfaces that direct the capillary interactions.
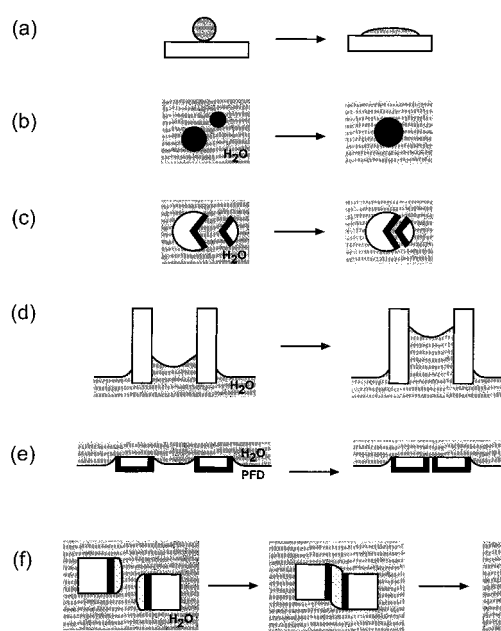

FIGURE 1. Six examples of systems that minimize the area of a high energy surface. (a) Water spreading on a SAM terminating in carboxylic acid groups. (b) Two drops of benzene in water coalescing into one drop. (c) A receptor with a hydrophobic area interacting with a hydrophobic ligand. (d) Water rising in a capillary to coat the high-energy glass surface. (e) Two objects floating at the PFD/H_2O interface interacting through lateral capillary forces to minimize the surface area at the interface. (f) Two objects with one face hydrophobic and coated with a hydrophobic liquid or liquid metal and suspended in water coming into contact. In both systems (e and f) the objects can move laterally with respect to the one another to maximize the overlap of their faces. The thick black lines indicate hydrophobic surfaces, and the thin lines indicate hydrophilic surfaces.

Bonds: Capillarity, the Hydrophobic Effect, Surface Tension, and Interfacial Free Energy

Capillary interactions have five attractive characteristics. (i) The characteristic decay length for lateral capillary forces is in the right range—from nanometer to millimeter, depending on the dimensions of the objects—to be useful with objects of the size (micrometer to centimeter) that we wished initially to explore. (ii) The strength of the capillary interactions can be adjusted to be comparable to the strength of the shear forces that are used to disrupt the aggregation. (iii) Capillary interactions can be used to assemble either 2D or 3D arrays. (iv) Capillary interactions are well understood conceptually (although their numerical analysis—using the Laplace equation—is often intractably complicated). (v) Designs of the surfaces that generate the menisci allow the capillary interactions to be made directional.

It is useful to understand the molecular basis of capillary interactions. Capillarity, surface tension, and the hydrophobic effect all reflect the same phenomenon—that is, the tendency of a system containing water or other liquids to minimize its interfacial free energy, usually by minimizing the area of the interface with the highest free energy (Figure 1). Molecules of a polar liquid or solid at an interface with a less polar phase (air, nonpolar polymer,

hydrophobic molecular interface) are less stable than those in the bulk. A system will thus tend to minimize the area of its exposed, high-energy interfaces. The spreading of a drop of water on a carboxyl-terminated SAM covers the surface with the highest surface free energy (that of the SAM), albeit at the expense of increasing the area of the water/air interface (Figure 1a). Coalescence of drops of benzene suspended in water, association of a hydrophobic ligand with a hydrophobic active site, and rise of water in a capillary all reflect changes in areas of interfaces that minimize interfacial free energies (Figure 1b–d).

The Design of Components for MESA

We describe two systems that generate ordered arrays of objects using MESA (Figure 1e,f). The first uses lateral capillary interactions to assemble millimeter-scale plates floating at the interface between perfluorodecalin (PFD) and water (Figure 1e).[6–9,16–22] The second also uses capillary forces (involving either a hydrophobic liquid or liquid metal) to direct the self-assembly of polymeric polyhedra (micrometer to centimeter in size) suspended in water into 3D aggregates (Figure 1f).[10–15]

Use of Polyhedral Components with Patterned Faces Allows the Capillary Interactions To Be Directional. To achieve structural complexity in 2D structures formed at the H_2O/PFD interface using capillary interactions, these interactions must be directional. The faces of the objects—small, polymeric plates—were patterned into hydrophobic and hydrophilic sets and regions. The hydrophobicity of the faces, and the arrangement of the faces on the object, determined the shape of the menisci and the directionality and strength of the capillary interactions.

The strongest capillary interactions between the objects were those that resulted in the largest decrease in interfacial free energy when the components came together—that is, as a first approximation, to the best matching of the contours of their menisci. This principle—designing the overlap of menisci to achieve strong capillary bonding—has an obvious if imprecise analogy to using the overlap of electronic orbitals to achieve strong molecular bonding (Figure 2a).

Nomenclature Describing the Number and Location of the Hydrophobic Faces, and the Sense of the Menisci. The lateral motion of the two plates shown in Figure 1e involving menisci of the same sense (i.e., two positive or two negative menisci) lowers the surface area of the PFD/H_2O interface and thus lowers the free energy of the system. The lateral capillary forces move the plates toward or away from one another; the vertical capillary forces move the plates out of or into the interface. In 3D MESA, two faces coated with a hydrophobic liquid or liquid metal and suspended in water come into contact and reduce the surface area of the hydrophobic liquid/water interface.

In all figures, the dark faces on the drawings of the objects and the thick lines indicate hydrophobic faces; the light faces and thin lines indicate hydrophilic faces. For the objects in the 2D system, we number the hydrophobic
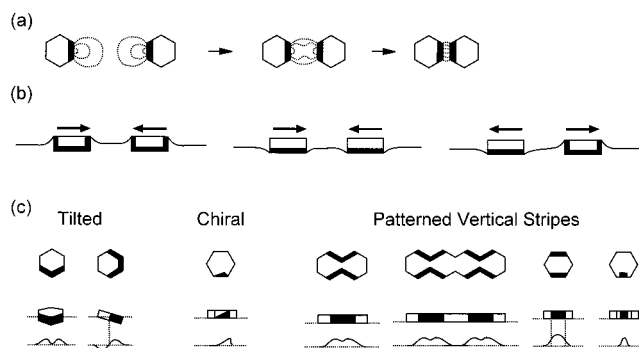

FIGURE 2. (a) The contours of the menisci (indicated by dashed lines) on two hexagons change as the hexagons approach one another. (b) Two *positive* menisci (those rising above the interface) pull the objects toward one another, two *negative* menisci (those sinking below the interface) pull the objects toward one another, and a negative meniscus repels a positive meniscus. (c) The contours of the menisci on various objects at the PFD/H_2O interface in 2D MESA. The top drawings are the top views of the objects, the middle drawings are the side views of the objects, and the bottom drawings are views of the contours of the menisci.

faces by placing the number of those faces in a square bracket. For example, we call a hexagon with two adjacent hydrophobic faces a [1,2] hexagon, and a hexagon with every other face hydrophobic a [1,3,5] hexagon.

In Figures 3–8, we show optical or scanning electron micrographs of the assemblies and schematic representations of the assemblies to aid the eye (the micrographs have scale bars and, thus, can be easily distinguished from the computer-drawn schemes). These micrographs show some of the best assemblies. The schematic representations of the assemblies are next to the micrographs and show the pattern of the hydrophobic and hydrophilic faces and, in some cases, how the objects were assembled into the arrays.

Engineering the Capillary Bond by Controlling the Shapes of Menisci. We wished to control the shapes of the menisci, to generate capillary bonds with different strengths. The better the match between contours of two menisci, the greater the reduction in the area of the PFD/H_2O interface as the two interacting plates come together, and the stronger the capillary bond. With this understanding, we designed a range of face structures that would test the strength and selectivity of the bonds.[6,7] The objective of this work was, in a sense, to begin to develop a "periodic table"—a set of plates having edges patterned to generate menisci with shapes and symmetries that would result in selective interactions. We used four strategies in 2D MESA (Figure 2c). That is, we patterned (i) the location of the hydrophobic faces so that the plates were tilted at the PFD/H_2O interface; (ii) the hydrophobic areas on the faces to be chiral (faces of opposite chirality interacted more strongly than those with the same chirality); (iii) the faces into vertical hydrophobic stripes; and (iv) the horizontal profile of the faces.

Similar methods were used in some of the 3D systems. Here, the hydrophobic patches were in the form of triangles, squares, and other geometric figures. The most

stable pair formed between faces that had hydrophobic patches that matched when juxtaposed.

Experimental Investigations of MESA: Two-Dimensional Assemblies

Methods. The objects used in the two-dimensional assembly were readily fabricated from poly(dimethylsiloxane) (PDMS). PDMS is hydrophobic (the advancing contact angle of water $\theta_a^{H_2O} \approx 108°$) but can be made hydrophilic by oxidation in an oxygen plasma ($\theta_a^{H_2O} < 30°$). Most objects used in these examples had densities of $\rho = 1.05$ g/cm^3. These plates float with their center of gravity well above the PFD/H$_2$O interface; the interactions between positive menisci at the hydrophobic faces thus dominate assembly. Faces that were to remain hydrophobic were protected from oxidation by tape or a temporary protective film (we often used correction fluid). The objects were agitated in a dish with PFD and H$_2$O on an orbital shaker; typical conditions were agitation at an orbital frequency, ω, of $\omega = 1.5$ s^{-1} for 30 min. The faster the rotation, the stronger the shear forces opposing assembly.

Hexagonal Plates. Many of our studies of two-dimensional assemblies used components with a common hexagonal shape, and with edges functionalized to be hydrophobic or hydrophilic.[6−8] We have examined all permutations (14 in all) of these edge-functionalized plates. This survey established a number of basic principles of MESA. (i) As expected, aggregates usually form in a way that juxtaposes hydrophobic edges. (ii) Plates with a noncentrosymmetric distribution of edges are tilted relative to the interface. This tilt can strongly influence the form of the aggregate. (iii) The menisci extend for several millimeters, and objects interact over this distance. (iv) The directionality and strength of interactions can be controlled by the design of the hydrophobic patterns; these interactions determine the structures of the aggregates in a predictable way. (v) The agitation of the assemblies occurs primarily by shear; increased agitation gives smaller aggregates but does not influence the structure of the aggregate. (vi) The assembly of the objects is reversible; objects with menisci that do not match dissociate more rapidly than those with menisci that match. (vii) Appropriate design gives edges that are selective in their interactions. (viii) The capillary interactions can be modeled to some degree by finite element simulation.

The [1] hexagons assembled into dimers, and the [1,3,5] and [1,2,4,5] hexagons assembled into open, hexagonal arrays (Figure 3). The trimers formed by [1,2] hexagons were strongly tilted (by 14°) relative to the plane of the PFD/H$_2$O interface: this tilt reflects the noncentrosymmetric distribution of vertical capillary forces.

Hierarchical Self-Assembly. Because good matches of the contours of menisci resulted in strong capillary bonds, it was possible to design patterns of hydrophobic edges that showed strong selectivity (Figure 4a).[8] The two objects (**1** and **2**) had the same area of hydrophobic face, but the
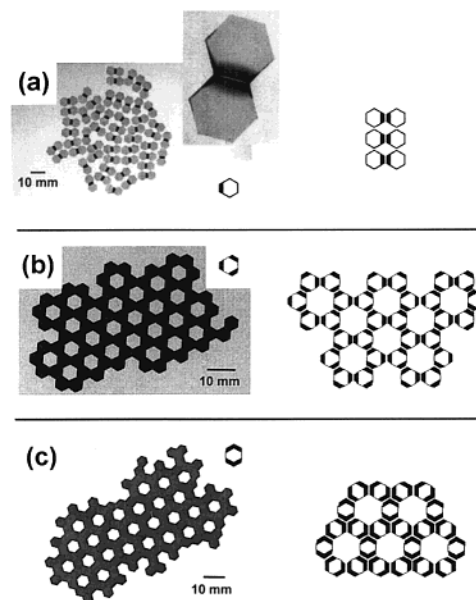

FIGURE 3. (a) [1] Hexagons assembled into dimers based on the attraction between the hydrophobic faces. (b and c) Both [1,3,5] and [1,2,3,4] hexagons assembled into open hexagonal arrays. Optical micrographs are shown on the left side, and schematic representations on the right side.
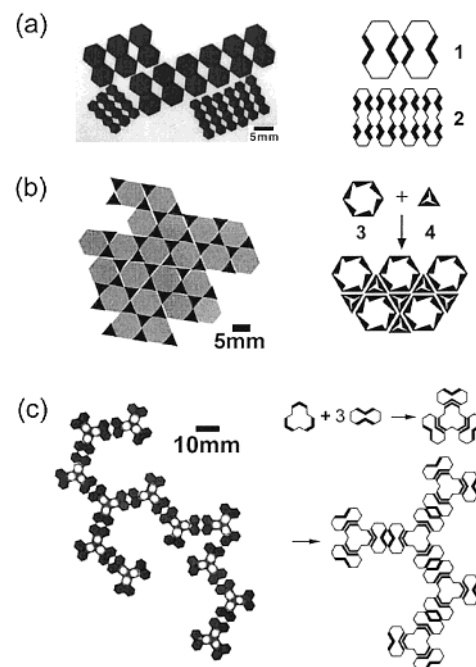

FIGURE 4. (a) Objects assembled to match the hydrophobic areas on each face. (b) Arrays formed by chiral hydrophobic patches. The dark triangular patches in the hexagons and triangles on the right-hand side of the figure indicate the pattern of the hydrophobic patches on the faces. (c) An extended hierarchical array. Optical micrographs are shown on the left side, and schematic representations on the right side.

menisci on **1** matched those on **2** poorly: as a result, both **1** and **2** formed homo-oligomers separately, but **1** did not form a stable hetero-oligomer with **2**. Chiral hydrophobic edges gave a more subtle selectivity.[8] The areas of the hydrophobic edges of **3** and **4** were the same, but both were chiral and of the opposite chirality. Association of **3**
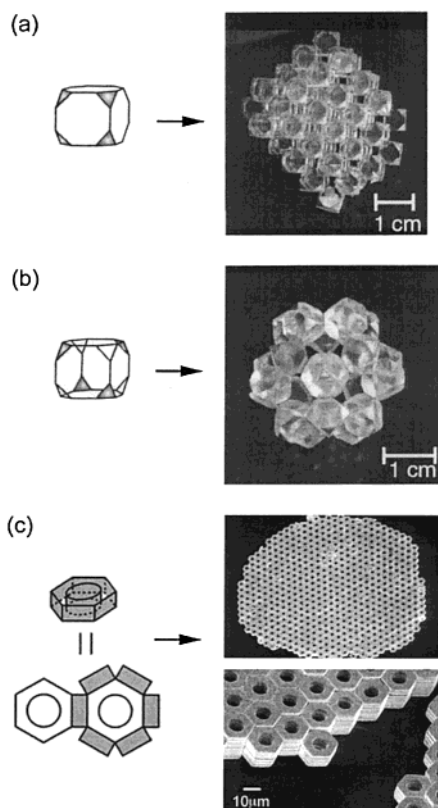
FIGURE 5. (a and b) Two examples of crystalline three-dimensional arrays. Self-assembly was accomplished by agitating the pieces in an aqueous KBr solution at 60 °C using molten alloy as adhesive. After completion of the self-assembly, the suspension was allowed to cool to room temperature, where the alloy solidified resulting in a stable structure. (c) Objects—10 μm in width—assembled into crystalline arrays. The schematic representations of the objects are shown on the left side. The dark faces are hydrophobic, and the light faces are hydrophilic. The optical micrographs (a and b) and the scanning electron micrograph (c) on the right side show examples of the assemblies.

with **4** occurred readily; association of **3** with **3**, or **4** with **4**, did not (Figure 4b).

Figure 4c demonstrates hierarchical self-assembly using mesoscale objects.[9] This assembly used two different PDMS objects containing concave and convex hydrophobic faces with complementary shapes. The capillary interactions between concave and convex hydrophobic faces are the strongest; the weakest interactions occur between two concave hydrophobic faces.

Three-Dimensional Assemblies

Conceptually, 3D systems are similar to the 2D system, although operationally somewhat different. To generate 3D assemblies, we coated selected faces of polyhedra with a hydrophobic liquid or low-melting liquid solder. The resulting polyhedra were agitated in suspension in an isodense medium. Capillary interactions pulled the liquid-coated faces together when they came into contact (Figure 1f).[10-15] Large, extended crystalline arrays formed from appropriately functionalized polyhedra (Figure 5a,b).[11,15] We used liquid metal for two reasons: (i) it has a high interfacial free energy with water ($\sim$400 mN m^{-1}) and gave
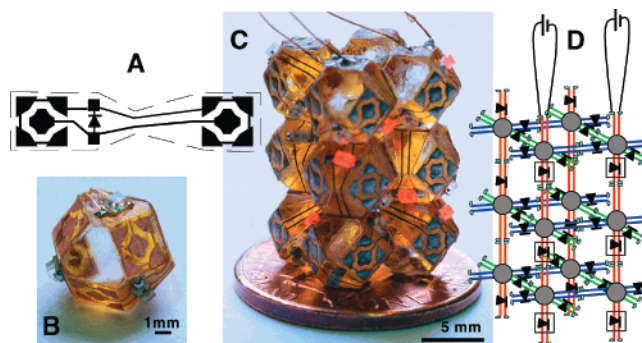

FIGURE 6. Self-assembled electrical network with parallel connectivity. (a) The basic pattern of copper dots, wires, and contact pads used. (b) A single patterned polyhedron prior to assembly. (c) A photograph of the assembled aggregate on top of a penny. The aggregate is connected to a battery via an isolated pair of wires. This lights up the six LEDs that are connected to each other in parallel. (d) An electrical circuit diagram showing the parallel network formed. The gray circles show the 12 polyhedra, and the LEDs are shown in black. Assembly results in the formation of 16 pairs of wires that consist of the red, green, and blue pairs.

stable arrays; (ii) solder connections constitute a step toward electrically functional, self-assembling systems. The 3D arrays were intrinsically more stable than the two-dimensional arrays, since each object is held in its place in the lattice by more contacts.

New Materials and New Functional Systems by MESA

Many of the assemblies we have described here could be as easily assembled by hand as by self-assembly. The design and fabrication of these assemblies are intellectually stimulating and important for what they teach about the self-assembly process. These assemblies do not, however, provide a new *capability* to fabrication or synthesis. To be useful, MESA must offer strategies that generate aggregates that could not be made by conventional means. Two examples are the self-assembly of small, nonspherical objects ($\leq$10 μm) into ordered arrays and the self-assembly of objects into functional systems.

3D Assemblies of 10-μm Scale Components. The challenge in applying MESA to submillimeter-sized objects is the fabrication of the polyhedral components with faces appropriately patterned. We have developed a combination of photolithography, electrochemistry, and metal evaporation that allows the fabrication of hexagonal plates (10 μm in size) in which the top and bottom faces are patterned independently of the side faces. These plates aggregate into ordered arrays, after hydrophobic faces are coated with a hydrophobic prepolymer (Figure 5c).[13] We believe that with development, this strategy in 3D MESA will provide a route to photonic band-gap materials.

Assemblies of Functional Arrays. We have successfully constructed small, 3D electrical networks (Figure 6).[14,15] Patterns of solder on the faces of polyhedra both held the polyhedra together (by capillarity) and made electrical connections between them.[15] Light-emitting diodes (LEDs) incorporated into the system traced the electrical circuits. Figure 6 shows a photograph of an assembled electrical
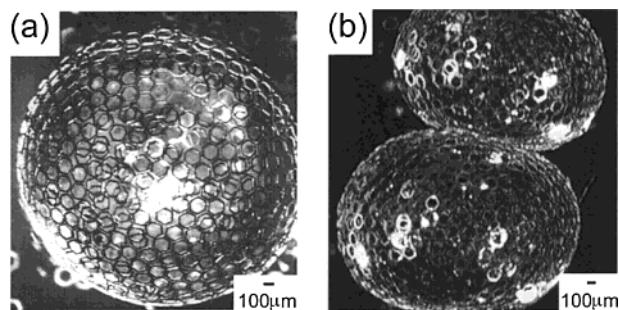
FIGURE 7. (a) Hexagons coating a drop of water in heptane. (b) The drops are stable even when pressed together.

network containing LEDs connected with parallel connectivity; we have also generated serial networks. These experiments are a first step toward the self-assembly of 3D microelectronic systems.

Models of Supramolecular Aggregates. We have developed a system that illustrates MESA on the surface of a spherical drop.[16] Small drops of one liquid were suspended in a second, immiscible liquid (chlorobenzene in H_2O, perfluorodecalin in H_2O, or H_2O in heptane). Hexagonal rings (100 μm in length, fabricated from electroplated gold) were added and self-assembled on the surface of the droplet (Figure 7). The hexagonal rings could be fabricated with the bottom and side faces hydrophobic and the top face hydrophilic, or vice versa; these rings floated at the interface of the two fluids. The hexagons stabilized the drops: two drops covered with hexagons would not fuse when pressed together (Figure 7b). Capillarity held the hexagons on the surface of the drop.

Mesoscale Biomimetic Systems. One of the most stimulating applications of MESA is the abstraction of important concepts in biological systems, and their use to join mesoscale objects. Several biological phenomena—ligand/receptor interactions,[18] DNA/DNA duplex formation,[19] and protein folding[20]—have already served as the basis for strategies for self-assembly. These systems use simple shapes interacting through simple interactions; as such, they may provide tests for computer models of biological systems and suggest new strategies for precision assembly.

Figure 8a shows the results of shape-selective recognition of a chiral object by a chiral cavity. The receptors (the larger objects in the picture) showed high selectivity in recognition of the ligands based on chirality. Figure 8b describes a system modeled on sequence-specific molecular recognition in DNA and RNA. The strands were made of sequences of four objects chosen to be analogues of the purine and pyrimidine bases of nucleic acids and connected via a flexible PDMS thread. When the smaller strand self-assembled with its complementary sequence along the longer strand, the array was stable. Other configurations were less stable and broke apart under agitation.

Conclusions

Molecule-Mimetic Chemistry. Chemistry builds complex structures using atoms as bricks and bonds as mortar. Can
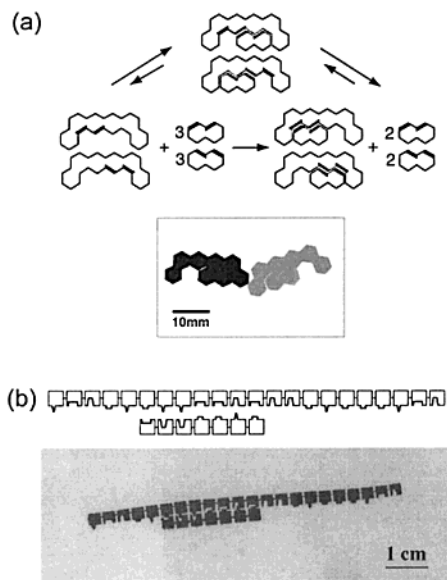

FIGURE 8. Self-assembled structures based on (a) shape-selective recognition and (b) sequence-specific recognition between a 22-membered single strand and a seven-membered probe. The representations of the objects are shown above the optical micrographs of the assemblies.

chemistry start from its experience with atoms and molecules and build a *new* "chemistry" using different components and connectors? We believe that the answer to this question is "yes" and have used the system comprising millimeter-scale objects and capillary interactions as a demonstration. The advantage of this system is that it is relatively easy to "design" the characteristics of capillary bonds; the corresponding characteristics of atomic/molecular bonds are fixed by the structure of the atoms and cannot be influenced by the chemist. Structures assembled from large components also have the attractive characteristic that determination of structure can be accomplished by the eye. The disadvantages of these systems are that the number of particles that can be observed is small, that the encounter frequency of their components is very low relative to atomic/molecular systems, and that their complexity—relative to the complexity generated by the many types of bonds that can form between the many elements of the periodic table—is also low. Still, it is a start, and by working with microfabricated components and by extending capillary interactions, or by supplementing them with electrical or magnetic interactions,[21] it will certainly be possible to build more complex systems.

What is the value of this exercise? Why is it different from playing with a child's building toys? We submit that there are several reasons for pursuing it. First, it is instructive and intellectually engaging to consider bonds and bonding abstractly, and to ask what principles can be taken from them and embedded in nonatomic/molecular systems. In this sense, MESA is engaging in the same sense that "biomimetic" studies involving molecules are engaging: biomimetic studies often do not imitate biology very closely, but they do suggest new principles of design. Second, building and fabrication—the assembly

of simple structures into complex ones—are among the most fundamentals of human activities, and new approaches to them are always interesting (and potentially useful). Third, and especially as the components become smaller, these methods will provide routes to structures that cannot be fabricated by other methods. True, the structures are not molecular, but the concepts are, and in any event, chemistry should have an expansive vision of its domain.

Molecular Chemistry Presently Has More To Offer to MESA Than MESA Does to Chemistry. MESA has been stimulated by chemistry, but the complexity of most chemical systems is too high to realize in a mesoscopic model. Chemistry, however, contributes to MESA in many ways: (i) through molecular control of surface chemistry and surface properties; (ii) through control of bulk properties—magnetic susceptibility, dielectric constant, density, and porosity—of the components; (iii) by providing phenomena to mimic; (iv) by providing routes for fabrication of nanometer- to millimeter-scale components, and (v) by providing possible molecular interactions for the forces between objects.

Toward Possible Applications. For MESA to be useful, the sizes of the components must be smaller (1−100 μm) and/or the assemblies must be functional. In related work by Nagayama et al., nanometer- and micrometer-sized spheres were assembled into close-packed arrays through lateral capillary forces.[48,49] This work demonstrates that capillary forces can be used to assemble objects as small as 25 nm into arrays. We do not yet know whether the capillary forces will still be directional on that size scale, although we do know from our work that objects with dimensions of 10 μm interact through directional capillary interactions.[13] The fabrication of objects on this size scale will continue to be a challenge, and new techniques for fabrication will be welcome.

Function can take a broad range of forms. The assemblies can be functional as models for systems to study (such as models of molecular and biological systems), or as structures that can act as components in devices (microelectronic, photonic, MEMS). Although there are no current commercial examples of functional devices fabricated by MESA (aside from those generated by fluidic self-assembly),[50,51] MESA has several characteristics that make it an attractive option for fabricating nanometer- and micrometer-sized arrays: (i) it can result in excellent registration between objects. (ii) It is error-correcting in the sense that misassembled arrays are relatively unstable. (iii) It is compatible with a variety of materials. (iv) It can generate electrical connections. (v) It generates structures with the right size for photonic band-gap materials, waveguides, MEMS, and high surface area catalysts. The direction of MESA will be decided in part by how small the components can be made, and in part by the kinds of structures that can be assembled from them.

References

(1) Whitesides, G. M.; Mathias, J. P.; Seto, C. T. Molecular Self-Assembly and Nanochemistry: A Chemical Strategy for the Synthesis of Nanostructures. *Science* **1991**, *254*, 1312−1319.

(2) Lindsey, J. S. Self-Assembly in Synthetic Routes to Molecular Devices. Biological Principles and Chemical Perspectives: A Review. *New J. Chem.* **1991**, *15*, 153−180.

(3) Fredericks, J. R.; Hamilton, A. D. Hydrogen Bonding Control of Molecular Self-Assembly: Recent Advances in Design, Synthesis, and Analysis. In *Comprehensive Supramolecular Chemistry*; Sauvage, J.-P., Hosseini, M. W., Eds.; Pergamon Press: Oxford, 1996; Vol. IX, Chapter 16.

(4) Hummer, G.; Garde, S.; Garcia, A. E.; Paulaitis, M. E.; Pratt, L. R. Hydrophobic Effects on a Molecular Scale. *J. Phys. Chem. B* **1998**, *102*, 10469−10482.

(5) Conn, M. M.; Rebek, J., Jr. Self-Assembling Capsules. *Chem. Rev.* **1997**, *97*, 1647−1668.

(6) Bowden, N.; Choi, I. S.; Grzybowski, B. A.; Whitesides, G. M. Mesoscale Self-Assembly of Hexagonal Plates Using Lateral Capillary Forces: Synthesis Using the "Capillary Bond". *J. Am. Chem. Soc.* **1999**, *121*, 5373−5391.

(7) Bowden, N.; Terfort, A.; Carbeck, J.; Whitesides, G. M. Self-Assembly of Mesoscale Objects into Ordered Two-Dimensional Arrays. *Science* **1997**, *276*, 233−235.

(8) Wu, H.; Bowden, N.; Whitesides, G. M. Selectivities Among Capillary Bonds in Mesoscale Self-Assembly. *Appl. Phys. Lett.* **1999**, *75*, 3222−3224.

(9) Choi, I. S.; Bowden, N.; Whitesides, G. M. Macroscopic, Hierarchical, Two-Dimensional Self-Assembly. *Angew. Chem., Int. Ed.* **1999**, *38*, 3078−3081.

(10) Terfort, A.; Bowden, N.; Whitesides, G. M. 3D Self-Assembly of Millimeter-Scale Components. *Nature* **1997**, *386*, 162−164.

(11) Tien, J.; Breen, T. L.; Whitesides, G. M. Crystallization of Millimeter-Scale Objects with Use of Capillary Forces. *J. Am. Chem. Soc.* **1998**, *120*, 12670−12671.

(12) Breen, T. L.; Tien, J.; Oliver, S. R. J.; Hadzic, T.; Whitesides, G. M. Design and Self-Assembly of Open, Regular, 3D Mesostructures. *Science* **1999**, *284*, 948−951.

(13) Tien, J.; Clark, T. D.; Duffy, D. C.; Whitesides, G. M. Self-Assembly of 3D Arrays of 10-μm-Sized Objects. Unpublished.

(14) Terfort, A.; Whitesides, G. M. Self-Assembly of an Operating Electrical Circuit Based on Shape Complementarity and the Hydrophobic Effect. *Adv. Mater.* **1998**, *10*, 470−473.

(15) Gracias, D. H.; Tien, J.; Breen, T. L.; Hsu, C.; Whitesides, G. M. Forming Electrical Networks in Three Dimensions by Self-Assembly. *Science* **2000**, *289*, 1170−1172.

(16) Huck, W. T. S.; Tien, J.; Whitesides, G. M. Three-Dimensional Mesoscale Self-Assembly. *J. Am. Chem. Soc.* **1998**, *120*, 8267−8268.

(17) Choi, I. S.; Weck, M.; Xu, B.; Jeon, N. L.; Whitesides, G. M. Mesoscopic, Templated Self-Assembly at the Fluid−Fluid Interface. *Langmuir* **2000**, *16*, 2997−2999.

(18) Choi, I. S.; Bowden, N.; Whitesides, G. M. Shape-Selective Recognition and Self-Assembly of mm-Scale Components. *J. Am. Chem. Soc.* **1999**, *121*, 1754−1755.

(19) Weck, M.; Choi, I. S.; Jeon, N. L.; Whitesides, G. M. Assembly of Mesoscopic Analogs of Nucleic Acids. *J. Am. Chem. Soc.* **2000**, *122*, 3546−3547.

(20) Choi, I. S.; Weck, M.; Jeon, N. L.; Whitesides, G. M. Mesoscale Folding: A Physical Realization of an Abstract, 2D Lattice Model for Molecular Folding. *J. Am. Chem. Soc.* **2000**, *122*, 11997−11998.

(21) Choi, I. S.; Huck, W. T. S.; Jeon, N. L.; Whitesides, G. M. Combination of Magnetic and Capillary Forces in Mesoscale Self-Assembly. Unpublished.

(22) Bowden, N.; Oliver, S. R. J.; Whitesides, G. M. Mesoscale Self-Assembly: Capillary Bonds and Negative Menisci. *J. Phys. Chem. B* **2000**, *104*, 2714−2724.

(23) Alivisatos, A. P. Perspectives on the Physical Chemistry of Semiconductor Nanocrystals. *J. Phys. Chem.* **1996**, *100*, 13226−13239.

(24) Joannopoulos, J. D.; Meade, R. D.; Winn, J. N. *Photonic Crystals: Molding the Flow of Light*; Princeton University Press: Princeton, NJ, 1995.

(25) Watson, J. D.; Crick, F. H. C. Genetical Implications of the Structure of Deoxyribose Nucleic Acid. *Nature* **1953**, *171*, 964−967.

(26) *Receptor−Ligand Interactions: A Practical Approach*; Hulme, E. C. Ed.; Oxford University Press: Oxford, 1992.

(27) Hunter, C. A. The Role of Aromatic Interactions in Molecular Recognition. *Chem. Soc. Rev.* **1994**, 101−109.

(28) Ulman, A. *Introduction to Ultrathin Organic Films: From Langmuir−Blodgett to Self-Assembly*; Academic Press, Inc.: Boston, 1991.

(29) Lehn, J. M. *Supramolecular Chemistry*; VCH: Weinheim, 1995.

(30) Braga, D.; Grepioni, F.; Desiraju, G. R. Crystal Engineering and Organometallic Architecture. *Chem. Rev.* **1998**, *98*, 1375−1405.

(31) Karplus, M.; Shakhnovich, E. Protein Folding: Theoretical Studies of Thermodynamics and Dynamics. In *Protein Folding*; Creighton, T. E., Ed.; W.H. Freeman: New York, 1992.

(32) Mirkin, C. A.; Letsinger, R. L.; Mucic, R. C.; Storhoff, J. J. A DNA Based Method for Rationally Assembling Nanoparticles into Macroscopic Materials. *Nature* **1996**, *382*, 607−609.

(33) Alivisatos, A. P.; Johnsson, K. P.; Peng, X.; Wilson, T. E.; Loweth, C. J.; Bruchez, M. P., Jr.; Schultz, P. G. Organization of Nanocrystal Molecules Using DNA. *Nature* **1996**, *382*, 609−611.

(34) Seeman, N. C. Nucleic Acid Nanostructures and Topology. *Angew. Chem., Int. Ed.* **1998**, *37*, 3220−3238.

(35) Trau, M.; Saville, D. A.; Aksay, I. A. Field-Induced Layering of Colloidal Crystals. *Science* **1996**, *272*, 706−709.

(36) Rothemund, P. W. K. Using Lateral Capillary Forces to Compute by Self-Assembly. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 984−989.

(37) Velev, O. D.; Lenhoff, A. M.; Kaler, E. W. A Class of Microstructured Particles Through Colloidal Crystallization. *Science* **2000**, *287*, 2240−2243.

(38) Murray, C. B.; Kagan, C. R.; Bawendi, M. G. Self-Organization of CdSe Nanocrystallites into 3D Quantum-Dot Superlaticces. *Science* **1995**, *270*, 1335−1338.

(39) Paunov, V. N. On the Analogy Between Lateral Capillary Interactions and Electrostatic Interactions in Colloid Systems. *Langmuir* **1998**, *14*, 5088−5097.

(40) Velikov, K. P.; Durst, F.; Velev, O. D. Direct Observation of the Dynamics of Latex Particles Confined inside Thinning Water−Air Films. *Langmuir* **1998**, *14*, 1148−1155.

(41) Lazarov, G. S.; Denkov, N. D.; Velev, O. D.; Kralchevsky, P. A.; Nagayama, K. Formation of Two-dimensional Structures from Colloidal Particles on Fluorinated Oil Substrate. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 2077−2083.

(42) Murray, C. A.; Grier, D. G. Video Microscopy of Monodisperse Colloidal Systems. *Annu. Rev. Phys. Chem.* **1996**, *47*, 421−462.

(43) Martin, J. E.; Odinek, J.; Halsey, T. C. Evolution of Structure in a Quiscent Electrorheological Fluid. *Phys. Rev. Lett.* **1992**, *69*, 1524−1527.

(44) Hwang, Y. H.; Wu, X.-L. Quasi Two-Dimensional Domain Structures of Magnetic Particles in a Static Field. *Phys. Rev. E* **1994**, *49*, 3102−3108.

(45) Burns, M. M.; Fournier, J. M.; Golovchenko, J. A. Optical Binding. *Phys. Rev. Lett.* **1989**, *63*, 1233−1236.

(46) Adams, M.; Dogic, Z.; Keller, S. L.; Fraden, S. Entropically Driven Microphase Transitions in Mixtures of Colloidal Rods and Spheres. *Nature* **1998**, *393*, 349−362.

(47) Wen, W.; Wang, N.; Ma, H.; Lin, Z.; Tam, W. Y.; Chan, C. T.; Sheng, P. Field Induced Structural Transition in Mesocrystallites. *Phys. Rev. Lett.* **1999**, *82*, 4248−4251.

(48) Kralchevsky, P. A.; Nagayama, K. Capillary Interactions Between Particles Bound to Interfaces, Liquid Films, and Biomembranes. *Adv. Colloid Interface Sci.* **2000**, *85*, 145−192.

(49) Yamaki, M.; Higo, J.; Nagayama, K. Size-Dependent Separation of Colloidal Particles in Two-Dimensional Convective Self-Assembly. *Langmuir* **1995**, *11*, 2975−2978.

(50) Cohn, M. B.; Bohringer, K. F.; Noworolski, J. M.; Singh, A.; Keller, C. G.; Goldberg, K. Y.; Howe, R. T. Microassembly Technologies for MEMS. *Proc. SPIE−Int. Soc. Opt. Eng.* **1998**, 2−16.

(51) Tu, J. K.; Talghader, J. J.; Hadley, M. A.; Smith, J. S. Fluidic Self-Assembly of Ingas Vertical-Cavity Surface-Emitting Lasers onto Silicon. *Electron. Lett.* **1996**, *31*, 1448−1449.