

Patterned Self-Assembled Monolayers and Meso-Scale Phenomena

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Introduction

Meso-scale systems, that is, structures and phenomena having spatial dimensions in the range extending from large molecules (perhaps 10 nm) through viruses to eukaryotic cells (10 μm), are one of the frontiers of chemistry. These systems are the home of complexity, and understanding this complexity requires new approaches to synthesis and fabrication. Among these approaches are those based on chemical concepts such as molecular self-assembly and synthesis of structures at thermodynamic equilibrium.^{1,2}

Meso-scale systems offer opportunities to explore phenomena that occur at dimensions larger than molecules but smaller than cells. The distinctive properties of meso-scale systems arise when the characteristic length of a process of interest, such as ballistic movement of an electron,³ excitation of a collective resonance by light,⁴ diffusion of a redox-active molecule close to an electrode,⁵ or attachment and spreading of a eukaryotic cell,⁶ is similar to a dimension of the structure in (or on) which it occurs. These processes involve interactions with many atoms or molecules rather than interactions with small, localized ensembles of atoms or molecules. Meso-scale systems bridge the molecular and the macroscopic. They display collective and often nonlinear behavior. Some meso-scale structures, although short-lived, arise because they are thermodynamically stable states; examples include statistical aggregates such as micelles and microemulsion particles⁷ and liquid crystals.⁸ Biology provides many other examples of longer-lived structures (for example, folded proteins⁹

and the nucleocapsides of viruses¹⁰). Nonlinear, dynamic processes can also involve meso-scale structures: representative processes include aggregation of colloids into fractal structures,¹¹ phase separation of polymers into microdomains,¹² and heterogeneous nucleation on surfaces (e.g., condensation,¹³ crystallization,¹⁴ and electrodeposition¹⁵).

Chemistry has been hindered in its exploration of many meso-scale phenomena by its limited ability to fabricate appropriate experimental systems: techniques for synthesizing *molecules* are much more advanced than techniques for fabricating *ensembles of molecules*. The work summarized in this Account uses self-assembled monolayers (SAMs) of organic molecules on metallic substrates,¹⁶ and procedures for forming patterns in the plane of the monolayer, to provide new approaches to two- and three-dimensional, quasi-planar, meso-scale structures. SAMs offer exquisite control over structure perpendicular to the plane of the monolayer: by varying the structure of the molecular constituents of the SAM, thickness can be manipulated at the 0.1-nm level, and interfacial composition and properties can be controlled over a wide range.¹⁶ Until recently, it has been difficult to control the composition or properties of SAMs in the plane of the monolayer, although e-beam writing¹⁷ and photolithography^{18,19} provide methods for *decomposing* SAMs in patterns. We have developed methods to

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fabricate SAMs with 100 nm to 100 μm patterns.^{20–29} They require only limited (and in some cases no) access to facilities for optical lithography and are thus particularly convenient for use in chemistry laboratories. They use molecular self-assembly to form SAMs selectively in meso-scale areas.

The procedures have been developed using SAMs formed from alkanethiols on gold, copper, and silver, and they rely on several characteristics of these SAMs. (i) SAMs formed from a long-chain, hydrophobic alkanethiol on gold, copper, or silver are effective nanoresists.^{20,21,25,26,30} For example, oxidative dissolution of gold^{20,21,25,26} and electroless plating of nickel²⁰ are inhibited or prevented by the presence of a SAM. (ii) A SAM of a short-chain alkanethiolate (especially a hydrophilic one) does not protect against corrosion, but does provide limited but very useful protection against formation of another alkanethiolate when the surface is exposed to a solution of an alkanethiol or dialkyl disulfide.²¹ (iii) It is possible to form patterns of SAMs by contact printing using an elastomeric stamp^{20,22,23,25} (or by other processes such as micro-writing²⁶) and to modify or remove SAMs on a surface selectively by mechanical scribing (micromachining),^{21,26–29} photooxidation,¹⁹ electrochemical reduction,³¹ or exposure to electrons, atoms, or X-rays.^{17,32} SAMs can confer on surfaces a broad range of interfacial free energies and composition; they therefore

allow control of wettability,^{23,27–29,33} chemical and electrical permeability,^{20,21,25,26,30,34} interactions with biomolecules,^{24,35} and other properties.

Methods for Fabricating Patterns in SAMs

Microcontact Printing. Perhaps the most useful and versatile method of pattern formation is microcontact printing (μCP , Figure 1).^{20,22,23,25} In μCP , an elastomeric stamp is produced by casting poly(dimethylsiloxane) (PDMS) onto an appropriate master. A negative image of the master is produced in the cured PDMS. A range of techniques can be used to produce the masters. We often use photolithography or X-ray lithography, but other structures exhibiting corrugations (e.g., mechanically ruled diffraction gratings) have also been used as masters. The elastomeric stamp of PDMS is inked with an ethanolic solution of hexadecanethiol (HDT) and placed in contact with the surface of a polycrystalline film of gold for 20–30 s. Hexadecanethiol transfers from the protruding regions of the stamp to the surface and forms a SAM in the region of contact. Because SAMs formed from HDT are not wetted by HDT, excess HDT on the stamp remains on the stamp and is not transferred to the surface. (This remarkable property, “autophobicity”, is key to the formation of patterns with sharply defined edges.)³⁶ Because the recessed features of the stamp do not touch the surface of the gold, and because the system of neat HDT and the SAM formed from it is autophobic, the regions of the gold that are not contacted by the stamp are also not derivatized by the HDT.

After removal of the stamp, the gold surface can be contacted with a dilute ethanolic solution containing a second alkanethiol (for example, 11-mercaptoundecanol, $\text{HS}(\text{CH}_2)_{10}\text{CH}_2\text{OH}$) or dialkyl disulfide; this second thiolate precursor selectively derivatizes the bare regions of the gold. Figure 1b shows the process of μCP and an example of a stamp and corresponding circuit pattern that was fabricated on a gold surface using this technique. Variants in this procedure permit a hydrophilic thiol to be used as the initial material for formation of a pattern. In favorable cases, features as small as 200 nm have been generated by μCP .²⁰

Microwriting. Microwriting (Figure 2), performed

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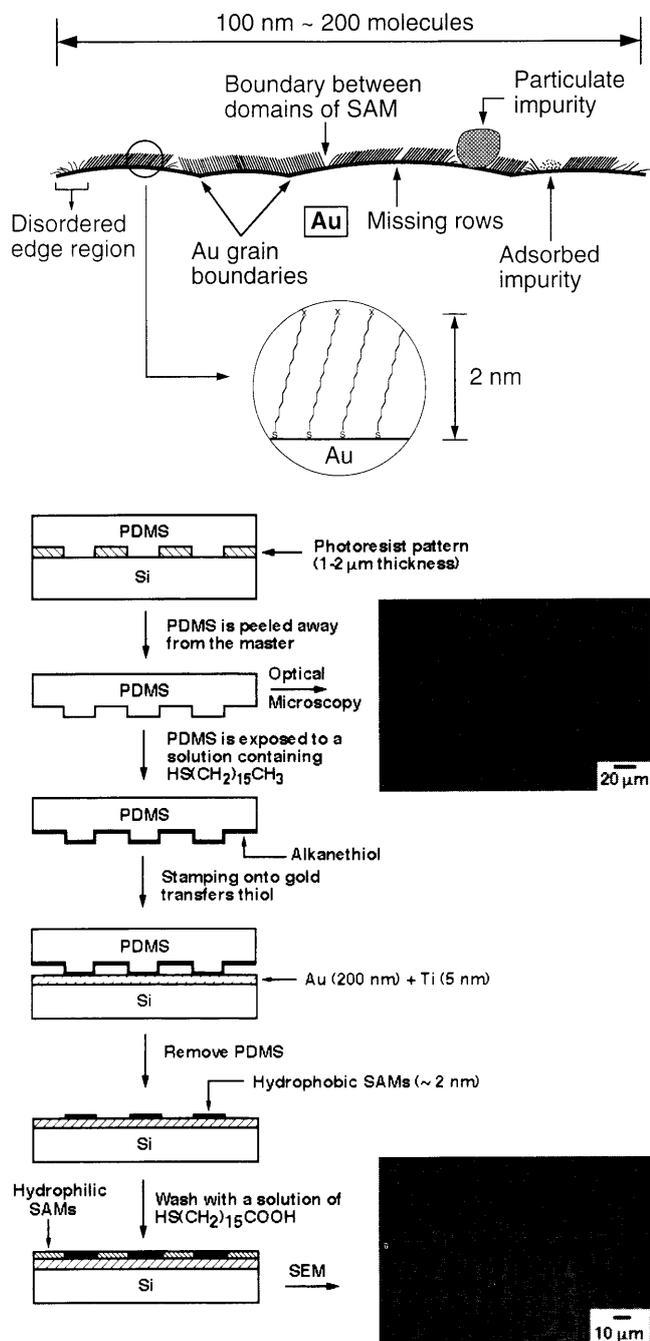


Figure 1. Microcontact printing of SAMs on surfaces of gold. The schematic representation at the top shows the structure formed at the smallest current scale of μ CP. The width of this feature is approximately 100 nm across (\sim 200 molecules of alkanethiolates); its thickness is \sim 2 nm. A number of irregularities in the structure contribute to its properties. The sequence of steps ending in the lower left outlines the processes used in μ CP. The top figure is an optical micrograph of a stamp, and the bottom is an electron micrograph of the corresponding circuit pattern fabricated with this stamp. The light regions are the hydrophobic regions.

by dispensing neat HDT from the tip of a fine pen or capillary onto the surface of a film of gold, also relies on the "autophobicity" of SAMs formed from HDT.^{21,26} By controlling the height of the capillary above the surface, the area of contact between the drop and the surface can be manipulated to control the "line width" of the resulting SAMs. Self-assembled monolayers with lateral dimensions of 10 μ m and macroscopic lengths (centimeters) can be routinely prepared using this method.

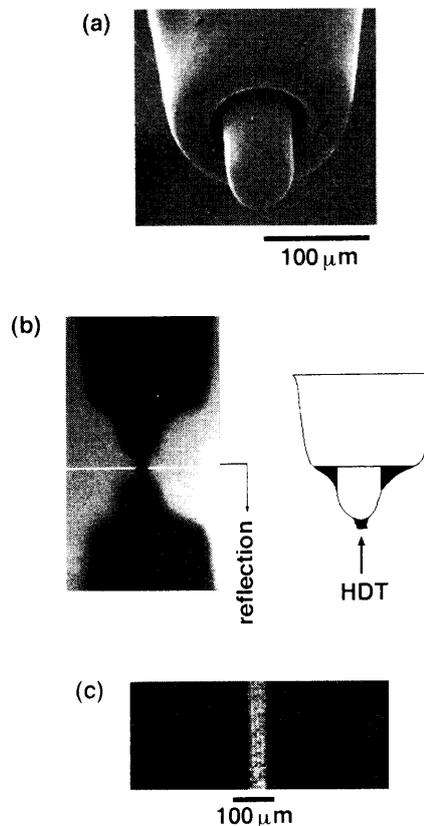


Figure 2. Microwriting: (a) an electron micrograph of a representative pen used for microwriting; (b) an optical photograph depicting the writing process with a drop of hexadecanethiol (HDT); (c) an electron micrograph of a patterned SAM prepared by microwriting (the light region is the SAM from HDT).

Micromachining. A combination of micromachining and molecular self-assembly provides the basis for a third principle that can be used to form meso-scale structures.^{21,26-29} The procedure has three steps (Figure 3): (i) formation of an initial SAM on the surface of a film of gold; (ii) selective removal of regions of the SAM by micromachining; and (iii) selective assembly of a second SAM on the machined regions of gold. Tools that we have used for micromachining include wires, carbon fibers, glass fibers, scalpel blades, electrochemically sharpened tungsten fibers, profilometer tips, and STM and AFM tips. By repeating steps ii and iii, this procedure can be used to prepare surfaces patterned with three or four regions capable of performing different functions;²⁷ lateral spatial resolutions of 100 nm have been achieved using the tip of a carbon fiber as the machining tool.²⁹ The ultimate limit to the spatial resolution of this method may turn out to be the rate of lateral diffusion of molecules in the SAM; this rate is presently unknown.

Other Techniques for Forming Patterns. These methods include modifying or damaging SAMs using electron and atomic beams,¹⁷ light,^{18,19} and electrochemistry.³¹ The mechanism of photooxidation of SAMs has been studied by Hemminger and Tarlov and seems to involve photooxidation of alkanethiolates to alkanesulfonates.¹⁹

Limits to Performance. For applications of patterned SAMs, the primary limits to function are defects in their two-dimensional structure. For use as resists, even nano-scale defects can nucleate etch

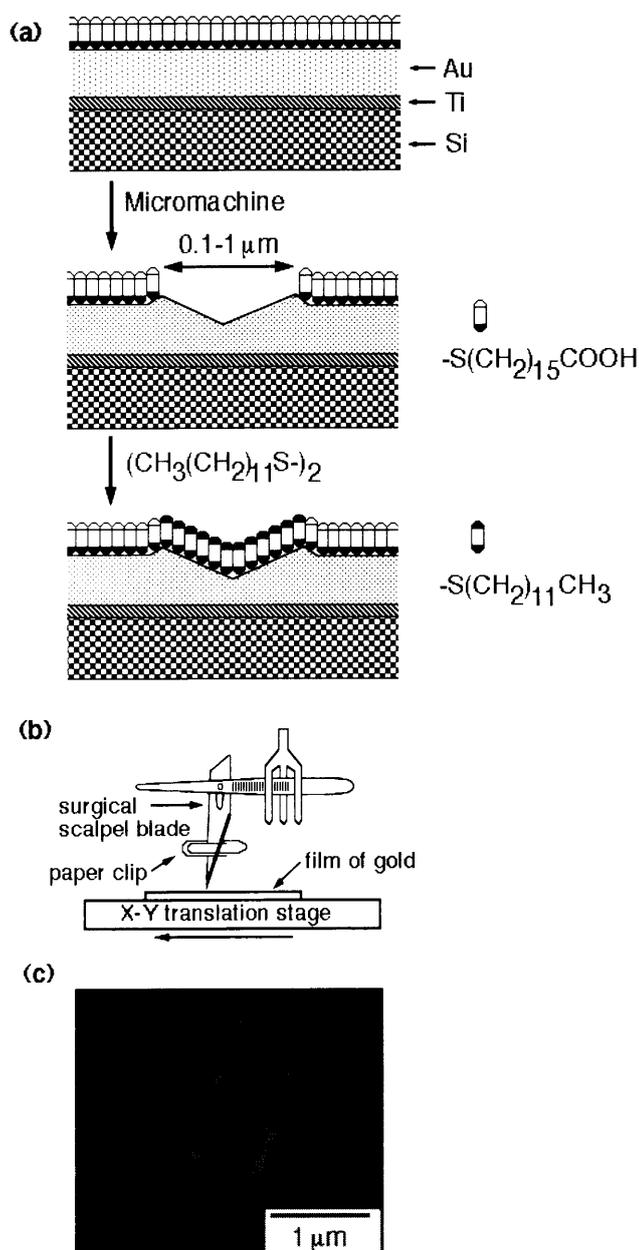


Figure 3. (a) Schematic illustration of the formation of 0.1–1- μm hydrophobic lines in a hydrophilic surface with micromachining and SAMs: Au, evaporated film of gold; Ti, evaporated film of titanium used to promote adhesion of gold to the underlying support (silicon or glass). (b) Schematic illustration of the apparatus used to position the blade and control the machining pressure. The blade was hung between a pair of tweezers that were mounted over an X–Y translation stage. The combined weight of the blade and attached paper clips maintained a constant load (~ 3 mN) on the tip during machining. The tip of the scalpel blade was translated across the film of gold at a rate of ~ 1 mm/s; this procedure produced grooves with continuous, uniform, and reproducible dimensions (~ 1 μm in width). (c) Cross-sectional profiles of the grooves show depths of ~ 0.05 mm and raised edges (~ 0.1 μm high and ~ 0.2 μm wide) formed by the plastic deformation of the gold during micromachining.

pits; for use as diffraction gratings, defects as large as micrometers may be unimportant. Detailed experiments aimed at understanding the processes that generate or eliminate defects are just beginning.³⁷

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Applications of Patterned SAMs

Planar Microfabrication. When a gold surface is exposed to a solution containing cyanide ion (CN^-) and an oxidant such as oxygen (O_2), the gold dissolves.³⁸ SAMs having 16–18 carbon atoms block this dissolution;^{20,21,25,26} other etchants can also be used.²⁰ The ability of SAMs having thicknesses of only 1–2 nm to provide protection against etching, used in combination with patterning, provides the basis for a family of methods for fabricating microstructures of gold. These planar structures, in turn, provide entries into more complex planar and three-dimensional structures. Figure 4 shows a series of electron micrographs that display the versatility of patterned SAMs in microfabrication. The smallest feature size that has been obtained is 200 nm (Figure 4b); the edge resolution in this structure is less than 50 nm.²⁰

In addition to producing microstructures of gold by selective etching, it is also possible to produce patterned substrates on which metals can be plated selectively.²⁰ When a surface with a patterned SAM of hexadecanethiolate is exposed to an electroless plating solution, nickel plates selectively on the bare regions. Selective electrochemical deposition of metals such as copper and lead, and of organic conductors such as poly(3-methylthiophene), also takes place on these bare regions.³⁹

Electrochemistry: Microelectrodes. Microelectrodes, that is, electrodes with at least one micrometer-scale dimension, make possible electrochemical measurements with a spatial resolution on the order of the size of the electrode.⁵ When micromachining and molecular self-assembly are combined, microelectrodes with a variety of geometries (grooves, wires, and micrometer-spaced pairs) can be readily prototyped in gold.⁴⁰ Their fabrication relies on two characteristics of SAMs. First, SAMs can effectively block the transfer of electrons between a film of gold and a contacting aqueous solution of redox-active molecules; micrometer-scale regions of bare gold machined into these surfaces behave as microelectrodes. Second, as described above, the selective etching of films of gold patterned with regions of monolayers formed from $\text{CH}_3(\text{CH}_2)_{15}\text{SH}$ and $\text{HO}(\text{CH}_2)_2\text{SH}$ forms microstructures of gold; these supported structures function as microelectrodes.

Spectroscopy: Patterned Substrates for Electron and Scanning Probe Microscopies. When experiments are conducted with scanning probe microscopies, whether the probe is a beam of electrons or a conducting or nonconducting tip, it is often advantageous to examine a single substrate with several well-defined regions of contrast. Such a substrate provides internal standards and frees the user from having to replace samples.^{20,41}

As an example, Figure 5a shows an atomic force microscopy (AFM) image and corresponding scanning electron microscopy (SEM) of a patterned series of lines produced through μCP . The thin lines were

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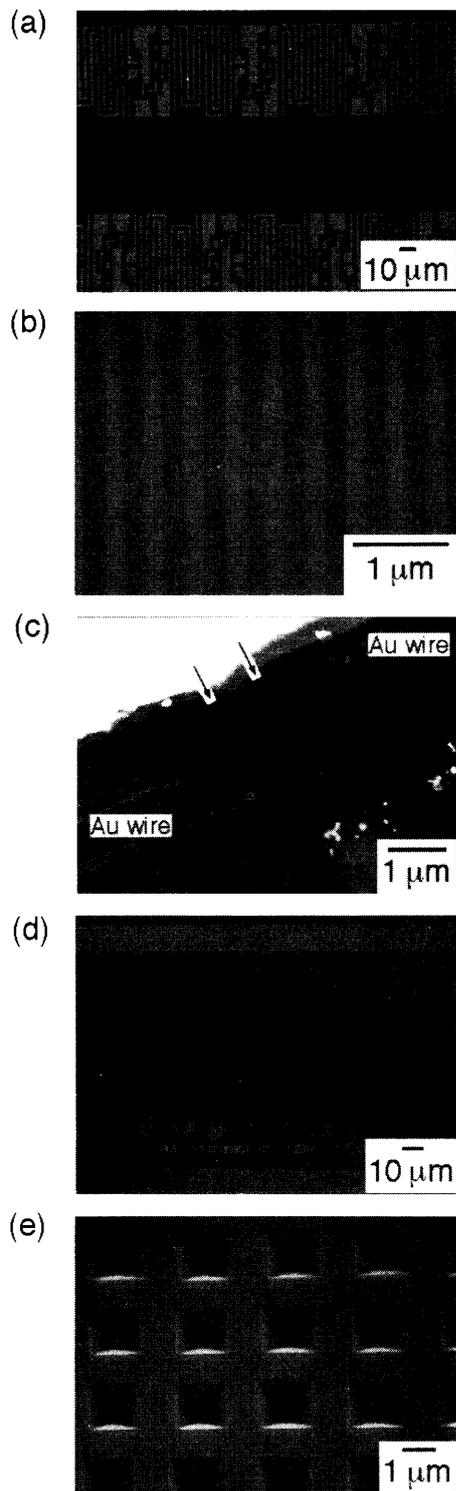


Figure 4. Microstructures fabricated using μ CP. (a) Gold structures generated by μ CP and etching. (b) The smallest features produced, to date, by μ CP. The width of the lines is 200 nm with edge resolution of 50 nm. (c) A microelectrode prepared by micromachining: collinear, 1- μ m wide, 100-nm-thick wires of gold separated by a 0.8- μ m-wide electrically insulating gap (indicated by the arrows). (d) Structures of nickel produced through selective electroless deposition on gold after μ CP. (e) Etched silicon structure produced through anisotropic etching of silicon (in KOH/2-propanol) using a mask of gold produced through μ CP and etching in a solution of cyanide ion.

produced by stamping a pattern of $\text{HS}(\text{CH}_2)_{15}\text{CH}_3$ onto a gold surface. The thicker lines were formed by subsequent exposure of the surface to $\text{HS}(\text{CH}_2)_{15}\text{COOH}$. Since the CH_3 -terminated regions adsorb fewer contaminants than the COOH -terminated re-

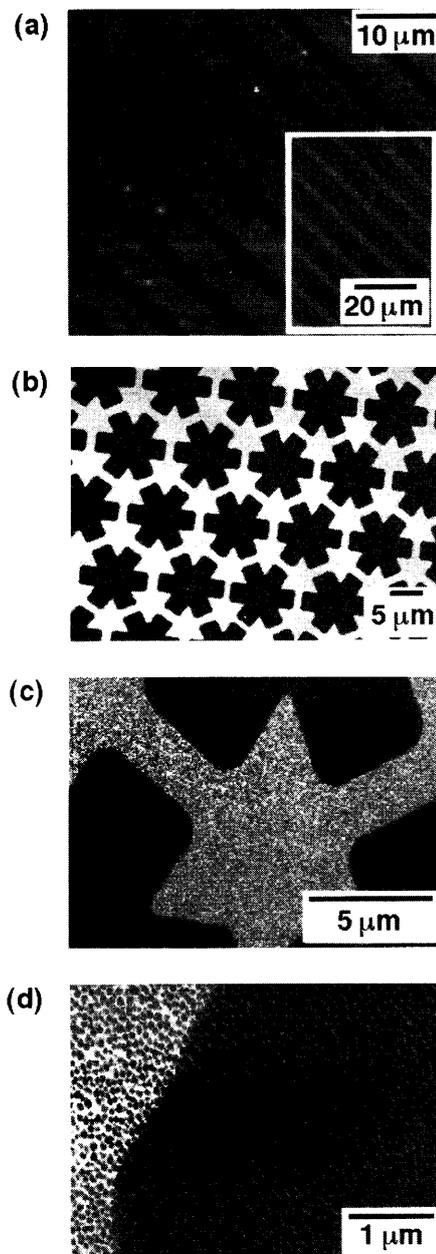


Figure 5. Images of surfaces after μ CP obtained by atomic force microscopy (AFM). (a) AFM image of a series of alternating hydrophobic and hydrophilic lines and an electron micrograph of a corresponding region. The hydrophobic regions are darker than the hydrophilic regions in the AFM image, whereas the hydrophilic regions are darker than the hydrophobic in the backscattered electron image. The contrast is reversed for the two images due to the differences in the imaging mechanisms.²⁰ (b–d) AFM images of features at successively increasing magnifications. The dark regions are hydrophobic SAMs (formed from $\text{HS}(\text{CH}_2)_{15}\text{CH}_3$), and the light regions are hydrophilic (formed from $\text{HS}(\text{CH}_2)_{15}\text{COOH}$).

gions, backscattered electrons are attenuated less than by the CH_3 -terminated regions, and the gray-scale image is reversed when examined by SEM. Figure 5b–d shows AFM images of a patterned surface at successive magnifications.

Optical Systems: Environmentally Sensitive Diffraction Gratings. Patterned multiple-component SAMs, in which the components differ in their hydrophilicity, can be used to control the condensation of droplets of water in predetermined shapes and arrays (Figure 6).²³ When a patterned surface is cooled, water condenses. Condensation occurs first on

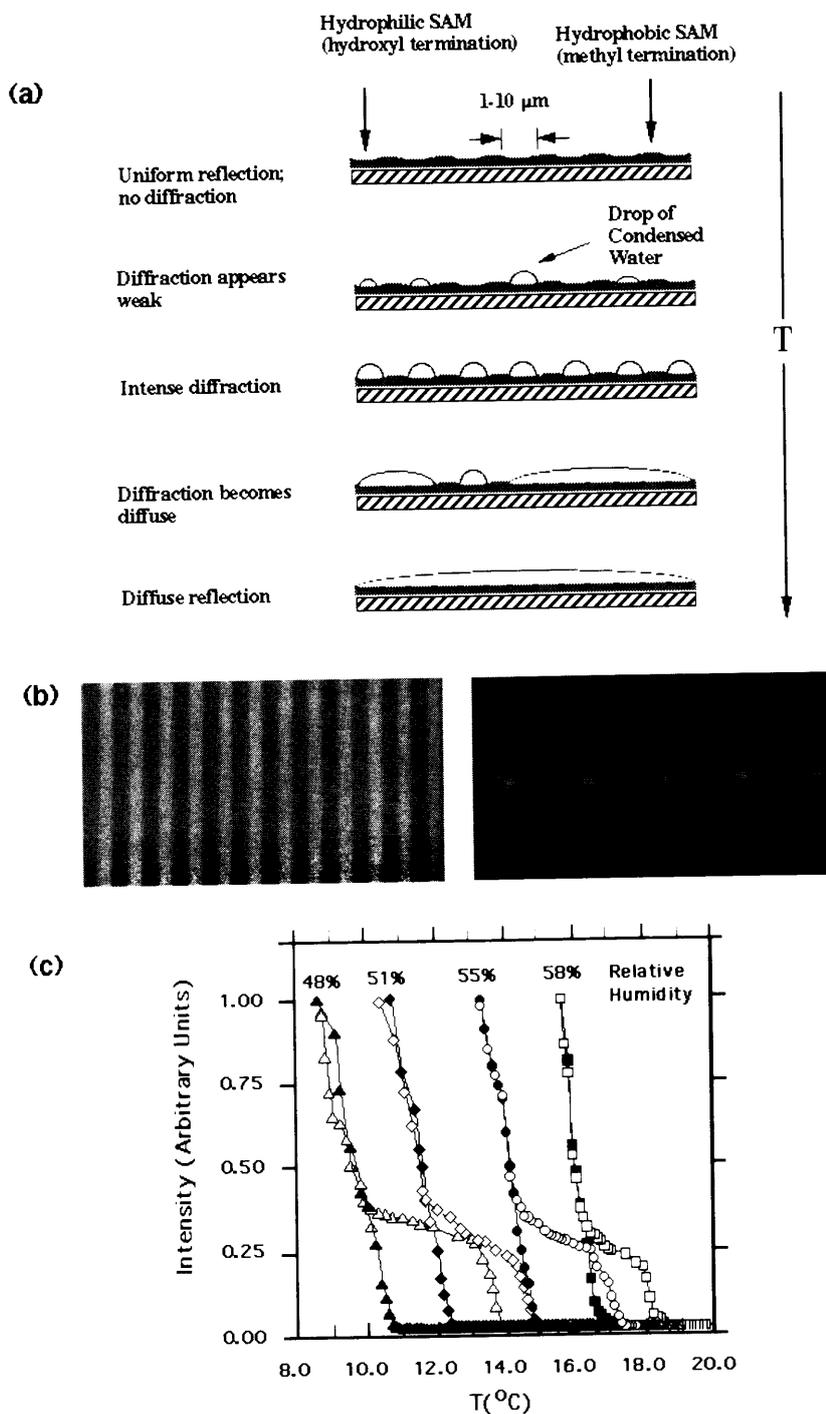


Figure 6. Condensation on patterned SAMs. (a) Pictorial representation of condensation on a patterned SAM. As the temperature is reduced, water vapor initially condenses on the hydrophilic regions. As the temperature continues to decrease, all of the hydrophilic regions are covered with water, and strong diffraction patterns are observed. Eventually the water droplets bridge across the hydrophobic regions and cover the entire surface, and diffraction of light no longer occurs. (b) Electron micrograph of a patterned surface and the corresponding diffraction pattern observed by reflecting a He:Ne laser off the surface after the formation of a condensation pattern. (c) Plot of the intensity of a first-order diffraction spot as a function of temperature at different relative humidities.

the more hydrophilic regions. The resulting periodic array of drops of water diffracts light, and the progress of condensation can be followed by measuring the change in intensity of a diffracted beam from a laser. Figure 6b shows a SEM of a surface comprising a two-component SAM and the corresponding diffraction pattern formed upon reflection of a laser beam after condensation of water. Figure 6c shows plots of the change in intensity of diffraction as the surface is cooled and warmed in atmospheres of constant relative humidities. The difference between the cooling and warming curves is probably due to pinning of the

drops, the kinetics of nucleation, and thermal balance in condensation and evaporation.

Patterned Formation of Crystals. When a surface having a SAM that is patterned into hydrophobic and hydrophilic regions is withdrawn slowly from an aqueous solution of some solute, the water is retained on the hydrophilic regions. As the water evaporates from the surface, crystals of the solute form (Figure 7).²⁰ Figure 7 shows crystals of copper sulfate (CuSO_4) formed when patterned microdrops of water are evaporated. The size of these crystals is noteworthy. The hydrophobic squares had 50- μm edges; the crys-

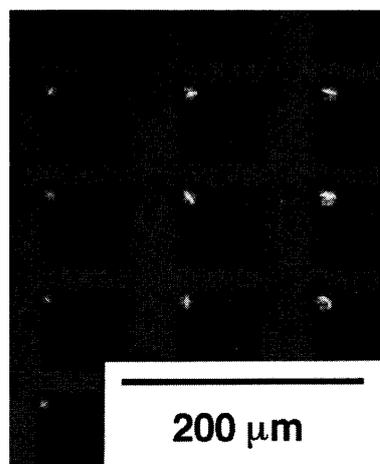


Figure 7. Directed assembly of crystals on patterned SAMs: an array of crystals that formed from microdrops containing 1 M CuSO_4 . The crystals formed in the upper, left corners due to the tilt of the sample during evaporation of the solution in the microdrops.

tals were, however, $<5 \mu\text{m}$ in size. Using this technique, stamps having relatively large features could be used to produce much smaller structures.

Three-Dimensional Microfabrication: Drops and Microlenses. We have fabricated small polymeric shapes using patterned SAMs having regions of different interfacial free energies to constrain the shapes of drops of prepolymer. Once a pattern consisting of hydrophobic and hydrophilic SAMs has been printed on gold, one can deposit an organic prepolymer selectively on the desired region of the surface.^{42,43} Self-organized polymeric structures form shapes that minimize interfacial free energies. Several polymers have been successfully used in this process: UV-cured polyurethane (NOA-60 or NOA-61, Norland) and PMMA (J-91, Summer), thermally cured PMMA (Novolac resin), and thermally cured epoxy resin (Devcon). The best results were obtained with the UV-cured polymers because they exhibited minimal shrinkage.

Figure 8a,b shows an array of microlenses made by translating patterned SAMs across the interface of a prepolymer of polyurethane and water. Figure 8c, made of PMMA, was fabricated by organizing the prepolymer in air. The shapes of these lenses can be calculated using a finite element analysis that minimizes the excess surface free energy and gravitational potential energy of each drop.²⁸

Cell Biology: Spatially Constrained and Indexed Cells. Many types of eukaryotic cells require attachment to a surface for growth. This attachment is typically mediated by specific cell-surface receptors. In the case of synthetic surfaces, proteins adsorbed onto the surface from the culture medium provide the epitopes that are recognized. By using the techniques of patterned self-assembly, it is possible to direct the

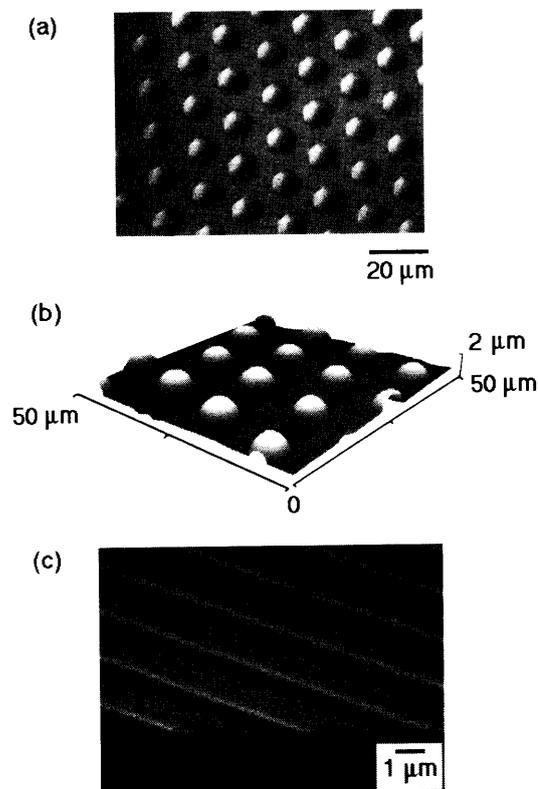


Figure 8. Assembly of three-dimensional shapes: (a) an electron micrograph of an array of microlenses fabricated by assembling a liquid prepolymer of polyurethane on a patterned surface followed by UV curing; (b) AFM image of the microlens array of part a; (c) an electron micrograph of an array of linear polymeric structures made of PMMA.

adsorption of proteins into spatially well-defined regions and, thereby, to pattern the attachment of cells. SAMs of alkanethiolates on gold have a substantial advantage over other techniques that have been used to pattern cells.⁴⁴ Because the chemistry of formation of SAMs is well-defined, and the formation of SAMs proceeds under mild conditions, it is possible to present complex and fragile ligands at their surfaces, and to engineer surfaces that resist the adsorption of proteins and attachment of cells.

Figure 9 shows an example of geometrically-constrained attachment of cells that was achieved through the use of patterned SAMs.²² A stamp was used to pattern the adsorption of HDT on gold. This surface was subsequently washed with an ethanolic solution of polyethylene glycol (PEG)-terminated alkanethiol ($\text{HS}(\text{CH}_2)_{11}(\text{OCH}_2\text{CH}_2)_6\text{OH}$). SAMs of this thiol effectively resist the adsorption of proteins.⁴⁵ Upon exposure of this surface to a solution of the extracellular matrix protein, laminin, adsorption of protein occurred exclusively on the hydrophobic SAMs formed from HDT.

Primary rat hepatocytes were plated on the laminin-coated substrate in defined media. Attachment of the hepatocytes occurred predominantly on the protein-coated islands. In addition to controlling the position of the attachment of the hepatocytes, the underlying substrate was able to control the size and spreading characteristics of the cells. Figure 9 shows that many cells adopt the shape of the island on which they

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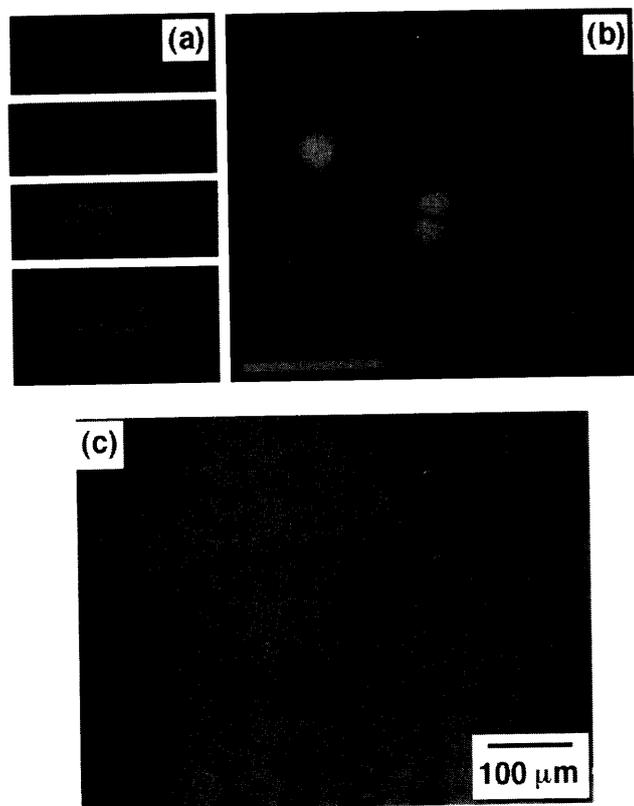


Figure 9. Comparisons of cell shapes on patterned and unpatterned surfaces. Hepatocytes plated on patterned substrates conformed to the shape of the adhesive islands (a), while those on unpatterned substrates did not (b). The cell bodies were visualized by fluorescence microscopy.²² (c) An electron micrograph of attached hepatocytes on a region showing several geometric shapes.

attach. In many cases cells exhibited corners that approximated 90° . More extensive studies have shown that the size of the island of attachment controls the physiological behavior of the cells.²² Cells attached to large islands tended to go into S-phase (as indicated by the increase in rate of DNA synthesis), while cells on smaller islands were less likely to be in S-phase, but produced greater amounts of albumin than cells in S-phase. This simple and flexible method for patterning the adsorption of mammalian cells through the patterned formation of SAMs may find use in areas of drug screening, tissue engineering, and fundamental studies in cellular biology.

Summary

Self-Assembled Monolayers. The spontaneous assembly of organic molecules on the surfaces of solids

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offers a flexible and convenient system with which to study certain meso-scale phenomena. Self-assembled monolayers are easily formed at ambient conditions and are stable for many weeks under normal laboratory conditions. Patterned and unpatterned SAMs are useful as resists for etching and plating, as substrates for microscopic studies of surface interactions in scanning probe microscopies, as optically addressable sensors, as substrates with which to study the condensation of liquids and polymer precursors, as microtemplates for crystallization, as surfaces for the attachment of proteins and cells, and in many other applications.

The ability to produce gold substrates with a wide range of thickness and optical transparency, and with electrical conductivity, make it an ideal substrate for many types of laboratory studies:⁴⁶ since the films of gold are relatively thin, the cost of the gold is a minimal consideration. In addition, gold itself can be used as a resist for etching procedures that would degrade the SAM (for example, etching silicon in strong bases).^{20,43} Although most of the work by us and others has been done on gold, silver and (to a certain degree) copper substrates are also useful.

Planar Patterning and Extension to 3-D Structures. At present the most flexible method of patterning SAMs is μ CP. The fidelity of printed features depends on several factors, including conformal contact between stamp and surface and the autophobicity of the system. Simple procedures such as etching, plating, condensation, and polymerization extend surface meso-fabrication into three dimensions. Combinations of two or more of these and other processes may provide methods to produce complex three-dimensional structures that are currently not available.

Applications. The most promising applications are those where complex surface functionality is required, or where ease of fabrication is crucial (such as prototyping microelectrodes). Although μ CP depends on contact of the stamp with the surface, the stamps have shown no degradation for over hundreds of uses that occurred over several months. Complex patterns can be easily and reproducibly fabricated in a chemical laboratory without the need for clean rooms or routine access to photolithographic equipment.

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