APPROACHES TO SYNTHESIS BASED ON NON-COVALENT BONDS

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Two self-assembling systems — SAMs (self-assembled monolayers) and aggregates based on CA•M (cyanuric acid•melamine lattice) — are not unique in non-covalent synthesis, but they illustrate many of the ideas of non-covalent synthesis, and suggest the ways in which this area differs in its philosophy and objectives from covalent synthesis.

1. Targets for Synthesis

What are the current targets for organic synthesis? The traditional activity of organic chemistry has been to synthesize molecules. The history of organic synthesis is reflected in its target molecules: dyes, polymers, specialty chemicals, natural products and pharmaceuticals have each been a favored subject at some period in the development of synthetic chemistry. A second function of organic synthesis has been to develop technology — often using molecules isolated from nature as stimuli — that is generally useful in synthesis.

The targets of synthetic activity — that is, the areas in which new methods and new strategies are most needed — are defined by the areas of science and technology that are themselves especially active and that rely heavily on molecules and materials. Four areas (among others) seem especially to define the fields that require new syntheses and synthetic technology:

1.1. MEDICINE

The pharmaceutical industry continues to require a high level of expertise in organic synthesis. While the specific classes of compounds that are required in medicinal

chemistry change with time, the strategies used to synthesize them represent an extension of paradigms that are now familiar in organic synthesis. Increasing emphasis and creativity is being placed on the development of low-cost processes, on processes that yield enantiomerically pure compounds, and on environmentally friendly processes. These challenging problems make certain that chemists will continue to be an important part of medicinal chemistry for as long as new drugs are developed.

1.2. BIOLOGY

Biology is now posing a range of new types of challenges to synthesis. Current efforts in the synthesis of molecules relevant to biology are concentrated on the major classes of biomolecules: polypeptides, proteins, nucleic acids and oligosaccharides. The need for efficient methods for the synthesis of biomolecules has been a valuable stimulus to synthetic chemistry. This motivation has resulted in several new methodologies including the incorporation of synthetic methods based on enzymes and fermentation into standard synthetic technology, and in the generation of new methodologies applicable to water-soluble and charged species, and to linear macromolecules such as proteins and polynucleotides. It seems probable that biological synthesis, in the future, will be a hybrid of chemical and biochemical methods, with the particular set of methods chosen depending on the efficiency and appropriateness of each to the problem at hand. Advanced targets for organic synthesis relevant to biology — for example, the synthesis of catalytically functional aggregates, of self-replicating structures, or of simple viruses — are still too complex to attract the attention of other than the most adventurous.

1.3. MATERIALS SCIENCE

Participation in materials science requires a more substantial change in attitude for organic synthesis than does biology. In biology, the targets are molecules with unfamiliar properties (for chemists) in that they have high molecular weights, are water soluble and are often highly charged. They are, nonetheless, still *molecules*. In materials science, the targets of synthesis are often molecules that either form or perform as *aggregates*. In many materials systems, the properties of interest may depend absolutely on aggregation or collective behavior. For example, liquid crystals, organic conductors and polymer matrices for high-performance composites all depend on the behavior of collections of molecules: the characteristics of single molecules are important only to the extent that they contribute to collective behavior. In synthesis directed toward materials, the desired

physical properties cannot be dissociated from synthesis, and a more complete understanding of the relationships between synthesis, processing and properties are required.

1.4. ENVIRONMENTALLY FRIENDLY SYNTHESIS

Probably the most serious problem now facing the chemical industry is to develop environmentally compatible technology for synthesis (especially large-scale synthesis). The field of environmentally friendly synthesis is a peculiar one. It is unarguably important, and it presents a range of interesting and engaging challenges. Despite these characteristics, very few academic synthetic chemists are working in it. Why? One reason is that the attention of the community of synthetic chemists has not yet been caught; a second is that there are surprisingly few leads to appropriate processes, and surprisingly few really good new ideas; a third is that economic and regulatory considerations are an integral part of all environmental synthesis, and academic chemists have traditionally been uncomfortable in problems requiring an understanding of economics. Whether the field of environmental synthesis is ultimately attacked by chemistry or by chemical engineering remains to be seen.

2. Covalent and Non-covalent Synthesis

Organic synthesis has been dominated by a single intellectual paradigm — that of "covalent synthesis." In this paradigm, molecules — that is, collections of atoms connected by strong, kinetically stable covalent bonds — are constructed in a series of steps focused on stepwise, efficient formation of covalent bonds. Are there alternatives to this paradigm? Both biology and materials science are replete with instances in which the crucial structural elements involve *non-covalent* bonding: examples include interactions between proteins in aggregates, the interactions that give molecular and liquid crystals their structures and properties, and the interactions that hold together the two strands of DNA itself. In each of these types of structures, covalent interactions are important, but they are not sufficient: it is often possible to modify or even cleave the amino acids in a protein and retain function, but the same polypeptide sequence in native and denatured states have very different function. In short, both covalent and non-covalent interactions are important.

One alternative to covalent synthesis as a paradigm in organic synthesis is its semantic converse — *non*-covalent synthesis. This paradigm is as important in complex systems as covalent synthesis. Instead of energetically strong interactions dictated by bond enthalpies, non-covalent synthesis utilizes weaker, non-covalent interactions that are governed by equilibrium thermodyamics: entropic considerations become as important as enthalpic ones. Non-covalent synthesis will never *replace* covalent synthesis: the components of a complex structure will undoubtedly always be based on covalent bonds. The *assembly* of these components into a functional aggregate can, however, be accomplished by either covalent or non-covalent methods.

What are the advantages of non-covalent synthesis? One way of addressing the question is to ask where non-covalent processes are already established to be important. One answer — and not necessarily the only answer — is when very large structures are required, and when the function of these structures must be controlled at room temperature. There is no practical method of making a molecule of the three-dimensional complexity of a protein by covalent synthesis: two-dimensional synthesis based on a reactions with very high yields, followed by non-covalent assembly (folding) is a more practical procedure. The resulting structures are, of course, unstable at even moderately elevated temperatures (one wonders what strategies life might have evolved if it had been necessary to survive environments of 500 C!). Similarly, the synthesis of a macroscopic crystal, one bond at a time, is entirely out of the question. Non-covalent synthesis is a strategy that is suited for preparation of these ensembles, where the yield losses that inevitably accompany covalent synthesis are unacceptable. Non-covalent bonding — aggregation, association, folding, annealing — is an efficient strategy, and one that can, in principle, proceed in 100% yield!

The issue of control is a more complex subject, and often has (at least in biological contexts) to do with transitions between different but well-defined conformational states. Although there are strong arguments for non-covalent structures (and non-covalent synthesis) in systems subject to modulation and control at room temperature, we will not address this subject here other than to note the obvious: only non-covalent structures based on bonds of strengths comparable to kT can be interconverted by thermal processes.

2.1. PRECENDENTS FOR NON-COVALENT SYNTHESIS

There are a wide range of precedents for non-covalent synthesis. Biological structures present a number of strategies based on structures in which hydrogen bonds and hydrophobic interactions are crucial [1]. Molecular crystals provide another very important set (and one in which the basic rules are still not defined!) [2-5]. Liquid crystals [6], black lipid films [7], micelles and liposomes [8], clathrates and co-crystals [9], bubble rafts [10], and phase-separated polymers [11], provide others. Not surprisingly, non-covalent interactions between covalently structured molecules are important and common throughout complex systems; what is missing is a rational process for using these interactions in synthesis.

2.2. THERMODYNAMIC AND KINETIC CONSIDERATIONS IN NON-COVALENT SYNTHESIS

A key idea in non-covalent synthesis is the importation of new ideas of bonding into synthesis. Covalent synthesis is based on the use of strong, kinetically stable networks of bonds to assemble kinetically metastable structures. A wide range of bond-types — coordination bonds, hydrogen bonds, charge transfer interactions, hydrophobic interactions, charge-charge interactions — are available for the construction of new structures, but have been largely ignored as explicit components of *synthetic* strategies (although they have, of course, been the object of extensive interest in physical organic chemistry, molecular recognition, biochemistry, solid-state chemistry and other areas). Other types of considerations are also important: for example, considerations of enthalpy dominate considerations of the energetics of covalent synthesis; in non-covalent synthesis, enthalpy and entropy are both important. When entropy enters considerations of synthetic strategy, ideas such as preorganization become important [12] .

3. Systems

We have focused our work in non-covalent synthesis on two systems: self-assembled, two-dimensional monolayers based on ordered structures of alkanethiolates chemisorbed on gold, and soluble three-dimensional aggregates held together by hydrogen bonds, and based on the lattice formed by the 1:1 aggregate of cyanuric acid and melamine (CA•M).
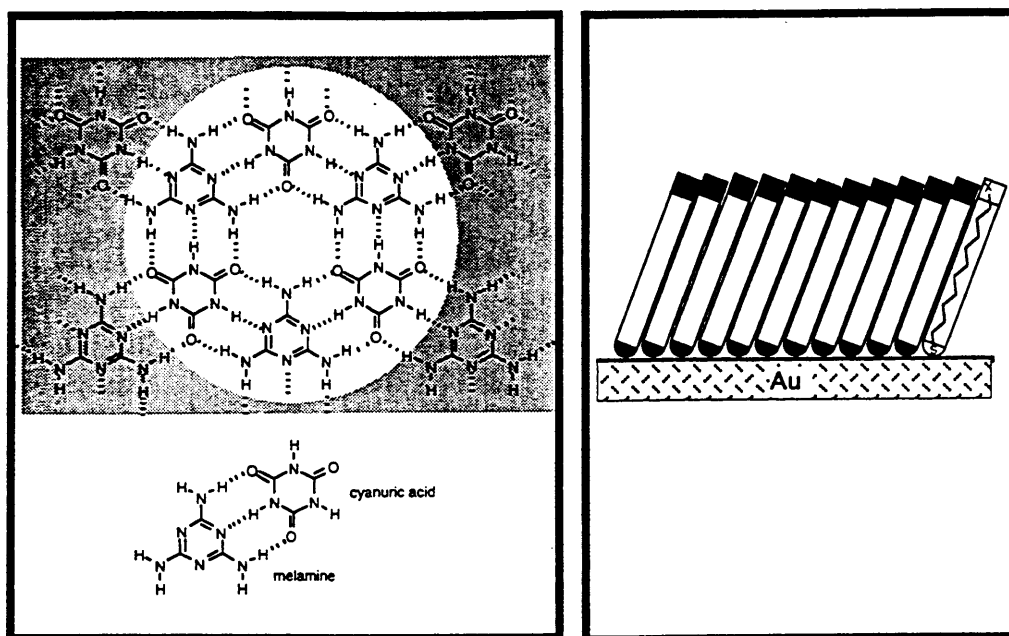
Figure 1. Representations of the CA•M lattice (left) and a
SAM (right, X = CH3, OH, COOH, CN, etc.)

3.1. SELF-ASSEMBLED MONOLAYERS

Self-assembled monolayers (SAMs) of long chain organic compounds on surfaces of metals and metal oxides are increasingly useful in applications which require structurally well-defined substrates. They are easily prepared in a wide variety of structures (thicknesses, degree of order, chain orientation with respect to the surface) and a range of functional groups can be incorporated into them. Several systems of SAMs have been investigated extensively, including those formed from alkanethiolates on gold, silver [13, 14] and copper [13, 15], alkanecarboxylic acids on alumina [16-18], alkane-hydroxamic acids on metal oxides [19], alkanephosphonates [20-24] on zirconium and aluminum oxides, alkyltrichlorosilanes or alkoxysilanes on silica [25-28] and Langmuir-Blodgett films on a range of supports [29, 30]. Of these, SAMs of alkanethiolates on gold — a system first used for rational organic surface chemistry by Nuzzo, Allara and coworkers [31-33] — has attracted the most attention. This system is exceptionally easy to work with, and is relatively stable. More importantly, it is very easy to introduce complex functionality onto a surface using it, and it thus offers a high potential for complex synthesis. SAMs are already significantly advanced as systems in materials science, and applications for them are appearing rapidly.

3.2. CYANURIC ACID•MELAMINE LATTICE

A second type of problem that we have examined is the design and synthesis of complex, high-molecular weight aggregated of molecules held together by networks of hydrogen bond. We have chosen to work with aggregates derived from the lattice of hydrogen bonds formed from the 1:1 aggregate of cyanuric acid and melamine (CA•M) [34] . This system has the advantage that synthesis of the molecules required is relatively straightforward, and that the components have high symmetry. A range of structures based on this system have been prepared. Simply mixing arbitrary derivatives of cyanuric acid and melamine together usually does not generate the desired species containing the cyclic CA3M3 "rosette": either the components dissociate in solution, or they precipitate as insoluble disordered aggregates or as linear or crinkled tapes.

Two types of designs have been successful in generating stable aggregates based on the CA•M lattice (Figure 2, left). In one, one set of components (typically the melamines, since they are easier to manipulate synthetically than are the cyanuric acids) is "preorganized" by attachment to a common "hub". This strategy *encourages* formation of the desired aggregates by reducing the change in translational (and perhaps conformational) entropy required to form the aggregate (relative to the corresponding change for the components independently free in solution). The second strategy introduces large substituents into the components to *discourage* formation of tapes and other, non-rosette structures by introducing large unfavorable steric interactions into these structures (Figure 2, right). There is, of course, an rich literature in the subject of molecular recognition, with extensive work in systems that exhibit of the phenomena of molecular recognition by Hamilton [34], Rebek [35], Stoddard [36], Lehn [37], Sauvage [38], Zimmerman [39], Breslow [40], Still [41] , Kunitake [42] , and Cram [12, 43], among others.
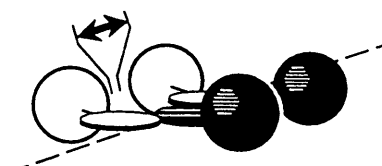
PREORGANIZATION   **PERIPHERAL CROWDING**
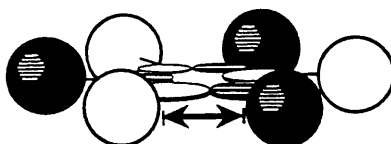
rosette   tape

Figure 2. Schematic representations of *preorganization* of three melamine by covalent attachment ot a center hub (left) and the formation of a rosette structure due to large groups (depicted here as spheres) by *peripheral crowding* (right). Melamines and cyanuric acid are represented as disks.

4. SELF-ASSEMBLED MONOLAYERS

SAMs illustrate a strategy for synthesis based on the idea of reduction in dimensionality. The generic idea underlying SAMs is to use a surface, or some other two-dimensional or pseudo two-dimensional systems, as a template and to assemble molecules on it in reasonably predictable geometry using appropriate coordination chemistry to connect the surface with the adsorbed molecules. For this strategy to work, one needs:

- A suitable coupling reaction to connect the adsorbate to the surface.
- Sufficient in-plane mobility for the adsorbate (at some stage in the processes that form the SAM) to allow it to order and to form a highly structured crystalline or quasicrystalline surface phase.
- A geometry for the adsorbate that is compatible with an ordered surface phase.
- The capability to pattern the system in the plane of the surface.

The first of these requirements is obvious: without coupling to the surface, the SAM cannot exist. The second is required to achieve high order. If the molecules cannot move on the surface, they cannot order. Bonding to the surface that is too tight interferes with the development of the ordered, crystalline, thermodynamic minimum state. The third requirement — an appropriate geometry — is currently not well understood. Most work with SAMs has been carried out with derivatives of fatty acids. These structures crystallize in the solid state in layers, with the long axes of the chains approximately parallel. Placing the same molecule in a SAM effectively freezes one plane from the crystal on an appropriate surface. How many other structures that form layers in the crystal can be transferred to a SAM remains to be established; there is virtually nothing known about the SAMs that might be drawn from most classes of organic molecules.

The fourth requirement — for techniques to form patterns in the plane of the SAM — is important for the development of molecule-like structures on surfaces. Consider a circular patch of SAM of a C_{16} hydrocarbon on a surface having a radius of 50 nm (this radius is now achievable using relatively straightforward techniques which we describe below). This patch will contain approximately 4×10^4 molecules, and have a "molecular weight" of approximately 10^7 D. This size is in the same range as very large polymers, and thus is approaching dimensions familiar to organic synthetic chemists (albeit from the upper range, rather than from the more familiar smaller sizes).

Patterning will, we believe, be an essential part of connecting self-assembling and non-covalent synthesis with more conventional methods of synthesis, and also will be essential for many applications requiring structures in the meso range of sizes.

The chemistry and structures of SAMs of alkanethiolates on gold have been extensively studied, and need not be reviewed here [44]. In brief, when fully equilibrated and in their most stable form, these SAMs seem to be two-dimensional quasicrystals, with the sulfur headgroups epitaxial on the gold surface. A 30° tilt of the trans-extended alkane chains brings these chains into van der Waals contact. Functional groups present on the termini of the chains are exposed to the solution. Conformational disorder in the system is concentrated in the terminal regions of the chains.

4.1. CHARACTERIZATION

Characterization of these structures can be accomplished using a number of techniques, with the most useful being XPS [45], polarized infrared external reflectance spectroscopy (PIERS) [46-48], measurement of contact angles, ellipsometry [49, 50] and, increasingly, STM/AFM [51-54]. Computation has also been very useful in understanding the order in these structures [55, 56]

4.2. MESO-SCALE STRUCTURES: MICRO-CONTACT PRINTING (μCP)

We have developed a number of techniques for patterning SAMs in the plane of the monolayer [57-64]. The objective of these methods is to provide procedures for achieving true meso-scale fabrication — that is, fabrication leading to structures with dimensions in the range of 10 nm to 10 μm — using techniques available in synthetic chemical laboratories. The most versatile of these techniques is one based on contact printing (which we call microcontact printing, μCP) [60, 64].

In microcontact printing, a pattern of a SAM (typically that from hexadecanethiol, since it performs well in μCP) is formed by a technique in which an elastomeric stamp is "inked" with the thiol, and then brought into contact with the surface of the gold. Features present on the stamp are transferred to patterns of SAM on the surface with remarkable fidelity: in favorable circumstances, it is possible to produce patterns with feature sizes of 200 nm, and with edge resolution for these features of approximately 50 nm. Once the initial pattern has been produced, the unpatterned areas can be filled in by exposure to a solution of another alkanethiol, an additional pattern can be generated by

stamping, or the initial pattern can be used as a mask to protect the gold film from etchants. This technique can, therefore, be used either to generate patterns of SAMs on a continuous gold film, or to generate discontinuous patterns of gold.
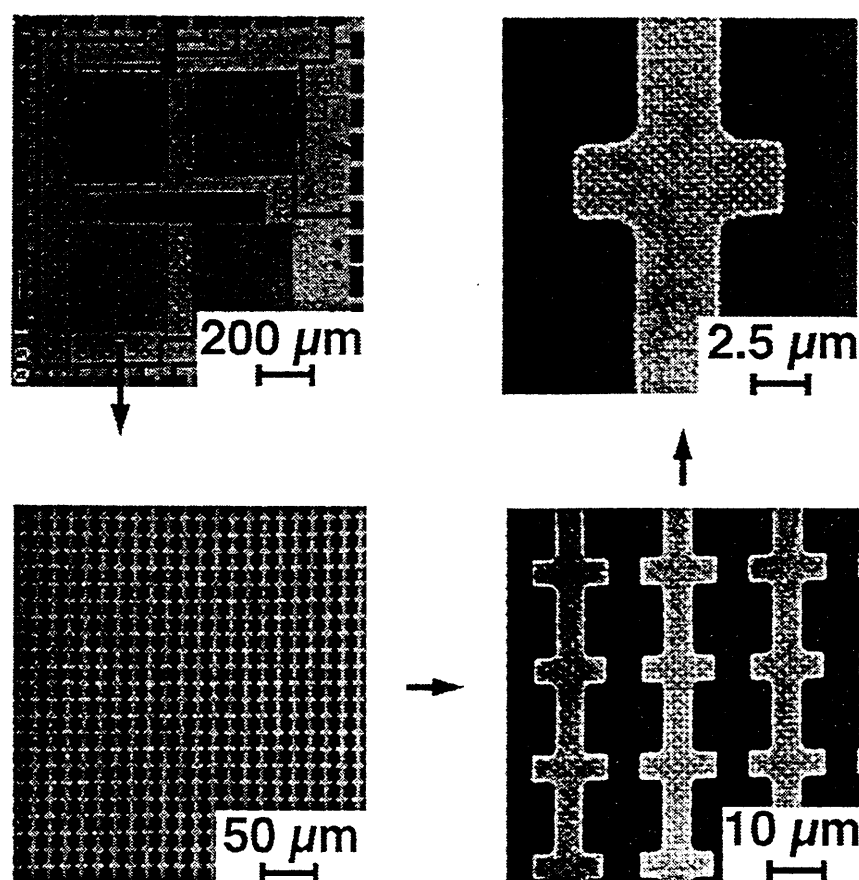

Figure 3. SEM micrographs of a pattern formed by μCP followed by chemical etching to remove gold not protected by the SAM.

The stamp used in μCP is most commonly fabricated by photolithographic procedures. An image is transferred into a film of photoresist, the exposed resist is developed to produce a three-dimensional structure, and this structure is then covered with the prepolymer from which the stamp is to be formed (typically poly(dimethylsiloxane), PDMS). The PDMS is allowed to cure, and then peeled from the master.
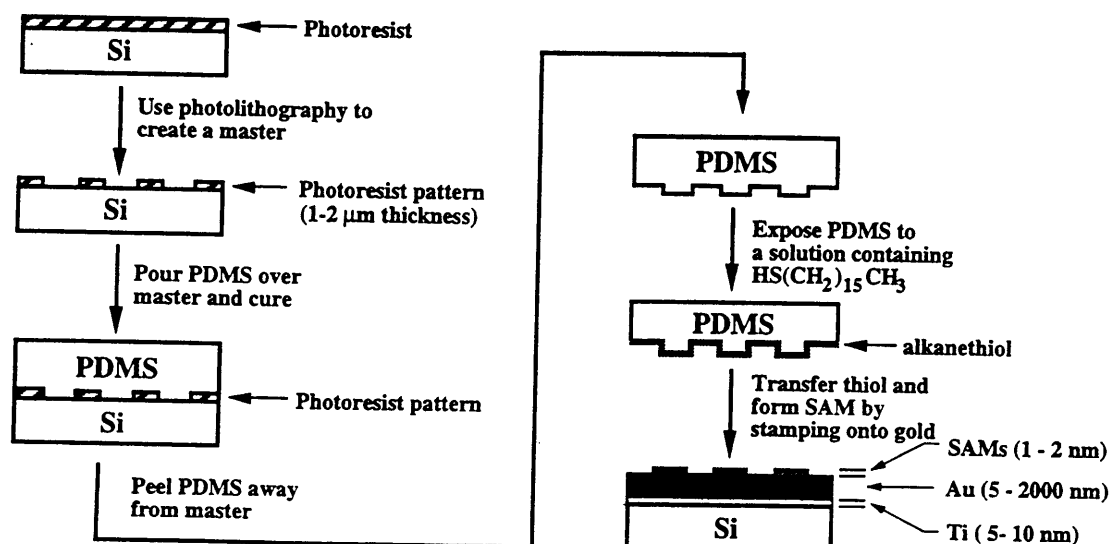
Figure 4. Schematic of the process used for μCP.

Because PDMS is an elastomer, it can generate conformal contact with a surface that is rough. We have not defined its ability to conform to steps, irregular surface topologies and imperfections on the surface of a gold film, but the fidelity of the contact printing does not seem to be limited by this capability. The ability of μCP to generate sharp edges depends on the production of *autophobic* SAMs: in these systems, the extent of reactive spreading of the alkanethiol is limited by the fact that the SAM that it forms is not wet by it, and definition of the edge of the SAM is determined by some combination of the rate of reactive spreading and the rate of formation of an organized, autophobic SAM.

4..3. EXTENSIONS TO QUASI THREE-DIMENSIONAL STRUCTURES.

Patterned gold structures on the surface of silicon/silicon dioxide can be used, in combination with anisotropic etches for silicon, to form three-dimensional structures of the surface of the silicon (Figure 5). Although there are serious limits to the types of structures that can be formed using these procedures, they are unquestionably useful in generating simple surface topologies (grooves, plateaus, ridges, etc.).
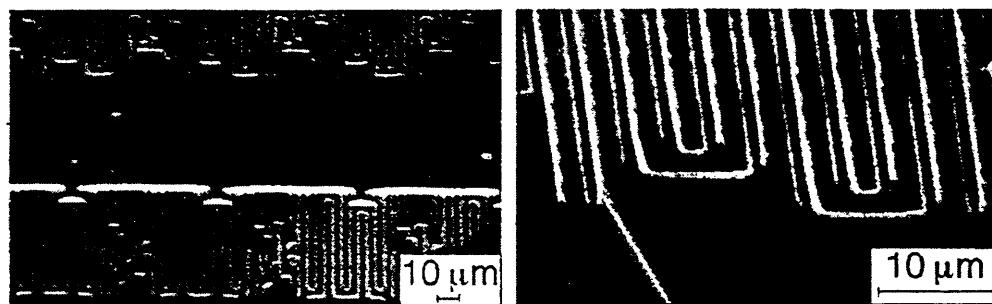
Figure 5. SEM micrographs of a three-dimensional structure fabricated by forming patterned SAMs and then using appropriate selective etches for gold and silicon [64].

5. HYDROGEN BONDED AGGREGATES BASED ON THE CA•M LATTICE

These structures are, in principle, more easily envisioned than SAMs: they do not involve reduced dimensionality or cooperative effects such as crystallization. They are effectively the application of the principles of molecular recognition to the assembly of large, three-dimensional structures. In practice, they are remarkably difficult to design, in part because controlling their entropy challenges the depth of understanding in organic of the second law of thermodynamics.

To achieve three-dimensional, non-covalent aggregates one needs:

* Bonding processes that occur at equilibrium, to permit the structure to reach a
  thermodynamic minimum
* Interactions that are directional, to simplify the task of design
* Practical synthesis of the components
* Applicable strategies such as "preorganization" to reduce the entropic cost of
  aggregation.

We have selected systems based on the CA•M lattice as being the simplest that we could identify that seemed to fit these criteria. The system is a very successful one, although it has so far generated aggregates of only intermediate sizes (Figure 6). These systems are easy to synthesize (although not necessarily easy to design!). They provide

wide latitude in three-dimensional structure, but stability, characterization and application are at a much earlier stage.
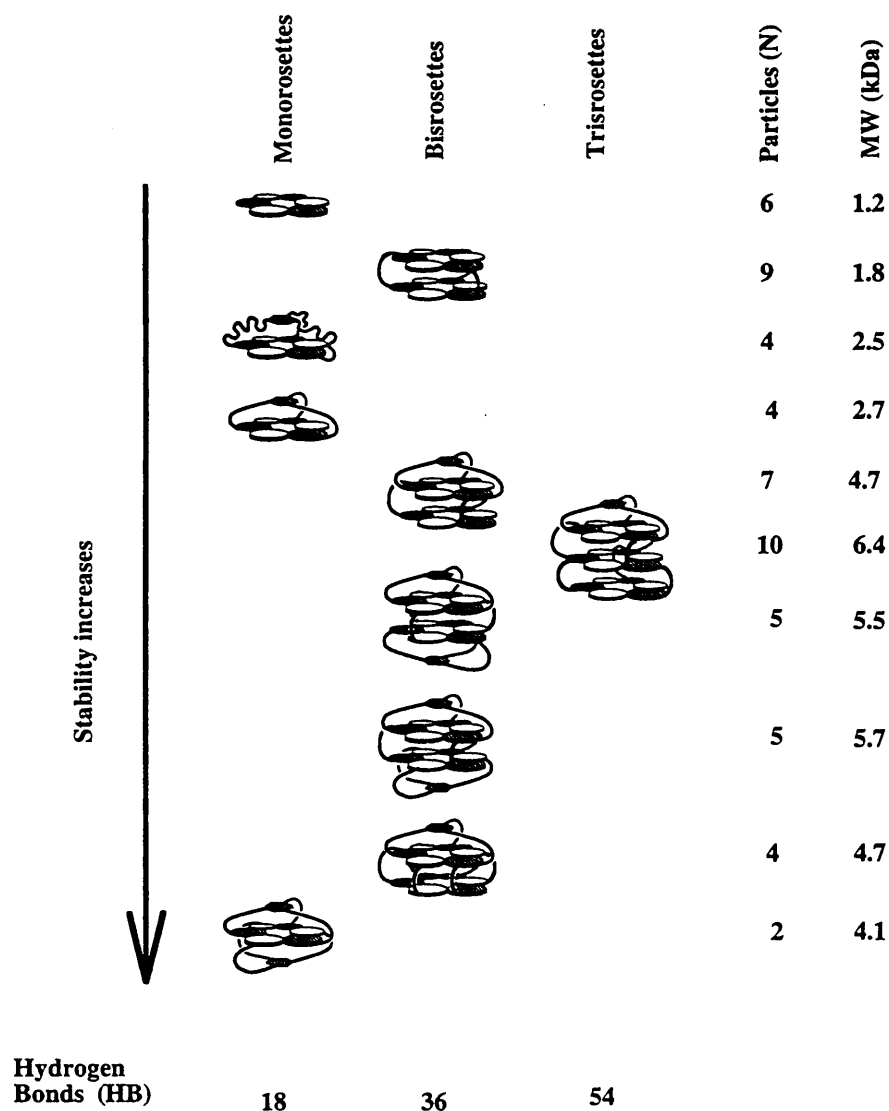

Figure 6. Aggregates based on the CA•M lattice arranged in approximate order of stability and the number of rosettes (mono-, bis-, or tris-) that they incorporate [65-73] . "Particles" refers to the number of separate molecules comprising the aggregate. "MW" is molecular weight in kDa.

5.1. CHARACTERIZATION

Characterization of these hydrogen-bonded aggregates poses some interesting challenges. It has not been possible to use mass spectroscopy with them: under all conditions that we have tried (including electrospray), they dissociate on introduction into

the spectrometer. Single-crystal x-ray diffraction has also not been generally useful because it has not been possible to grow crystals (although one relevant crystal structure of an aggregate containing a rosette has been obtained) [74]. A range of techniques have, however, provided information that has contributed to characterization of the complexes. Vapor pressure osmometry gives a approximate measure of average molecular weight. (A major uncertainty with VPO is compensating simultaneously for the non-idealities in the solution behavior of the aggregate and the internal standard. If this problem could be solved, VPO would be a very valuable quantitative technique.) Proton NMR spectroscopy, especially of the N-H region characteristic of the cyanuric acid moieties, is exceptionally useful in showing the symmetry of the aggregates, and in revealing the presence of isomers [75]. Gel permeation chromatography has been astonishingly useful in providing qualitative indications of stability. The peak shape of an aggregate as it emerges from the gel permeation column immediately gives an indication of the rate at which the aggregate dissociates on the column: if the peak is sharp, dissociation is slow relative to the time of passage through the column, and the complex is relatively stable; if the peak is broad and tails, dissociation is probably occurring on the column. Although qualitative, GPC provides a highly useful method of screening aggregates for relative stability.

The set of methods currently used for characterization provides a set of strong inferences that can help to prove or disprove a hypothesized structure for an aggregate. They do not provide the type of unambiguous proof of structure on which much of organic chemistry is built, and the development of new techniques for the characterization of non-covalent aggregates would be a welcome and useful addition to the field.

5.2. LARGE STRUCTURES

The current techniques for the design and preparation of hydrogen-bonded aggregates offer relatively straightforward approaches to structures with molecular weights in the range of 5 - 8 kD; extensions of these techniques should make it possible to prepare aggregates with molecular weights of approximately 10 kD. (The range we have set as a target is substantially larger. Proteins of average size are typically 30 kD; tRNAs are closer to 100 kD.)

6. PROGNOSIS: WHAT CAN NON-COVALENT SYNTHESIS OFFER?

Non-covalent synthesis offers one approach to large, structured collections of molecules (and hence of atoms and functional groups). Covalent synthesis provides the most flexible methodology now available for preparing stable molecules with sizes up to a few hundred atoms and a few thousand molecular weight. Beyond this range, either the flexibility of the synthetic method is compromised in order to achieve the required overall yield (as in polymerization), or yields become very (often impractically) small. Non-covalent structures may provide a compromise between the structural precision of covalent synthesis but unattractive yields characteristic of covalent synthesis, and the high molecular weights but weak structural specification provided by polymerization. Non-covalent aggregates are, however, generally less stable than covalent molecules. (It is, however, worth noting the obvious: not all covalent molecules are stable; some non-covalent systems *are* very stable — CA•M, which survives for substantial periods of time at 300 °C is an example; high stability is not required in all applications.)

6.1. STRUCTURE

The development of methods for generating large structures by non-covalent synthesis will certainly occur. Aggregates based on the CA•M structure are moving rapidly toward the sizes characteristic of small biopolymers; it should be equally possible to extend aggregates of the types examined by Lehn and coworkers — based on transition metal coordination compounds — into this range of sizes [37]. Whether patterned SAMs should be considered "aggregates" or even the products of non-covalent synthesis is an issue partially of semantics, but these structures are now made in very *large* sizes routinely, and methodology is moving from these macroscopic aggregates (1 cm^2 of a SAM of hexadecanethiolate on gold contains approximately 5×10^{14} molecules of the thiolate, or 3×10^{16} atoms, excluding the gold atoms in the system) to sizes more recognizable as quasimolecular entities (a 100 nm x 100 nm square of SAM — a size that can now be approached experimentally — contains 5×10^4 molecules of alkanethiolate, and has a molecular weight of approximately 10^7).

Non-covalent synthesis is thus approaching molecular aggregates in the range considered "big" from both below and above, and with development will provide a number of new methods of synthesizing (or "fabricating") these types of structures.

6.2. FUNCTION

SAMs are already established as providing a range of functions. They control surface properties such as interfacial free energy [76], wettability [58, 77, 78] and adhesion strength [79-81] ; they influence corrosion [82] and adhesion [83-85]; they can act as resists [59, 60, 86, 87]; they serve as electroactive layers on electrodes [88-94]. Many more functions will undoubted be developed for this class of materials. Hydrogen-bonded aggregates have, as yet, no functions.

7. WHAT LIMITS NON-COVALENT SYNTHESIS?

In the short term, the most serious limitation to the construction of large, *soluble* aggregates by non-covalent synthesis is probably the absence of systems that can be used to build stable aggregates in water. Most work in non-covalent synthesis is presently carried out in the traditional, non-aqueous solvents of organic chemistry. Hydrogen bonding is the bond type most used in assembly (metal-ligand coordination is probably second) of the aggregates. Going to water-soluble systems, and incorporating hydrophobic interactions into the design of the aggregates, would not only make the systems more relevant to biochemistry, but, perhaps more importantly, provide reliable strategies based on incorporation of charged groups to keep the relatively structured and conformationally limited species that are the targets of this kind of work in solution. It is not an accident that the backbone of DNA has a charged phosphate between every base, or that proteins are at their lowest solubility when at their isoelectric point (where they are overall electrically neutral).

In the long term, the most pressing need for non-covalent synthesis and self-assembly of macromolecular assemblies is to find applications for them. The state of these activities depends upon the area. SAMs and some other systems directed toward materials science are finding a number of applications in areas ranging from protective coatings to sensors. Applications for the hydrogen-bonded aggregates are substantially less obvious. Catalysis by design is still unattainable in any field, and it is not likely that enzyme-like activity will emerge soon from these aggregates; applications in materials science are just beginning to be explored.

Footnotes and References.

1.   Lindsey, J. S. (1991) Self-Assembly in Synthetic Routes to Molecular Devices. Biological Principles and Chemical Perspectives: A Review, *New J. Chem.* **15**, 10988-11002.

2.   Zerkowski, J. A., MacDonald, J. C., Seto, C. T., Wierda, D. A., and Whitesides, G. M. (1994) The Design of Organic Structures in the Solid State: Molecular Tapes based on the Network fo Hydrogen Bonds Present in Cyanuric Acid•Melamine Complex, *J. Am. Chem. Soc.* **116**, 2382-2391.

3.   Zerkowski, J. A., and Whitesides, G. M. (1994) Steric Control of Secondary, Solid-State Architecture in 1:1 Complexes of Melamines and Barbiturates That Crystallize as Crinkled Tapes, *J. Am. Chem. Soc.* **116**, 4298-4304.

4.   Zerkowski, J. A., Mathias, J. P., and Whitesides, G. M. (1994) New Varieties of of Crystalline Architectures Produced by Small Changes in Molecular Structure in Tape Complexes of Melamines and Barbiturates, *J. Am. Chem. Soc.* **116**, 4305-4315.

5.   Zerkowski, J. A., and Whitesides, G. M. (submitted) Investigations into the Robustness of Hydrogen-Bonded Crystalline Tapes, *J. Am. Chem. Soc.*

6.   Saeva, F. D. (1979) *Liquid Crystals: the Fourth State of Matter*; M. Dekker, New York.

7.   Fujiwara, H., and Yonezawa, Y. (1991) Photoelectric Response of a Black Lipid-Membrane containing an Amphiphilic Azobenzene Derivative, *Nature* **351**, 724-726.

8.   Menger, F. M. (1991) Groups of Organic-Molecules that Operate Collectively, *Angew. Chem. Int. Ed. Engl.* **30**, 1086-1099.

9.   Etter, M. C. (1990) Encoding and Decoding Hydrogen-Bond Patterns of Organic Compounds, *Acc. Chem. Res.* **23**, 120-126.

10. Georges, J. M., Meille, G., Loubet, J. L., and Tolen, A. M. (1986) Bubble Raft Model for Indentation with Adhesion, *Nature* **320**, 342-344.

11. Noshay, A., and McGrath, J. E. (1977) *Block Copolymers: Overview and Critical Survey*; Academic Press, New York.

12. Cram, D. J. (1988) The Design of Molecular Hosts, Guests, and Their Complexes (Nobel Lecture)., *Angew. Chem., Int. Ed. Eng.* **27**, 1009-1026.

13. Laibinis, P. E., and Whitesides, G. M. (1992) Omega-Terminated Alkanethiolate Monolayers on Surfaces of Copper, Silver and Gold have Similar Wettabilities, *J. Am. Chem. Soc.* **114**, 1990-1995.

14. Walczak, M. M., Chung, C., Stole, S. M., Widrig, C. A., and Porter, M. D. (1991) Structure and Interfacial Properties of Spontanously Adsorbed n-Alkanethiolate Monolayers on Evaporated Silver Surfaces, *J. Am. Chem. Soc.* **113**, 2370-2378.

15. Laibinis, P. E., Whitesides, G. M., Allara, D. L., Tao, Y.-T., Parikh, A. N., and Nuzzo, R. G. (1991) Comparison of the Structures and Wetting Properties of SAMs of N-Alkanethiols on the Coinage Metals Surfaces, Cu, Ag, Au, *J. Am. Chem. Soc.* **113**, 7152-7167.

16. Allara, D. L., and Nuzzo, R. G. (1985) Spontaneously Organized Molecular Assemblies. 1. Formation, Dynamics, and Physical Properties of n-Alkanoic Acids Adsorbed from Solution on an Oxidized Aluminum Surface, *Langmuir* **1**, 45-52.

17. Allara, D. L., and Nuzzo, R. G. (1985) Spontaneously Organized Molecular Assemblies. 2. Quantitative Infrared Spectroscopic-Determination of Equillibrium Structures of Solution-Adsorbed n-Alkanoic Acids on an Oxidized Aluminum Surface, *Langmuir* **1**, 52-66.

18. Tao, Y.-T. (1993) Structural Comparison of Self-Assembled Monolayers of N-Alkanoic Acids on the Surfaces of Silver, Copper, and Aluminum, *J. Am. Chem. Soc.* **115**, 4350-4358.

19. Folkers, J. P., Buchholz, S., Laibinis, P. E., Gorman, C. B., Whitesides, G. M., and Nuzzo, R. Self-Assembled Monolayers of Long-Chain Hydroxamic Acids on the Native Oxide of Metals, Manuscript in preparation.

20. Putvinski, T. M., Schilling, M. L., Katz, H. E., Chidsey, C. E. D., Mujsce, A. M., and Emerson, A. B. (1990) Self-Assembly of Organic Multilayers with Polar Order using Zirconium Phosphate Bonding between Layers, *Langmuir* **6**, 1567-1571.

21. Schilling, M. L., Katz, H. E., Stein, S. M., Shane, S. F., Wilson, W. L., Buratto, S., Ungashe, S. B., Taylor, G. N., Putvinski, T. M., and Chidsey, C. E. D. (1993) Structural Studies of Zirconium Alkylphosphonate Monolayers and Multilayer Assemblies, *Langmuir* **9**, 2156-2160.

22. Hong, H.-G., Sackett, D. D., and Mallouk, T. E. (1991) Adsorption of Well-Ordered Zirconium Phosphonate Multilayer Films on High Surface Area Silica, *Chem. Mater.* **3**, 521-527.

23. Katz, H. E., Scheller, G., Putvinski, T. M., Schilling, M. L., Wilson, W. L., and Chidsey, C. E. D. (1991) Polar Orientation of Dyes in Robust Multilayers by Zirconium Phosphate-Phosphonate Interlayers, *Science* **254**, 1485-1487.

24. Lee, H., Kepley, L. J., Hong, H.-G., Akhter, S., and Mallouk, T. E. (1988) Adsorption of ordered zirconium phosphonate multilayer films on silicon and gold surfaces, *J. Phys. Chem.* **92**, 2597-2601.

25. Maoz, R., and Sagiv, J. (1984) On the formation and structure of SAMs 1. A comparative ATR-wettability study of LB and adsorbed films on flat substrates and glass microbeads, *J. Coll. Interf. Sci.* **100**, 465-496.

26. Gun, J., Iscovici, R., and Sagiv, J. (1984) On the Formation and Structure of SAMs II. A Comparative Study of LB and Adsorbed Films Using Ellipsometry and IR Reflection-Absorption Spectroscopy, *J. Coll. Interf. Sci.* **101**, 201-213.

27. Pomerantz, M., Segmüller, A., Netzer, L., and Sagiv, J. (1985) Coverage of Si Substrates by SAMs and Multilayers as Measured by IR, Wettability, and X-ray Diffraction, *Thin Solid Films* **132**, 153-162.

28. Wasserman, S. R., Whitesides, G. M., Tidswell, I. M., Ocko, B. M., Pershan, P. S., and Axe, J. D. (1989) The Structure of Self-Assembled Monolayers of Alkylsiloxanes on Silicon: A Comparison of Rresults from Ellipsometry and Low-Angle-X-ray Reflectivity, *J. Am. Chem. Soc.* **111**, 5852-5861.

29. Möbius, D. (1981) Molecular Cooperation in Monolayer Organizates, *Acc. Chem. Res.* **14**, 63-68.

30. Swalen, J. D., Allara, D. L., Andrade, J. D., Chandross, E. A., Garoff, S., Israelachivili, J., McCarthy, T. J., Murray, R., Pease, R. F., Rabolt, J. F., Wynne, K. J., and Yu, H. (1987) Molecular Monolayers and Films, *Langmuir* **3**, 932-950.

31. Nuzzo, R. G., and Allara, D. L. (1983) Adsorption of Bifunctional Organic Disulfides on Gold Surfaces, *J. Am. Chem. Soc.* **105**, 4481-4483.

32. Nuzzo, R. G., Fusco, F. A., and Allara, D. L. (1987) Spontaneously Organized Molecular Assemblies. 3. Preparation and Properties of Solution Adsorbed Monolayers of Organic Disulfides on Gold Surfaces, *J. Am. Chem. Soc.* **109**, 2358-2368.

33. Chidsey, C. E. D., Porter, M. D., and Allara, D. L. (1986) Electrochemical Characterization of N-Alkyl Thiol, Sulfide, and Disulfide Monolayers on Gold, *J. Electrochem. Soc.* **133**, 130.

34. Geib, S. J., Vicent, C., Fan, E., and Hamilton, A. D. (1993) A Self-Assembling Hydrogen-Bonded Helix, *Angew. Chem., Int. Ed. Eng.* **32**, 119-121.

35. Wyler, R., deMendoza, J., and Rebek, J. (1993) A Synthetic Cavity Assembles Though Self-Complimentary Hydrogen Bonds., *Angew. Chem., Int. Ed. Eng.* **32**, 1699-1701.

36. Ballardini, R., Balzani, V., Gandolfi, M. T., Prodi, L., Venturi, M., Philp, D., Ricketts, H. G., and Stoddart, J. F. (1993) A Thermodynamically Driven Molecular Machine, *Angew. Chem., Int. Ed. Eng.* **32**, 1301-1303.

37. Baxter, P., Lehn, J. M., DeCian, A., and Fisher, J. (1993) Self-Assembly, Structure, and Sponteous Resolution of a Trinuclear Triple Helix from an Oligobipyridine Ligand and Ni(II) Ions, *Angew. Chem., Int. Ed. Eng.* **32**, 703-706.

38. Nierengarten, J. F., Dietrich-Buchecker, C. O., and Sauvage, J. P. (1994) Synthesis of Doubly Interlocked 2-Catenanes, *J. Am. Chem. Soc.* **116**, 375-376.

39. Zimmerman, S. C., Saionz, K. W., and Zeng, Z. (1993) Chemically Bonded Stationary Phases that Use Synthetic Hosts Containing Aromatic Binding Clefts: HPLC Analysis of Nitro-Substituted Polycyclic Aromatic Hydrocarbons., *Proc. Natl. Acad. Sci., U.S.A.* **90**, 1190-1193.

40. Breslow, R., and Graft, A. (1993) Geometry of Enolization Using a Bifunctional Cyclodextrin Based Catalyst, *J. Am. Chem. Soc.* **115**, 10988-9.

41. Borchardt, A., and Still, W. C. (1994) Synthetic Receptor Binding Elucidated with an Encoded Combinatorial Library, *J .Am. Chem. Soc.* **116**, 373-4.

42. Kunitake, T. (1992) Synthetic Bilayer Membranes: Molecular Design, Self-Organization, and Application, *Angew. Chem., Int. Ed. Eng.* **31**, 709-726.

43. Helgeson, R. C., Selle, B. J., Goldberg, I., Knobler, C. B., and Cram, D. J. (1993) 18-Membered-Ring Sperands Containing Five Anisyl Groups, *J. Am. Chem. Soc.* **115**, 11506-7.

44. For a review of SAM structure, characterization and physical properties, see: Whitesides, G. M., and Gorman, C. B. (1994) Self-Assembled Monolayers: Models for Organic Surface Chemistry in A. T. Hubbard (ed), *Handbook of Surface Imaging and Visualization*; CRC Press, Boca Raton, Florida.

45. Bain, C. D., and Whitesides, G. M. (1989) Attenuation Lengths of Photoelectrons in Hydrocarbon Films, *J. Phys. Chem.* **93**, 1670-1673.

46. Nuzzo, R. G., Dubois, L. H., and Allara, D. L. (1990) Fundamental Studies of Microscopic Wetting on Organic Surfaces. 1. Formation and Structural Characterization of a Self-Consistent Series of Polyfunctional Organic Monolayers, *J. Am. Chem. Soc.* **112**, 558-569.

47. Nuzzo, R. G., Korenic, E. M., and Dubois, L. H. (1990) Studies of the Temperature-Dependent Phase Behavior of Long Chain N-Alkyl Thiol Monolayers on Gold, *J. Chem. Phys.* **93**, 767-773.

48. Dubois, L. H., and Nuzzo, R. G. (1992) Synthesis, Structure, and Properties of Model Organic-Surfaces, *Annu. Rev. Phys. Chem.* **43**, 437-463.

49. Bain, C. D., and Whitesides, G. M. (1989) Formation of Monolayers by the Coadsorption of Thiols on Gold: Variation in the Length of the Alkyl Chain, *J. Am. Chem. Soc.* **111**, 7164-7175.

50. Bain, C. D., Troughton, E. B., Tao, Y.-T., Evall, J., Whitesides, G. M., and Nuzzo, R. G. (1989) Formation of Monolayer Films by the Spontaneous Assembly of Organic Thiols from Solution onto Gold, *J. Am. Chem. Soc.* **111**, 321-335.

51. Schöenbert, C., Sondag-Huethorst, J. A. M., Jorritsma, J., and Fokkink, L. G. J. What are the "Holes" in Self-Assembled Monolayers of Alkanethiols on gold?, Submitted.

52. Kim, Y.-T., McCarley, R. L., and Bard, A. J. (1993) Observation of N-Octadecanethiol Multilayer Formation from Solution onto Gold, *Langmuir* **9**, 1941-1944.

53. Alves, C. A., Smith, E. L., and Porter, M. D. (1992) Atomic Scale Imaging of Alkanethiolate Monolayers at Gold Surfaces with Atomic Force Microscopy, *J. Am. Chem. Soc.* **114**, 1222-1227.

54. Pan, J., Tao, N., and Lindsay, S. M. (1993) An AFM Study of Self-Assembled Octadecyl Mercaptan Monolayer Adsorbed on Gold(111) Under Potential Control, *Langmuir* **9**, 1556-1560.

55. Hautman, J., and Klein, M. L. (1989) Simulation of a Monolayer of Alkyl Thiol Chains, *J. Chem. Phys.* **91**, 4994-5001.

56. Siepmann, J. I., and McDonald, I. R. (1993) Domain Formation and System-Size Dependence in Simulations of Self-Assembled Monolayers, *Langmuir* **9**, 2351-2355.

57. Abbott, N. L., Folkers, J. P., and Whitesides, G. M. (1992) Manipulation of the Wettability of Surfaces on the 0.1- to 1-Micrometer Scale through Micromachining and Molecular Self-Assembly, *Science* **257**, 1380-1382.

58. Biebuyck, H. A., and Whitesides, G. M. Self-Organization of Organic Liquids on Patterned Self-Assembled Monolayers of Alkanethiolates on Gold, Submitted.

59. Kumar, A., Biebuyck, H. A., Abbott, N. L., and Whitesides, G. M. (1992) The Use of Self-Assembled Monolayers and a Selective Etch to Generate Patterned Gold Features, *J. Am. Chem. Soc.* **114**, 9188-9189.

60. Kumar, A., and Whitesides, G. M. (1993) Features of Gold having Micrometer to Centimeter Dimensions can be formed through a combination of Stamping with an

Elastomeric Stamp and and Alkanethiol "Ink" Followed by Chemical Etching, *Appl. Phys. Lett.* **63**, 2002-2004.

61. Kumar, A., and Whitesides, G. M. (1994) Patterned Condensation Figures as Optical Diffraction Gratings, *Science* **263**, 60-62.

62. López, G. P., Biebuyck, H. A., and Whitesides, G. M. (1993) Scanning Electron Microscopy can Form Images of Patterns in Self-Assembled Monolayers, *Langmuir* **9**, 1513-1516.

63. López, G. P., Biebuyck, H. A., Frisbie, C. D., and Whitesides, G. M. (1993) Imaging of Features on Surfaces by Condensation Figures, *Science* **260**, 647-649.

64. Wilbur, J. L., Kumar, A., Kim, E., and Whitesides, G. M. (in press) Microcontact Printing of Self-Assembled Monolayers: A Flexible New Technique for Microfabrication, *Adv. Mater.*

65. Mathias, J. P., Simanek, E. E., Zerkowski, J. A., Seto, C. T., and Whitesides, G. M. (1994) Structural Preferences for Hydrogen-Bonded Networks in Organic Solution- The Cyclic CA3•M3 'Rosette', *J. Am. Chem. Soc.* **116**, 4316-4325.

66. Mathias, J. P., Simanek, E. E., and Whitesides, G. M. (1994) Self-Assembly Through Hydrogen Bonding: Peripheral Crowding-A New Strategy for the Preparation of Stable Supramolecular Aggregates Based on the Parallel, Connected Rosettes, *J .Am. Chem. Soc* **116**, 4326-4340.

67. Seto, C. T., and Whitesides, G. M. (1993) Molecular Self-Assembly Through Hydrogen-Bonding: Supramolecular Aggregates Based on the Cyanuric Acid•Melamine Lattice, *J. Am. Chem. Soc.* **115**, 905-916.

68. Seto, C. T., and Whitesides, G. M. (1990) Self-Assembly Based on the Cyanuric Acid-Melamine Lattice, *J .Am. Chem. Soc.* **112**, 6409-6411.

69. Mathias, J. P., Seto, C. T., and Simanek, E. E. (1994) Self-Assembly Through Hydrogen Bonding: Preparation and Characterization of Three New Types of Supramolecular Aggregates Based on Parallel, Cyclic CA3•M3 'Rosettes', *J. Am. Chem. Soc.* **116**, 1725-1736.

70. Mathias, J. P., Simanek, E. E., and Seto, C. T. (1993) Self-Assembly Through Hydrogen Bonding: Preparation of a Supramolecular Aggregate Composed of 10 Molecules, *Angew. Chem. Int. Ed. Engl.* **32**, 1766-1769.

71. Seto, C. T., and Whitesides, G. M. (1991) Self-Assembly of a Hydrogen-Bonded 2+3 Supramolecular Complex, *J. Am. Chem. Soc.* **113**, 712-713.

72. Seto, C. T., Mathias, J. P., and Whitesides, G. M. (1993) Molecular Self-Assembly Through Hydrogen-Bonding: Aggregation of Five Molecules to Form a Discrete Supramolecular Structure, *J. Am. Chem. Soc.* **115**, 1321-1329.

73. Seto, C. T., and Whitesides, G. M. (1993) Synthesis, Characterization, and Thermodynamic Analysis of a 1+1 Self-Assembling Structure Based on the Cyanuric Acid-Melamine Lattice, *J. Am. Chem. Soc.* **1993**, 1330-1340.

74. Zerkowski, J. A., Seto, C. T., and Whitesides, G. M. (1992) Solid-State Structures of 'Rosette' and 'Crinkled Tape' Motifs Derived from the Cyanuric Acid•Melamine Lattice, *J. Am. Chem. Soc.* **114**, 5473-5475.

75. Simanek, E. E., Wazeer, M. I. M., Mathias, J. P., and Whitesides, G. M. (submitted) 1H NMR Spectroscopy of the Hydrogen-bonded Imide Groups of Hub(M)3:3CA Provides a Useful Method for the Characterization of these Aggregates, *J. Org. Chem.*

76. Schrader, M. E., and Loeb, G. I. (1992) *Modern Approaches to Wettability*; Plenum Press, New York.

77. Whitesides, G. M., Biebuyck, H. A., Folkers, J. P., and Prime, K. L. (1991) Acid-Base Interactions in Wetting, *J. Adhesion Sci. Technol.* **5**, 57-69.

78. Lee, T. R., Carey, R. I., Biebuyck, H. A., and Whitesides, G. M. (1994) The Wet... of Monolayers Films Exposing Ionizable Acids and Bases, *Langmuir* **10**, 741-749.

79. Chaudhury, M. K., and Owen, M. J. (1993) Correlation between Adhesion Hysteresis and Phase State of Monolayer Films, *J. Phys. Chem.* **97**, 5722-5726.

80. Chaudhury, M. K., and Whitesides, G. M. (1991) Direct Measurement of Interfacial Interactions between Semispherical Lenses and Flat Sheets of PDMS and Their Chemical Derivatives, *Langmuir* **7**, 1013-1025.

81. Chaudhury, M. K., and Owen, M. J. (1993) Adhesion Hysteresis and Friction, *Langmuir* **9**, 29-31.

82. Laibinis, P. E., and Whitesides, G. M. (1992) SAMs of N-Alkanethiolates on Copper are Barrier Films that Protect the Metal Against Oxidation by Air, *J. Am. Chem. Soc.* **114**, 9022-9028.

83. DiMilla, P. A., Folkers, J. P., Biebuyck, H. A., Härter, R., López, G. P., and Whitesides, G. M. (1994) Self-Assembled Monolayers of Alkanethiolates can be Formed on Transparent Films of Gold: Application to Studies of Protein Adsorption and Cell Attachment and Growth, *J. Am. Chem. Soc.* **116**, 2225-2226.

84. Singhvi, R., Kumar, A., Lopez, G. P., Stephanopoulos, G. N., Wang, D. I. C., Whitesides, G. M., and Ingber, D. E. (1994) Engineering Cell Shape and Function, *Science* **264**, 696-698.

85. López, G. P., Albers, M. W., Schreiber, S. L., Carroll, R., Peralta, E., and Whitesides, G. M. (1993) Convenient methods for patterning the adhesion of mammalian-cells to surfaces using SAMs of alkanethiolates on gold, *J. Am. Chem. Soc.* **115**, 5877-5878.

86. Ross, C. B., Sun, L., and Crooks, R. M. (1993) Scanning Probe Lithography. 1. STM Induced Lithography of Self-Assembled N-Alkanethiol Monolayer Resists, *Langmuir* **9**, 632-636.

87. Tiberio, R. C., Craighead, H. G., Lercel, M., Lau, T., Sheen, C. W., and Allara, D. L. (1993) SAM Electron Beam Resist on GaAs, *Appl. Phys. Lett.* **62**, 476-478.

88. Chidsey, C. E. D., Bertozzi, C. R., Putvinski, T. M., and Mujsce, A. M. (1990) Coadsorption of Ferrocene-terminated and Unsubstituted Alkanethiols on Gold: Electroactive SAMs, *J. Am. Chem. Soc.* **112**, 4301-4306.

89. Chidsey, C. E. D., and Loiacono, D. N. (1990) Chemical Functionality in SAMs: Structural and Electrochemical Properties, *Langmuir* **6**, 682-691.

90. Chidsey, C. E. D. (1991) Free Energy and Temperature Dependence of Electron Transfer at the Metal-Electrolyte Interface, *Science* **251**, 919-922.

91. Collinson, M., Bowden, E. F., and Tarlov, M. J. (1992) Voltammetry of Covalently Immobilized Cytochrome c on Self-Assembled Monolayer Electrodes, *Langmuir* **8**, 1247-1250.

92. Finklea, H. O., Avery, S., Lynch, M., and Furtsch, T. (1987) Blocking Oriented Monolayers of Alkyl Mercaptans on Gold Electrodes, *Langmuir* **3**, 409-413.

93. Hickman, J. J., Ofer, D., Zou, C., Wrighton, M. S., Laibinis, P. E., and Whitesides, G. M. (1991) Selective Functionalization of Gold Microstructures with Ferrocenyl Derivatives via Reaction with Thiols or Disulfides: Characterization by Electrochemistry and Auger Electron Spectroscopy, *J. Am. Chem. Soc.* **113**, 1128-1132.

94. Miller, C., Cuendet, P., and Grätzel, M. (1991) Adsorbed Omega-Hydroxy Thiol Monolayers on Gold Electrodes: Evidence for Electron Tunnelling to Redox Species in Solution, *J. Phys. Chem.* **95**, 877-886.