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Self-Assembled Monolayers of Thiolates on Metals as a Form of Nanotechnology

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1. Introduction

1.1. What Is Nanoscience?

Nanoscience includes the study of objects and systems in which at least one dimension is 1−100 nm. The objects studied in this range of sizes are larger than atoms and small molecules but smaller than the structures typically produced for use in microtechnologies (e.g., microelectronics, photonics, MEMS, and microfluidics) by fabrication methods such as photolithography. The dimensions of these systems are often equal to, or smaller than, the characteristic length scales that define the physical properties of materials. At these sizes, nanosystems can exhibit interesting and useful physical behaviors based on quantum phenomena (electron confinement,[1] near-field optical effects,[2] quantum entangle-

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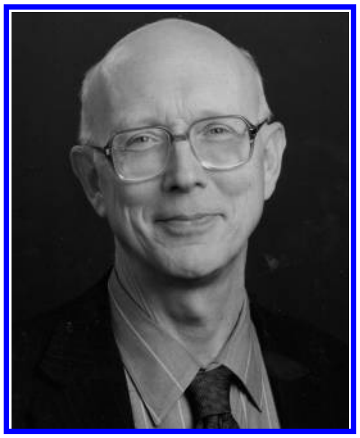


George M. Whitesides received his A.B. degree from Harvard University in 1960 and his Ph.D. degree from the California Institute of Technology in 1964. A Mallinckrodt Professor of Chemistry from 1982 to 2004, he is now a Woodford L. and Ann A. Flowers University Professor. Prior to joining the Harvard faculty in 1992, he was a member of the chemistry faculty of the Massachusetts Institute of Technology. His research interests include physical and organic chemistry, materials science, biophysics, complexity, surface science, microfluidics, self-assembly, micro- and nanotechnology, and cell–surface biochemistry.

ment,[3] electron tunneling,[4−6] and ballistic transport[7]) or subdomain phenomena (superparamagnetism,[8,9] overlapping double layers in fluids[10]).

Chemistry has played a key role in the development of nanoscience. Making and breaking bonds between atoms or groups of atoms is a fundamental component of chemistry; the products of those reactions are structures−molecules−that range in size from 0.1 to 10 nm. The development of new synthetic methods has made it possible to produce uniform nanostructures with sizes ranging from 1 to 100 nm and with new shapes (spheres, rods, wires, half-shells, cubes) and compositions (organics, metals, oxides, and semiconductors); examples include nanocrystals,[9] nanowires,[11] block copolymers,[12] and nanotubes.[13] Some of these new structures will be applied in materials science as catalysts, in medicine as components of systems for drug delivery, in magnetic storage media, and in electronic and optical devices.

Biology is a source of inspiration for nanoscience. The cell (the fundamental unit of life) is, in one view, essentially a collection of sophisticated nanomachines. Some of the components of the cell with nanometer-scale dimensions include catalysts and other functional systems (enzymes, ribozymes, proteins, and protein−RNA aggregates), lipid bilayers, ion channels, cytoskeletal elements (actin filaments and microtubules), DNA and RNA, motor proteins, vacuoles, and mitochondria.[14] These biological systems interact with one another through complex chemical pathways that regulate their activities; they self-assemble in a hierarchical manner to generate complicated, “soft” structures; they act cooperatively to sense their local environment and modify it; they enable collective functions such as motility, replication, metabolism, and apoptosis. Biological systems offer many examples of nanostructures interacting in complex networks and suggest new strategies with which to build artificial nanosystems, from the “bottom up”.

New tools for observing and manipulating atomic-, molecular-, and colloidal-scale objects, such as scanning probe and electron microscopies, have also been a significant factor in the emergence of nanoscience and nanotechnology. The remarkable ability to visualize, manipulate, and shape nanometer-scale structures with atomic resolution has, in turn, led to some fantastic ideas for new technologies, such as “assemblers”, nanorobots, and “grey goo”, that have attracted popular and regulatory attention.[15] Although these ideas are more science fiction than science/technology, they have contributed (for better and for worse) to a public interest in research in nanoscience that is now producing the beginnings of potentially important technologies; examples include composite materials with tailored toughness, electrical conductivity, or other physical properties, ultradense memories, organic electronics, new classes of biosensors, and electronic devices based on quantum effects.

1.2. Surfaces and Interfaces in Nanoscience

One distinguishing characteristic of nanometer-scale structures is that, unlike macroscopic materials, they typically have a high percentage of their constituent atoms at a surface. The volume of an object ($V \propto l^3$, where l is the characteristic length) decreases more quickly than its surface area ($S \propto l^2$) as the size diminishes: $S/V \propto l^{-1}$, where l has atomic or molecular dimensions. This scaling behavior leads, in the most extreme case, to structures where nearly every atom in the structure is interfacial. In some sense, nanostructures are "all surface".[16]

We believe that surfaces represent a fourth state of matter—they are where the gradients in properties are greatest. (In bulk phases of matter—gas, liquid, solid—the gradients are usually zero.) Atoms or molecules at the surface of a material experience a different environment from those in the bulk and thus have different free energies, electronic states, reactivities, mobilities, and structures.[17,18] The structure and chemical composition *within* macroscopic objects determines many physical properties, e.g., thermal and electrical conductivity, hardness, and plasticity. In contrast, the physical properties of nanostructures depend to a much greater extent on their surface and interfacial environment than do bulk materials.

1.3. SAMs and Organic Surfaces

Bare surfaces of metals and metal oxides tend to adsorb adventitious organic materials readily because these adsorbates lower the free energy of the interface between the metal or metal oxide and the ambient environment.[18] These adsorbates also alter interfacial properties and can have a significant influence on the stability of nanostructures of metals and metal oxides; the organic material can act as a physical or electrostatic barrier against aggregation, decrease the reactivity of the surface atoms, or act as an electrically insulating film. Surfaces coated with adventitious materials are, however, not well-defined: they do not present specific chemical functionalities and do not have reproducible physical properties.(e.g., conductivity, wettability, or corrosion resistance).

Self-assembled monolayers (SAMs) provide a convenient, flexible, and simple system with which to tailor the interfacial properties of metals, metal oxides, and semiconductors. SAMs are organic assemblies formed by the adsorption of molecular constituents from solution or the gas phase onto the surface of solids or in regular arrays on the surface of liquids (in the case of mercury and probably other liquid metals and alloys); the adsorbates organize spontaneously (and sometimes epitaxially) into crystalline (or semicrystalline) structures. The molecules or ligands that form SAMs have a chemical functionality, or "headgroup", with a specific affinity for a substrate; in many cases, the headgroup also has a high affinity for the surface and displaces adsorbed adventitious organic materials from the surface. There are a number of headgroups that bind to specific metals, metal oxides, and semiconductors (Table 1). The most extensively studied class of SAMs is derived from the adsorption of alkanethiols on gold,[19−27] silver,[26,28,29] copper,[26] palladium,[30,31] platinum,[32] and mercury.[33] The high affinity of thiols for the surfaces of noble and coinage metals makes it possible to generate well-defined organic surfaces with useful and highly alterable chemical functionalities displayed at the exposed interface.[23,34]

1.4. SAMs as Components of Nanoscience and Nanotechnology

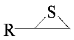
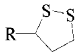
SAMs are themselves nanostructures with a number of useful properties (Figure 1). For example, the thickness of a SAM is typically 1−3 nm; they are the most elementary form of a nanometer-scale organic thin-film material. The composition of the molecular components of the SAM determines the atomic composition of the SAM perpendicular to the surface; this characteristic makes it possible to use organic synthesis to tailor organic and organometallic structures at the surface with positional control approaching ~0.1 nm. SAMs can be fabricated into patterns having 10−100-nm-scale dimensions in the plane of a surface by patterning using microcontact printing (μCP),[130,131] scanning probes,[132−134] and beams of photons,[135−138] electrons,[139] or atoms.[140,141] Phase-separated regions in SAMs comprising two or more constituent molecules can have ~100-nm^2-scale dimensions.[142]

SAMs are well-suited for studies in nanoscience and technology because (1) they are easy to prepare, that is, they do not require ultrahigh vacuum (UHV) or other specialized equipment (e.g., Langmuir−Blodgett (LB) troughs) in their preparation, (2) they form on objects of all sizes and are critical components for stabilizing and adding function to preformed, nanometer-scale objects—for example, thin films, nanowires, colloids, and other nanostructures, (3) they can couple the external environment to the electronic (current−voltage responses, electrochemistry) and optical (local refractive index, surface plasmon frequency) properties of metallic structures, and (4) they link molecular-level structures to macroscopic interfacial phenomena, such as wetting, adhesion, and friction.

1.5. Scope and Organization of the Review

This review focuses on the preparation, formation, structure, and applications of SAMs formed from alkanethiols (and derivatives of alkanethiols) on gold, silver, copper, palladium, platinum, mercury, and alloys of these metals. It emphasizes advances made in this area over the past 5 years (1999−2004). It does not cover organic assemblies formed by Langmuir−Blodgett techniques,[143] from alkylsiloxanes and alkylsilanes,[144] or from surfactants adsorbed on polar surfaces.[145] The objectives of this review are as follows: (1) to review the structure and mechanism of formation of SAMs formed by adsorption of *n*-

Table 1. Combinations of Headgroups and Substrates Used in Forming SAMs on Metals, Oxides, and Semiconductors

Ligand	Substrates	Morphology of Substrate	
		Thin Films or Bulk Material	Nanoparticles or Other Nanostructures
ROH	Fe_xO_y		35
	Si-H	36	
	Si	37	
RCOO-/RCOOH	α-Al_2O_3	38,39	
	Fe_xO_y		40
	Ni		41,42
	Ti/TiO_2	43	
RCOO–OOCR	Si(111):H	44	
	Si(100):H		
Ene-diol	Fe_2O_3		45
RNH_2	FeS_2	46	
	Mica	47	
	Stainless Steel 316L	48	
	$YBa_2Cu_3O_7$-δ	49	
	CdSe		50
RC≡N	Ag	51	
	Au		
R-N≡$N^+(BF_4^-)$	GaAs(100)	52	
	Pd	52	
	Si(111):H	52	
RSH	Ag	26	53,54
	$Ag_{90}Ni_{10}$	55	
	AgS		56
	Au	26	57
	AuAg		58
	AuCu		58
	Au_xPd_{1-x}		58
	CdTe		59
	CdSe		60
	CdS		61,62
	Cu	26	58
	FePt		63-66
	GaAs	67	
	Ge	68	
	Hg	69-71	
	HgTe		72
	InP	73	
	Ir		74
	Ni	75	
	PbS		76-78
	Pd	30	74,79
	PdAg		58
	Pt	32	80
	Ru		81
	Stainless Steel 316L	48	
	$YBa_2Cu_3O_7$-δ	82	
	Zn	83	
	ZnSe	84	
	ZnS		85
RSAc	Au	86	
	Au		87
RSR'	Au	88	
RSSR'	Ag	89	90
	Au	20	90-92
	CdS		61
	Pd	30	
	Au	93	
RCSSH	Au	94	
	CdSe		95
$RS_2O_3^-Na^+$	Au	96	98
	Cu	97	
RSeH	Ag	99	
	Au	100,101	
	CdS		60
	CdSe		102
RSeSeR'	Au	101	
R_3P	Au		103
	FeS_2	46	
	CdS		104
	CdSe		104
	CdTe		104
R_3P=O	Co		105,106
	CdS		104
	CdSe		104
	CdTe		104
RPO_3^{2-}/RP(O)$(OH)_2$	Al	107	
	Al-OH	108	
	$Ca_{10}(PO_4,CO_3)_6(OH)_2$	109	
	GaAs	110	
	GaN	110	
	Indium tin oxide (ITO)	111	
	Mica	112	
	TiO_2	113,114	
	ZrO_2	114,115	
	CdSe		116-118
	CdTe		118,119
RPO_4^{2-}	Al_2O_3	120	
	Nb_2O_5	120	
	Ta_2O_3	121	
	TiO_2	120,122	
RN≡C	Pt	123	124
RHC=CH_2	Si	37	
RC≡CH	Si(111):H	125	
$RSiX_3$ X = H, Cl, OCH_2CH_3	HfO_2	126	
	ITO	127	
	PtO	128	
	TiO_2	113,126,129	
	ZrO_2	126,129	

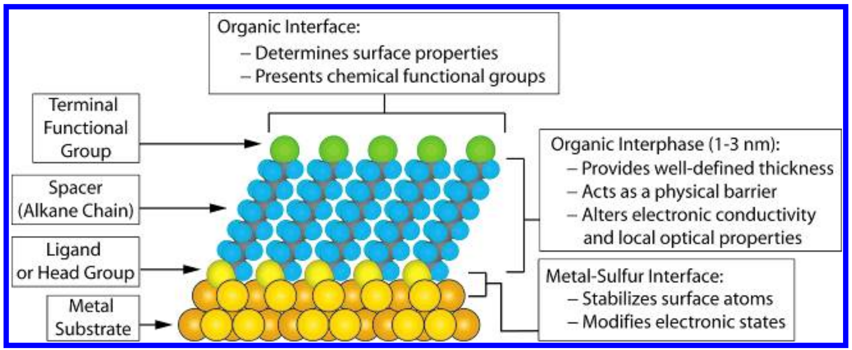


Figure 1. Schematic diagram of an ideal, single-crystalline SAM of alkanethiolates supported on a gold surface with a (111) texture. The anatomy and characteristics of the SAM are highlighted.

alkanethiols on metals, including an analysis of the thermodynamics and kinetics of these systems; (2) to illustrate applications of SAMs where (i) they act as nanostructures themselves, e.g., ultrathin films,

(ii) they enable other nanosystems, e.g., nanoparticles, (iii) they interact with biological nanostructures—proteins, etc., (iv) and they form patterns on surfaces with critical dimensions below 100 nm; (3) to outline what is *not* understood about these SAMs and which of their properties are not yet controlled; and (4) to sketch some of the important opportunities that still remain for future progress in research involving SAMs.

2. Preparation of SAMs

The early literature on SAMs (1983−1993) focused largely on the assemblies formed by the adsorption of organosulfur compounds from solution or the vapor phase onto planar metal substrates of gold and silver.[20,21,29,88,146−153] These studies used three types of organosulfur compounds: alkanethiols ($HS(CH_2)_nX$), dialkyl disulfides ($X(CH_2)_mS-S(CH_2)_nX$), and dialkyl sulfides ($X(CH_2)_mS(CH_2)_nX$), where n and m are the number of methylene units and X represents the end group of the alkyl chain ($-CH_3$, $-OH$, $-COOH$). The experiments established many of the basic structural characteristics of these systems (surface structure, chain organization, orientation), practical protocols for preparing SAMs (concentrations, length of time for immersion, solvents, temperature), and some details of the thermodynamics and kinetics governing the process of assembly. Comprehensive reviews of the early work are available.[22,144,154]

A major portion of the research on SAMs since the early 1990s has continued to expand the types of substrates used to support SAMs, and, to some degree, the types of molecules used to form them. Table 1 indicates, however, that the variety of ligands studied is still limited to functionalities formed from a small set of elements in a narrow range of oxidation states and that much of the work has continued to focus on SAMs formed from thiols. Nevertheless, the past decade has seen a significant expansion in studies that exploit the assembly of SAMs on nanostructures. The availability of new types of nanostructures with well-defined shapes and sizes on planar supports (metal structures on silicon wafers or glass slides) and in solution (nanocrystals, templated structures) has stimulated wide application of SAMs for stabilizing these new structures of metallic (and other) nanoscale materials and manipulating the interfacial/surface properties of these materials. This section of the review describes some of the types of substrates most widely used for supporting SAMs and reviews what is known about the methods for preparing SAMs from different organosulfur compounds in solution and from the vapor phase.

2.1. Types of Substrates

The surface on which a SAM forms and the physical object supporting that surface often are referred to as the "substrate". Types of substrates range from planar surfaces (glass or silicon slabs supporting thin films of metal, metal foils, single crystals) to highly curved nanostructures (colloids, nanocrystals, nanorods). Planar substrates are used widely for characterizing the structure−property relationships of SAMs because they are convenient (easy to prepare) and compatible with a number of techniques for surface analysis and spectroscopic/physical characterization such as reflectance absorption infrared spectroscopy (RAIRS),[155,156] Raman spectroscopy,[151] X-ray photoelectron spectroscopy (XPS),[157,158] high-resolution electron energy loss spectroscopy (HREELS),[158] near-edge X-ray absorption fine structure spectroscopy (NEXAFS),[159] helium atom scattering,[160,161] X-ray diffraction,[161,162] contact angle goniometry,[154] optical ellipsometry,[21,156] surface plasmon resonance (SPR) spectroscopy,[156] mass spectrometry,[163] and scanning probe microscopy (SPM).[5,153,164,165] Other metallic nanostructures, such as nanoparticles or those formed by templating, also can support SAMs, and these systems have been characterized by many techniques including electron microscopy,[166] SPM,[167,168] edge X-ray absorption fine structure spectroscopy (EXAFS) and X-ray absorption near-edge spectroscopy (XANES),[169] infrared spectroscopy,[170,171] UV−vis spectroscopy,[172] differential scanning calorimetry (DSC),[170,173] mass spectroscopy,[174] high-pressure liquid chromatography,[175] electrochemistry (see section 9.5),[176] and NMR spectroscopy.[170]

The criteria important for selecting the type of substrate and method of preparation are dependent on the application for which the SAM is used. For example, polycrystalline films are sufficient for many applications on planar substrates such as etch resists (section 8.1), templates for crystallization (section 8.3), and model surfaces for biological studies (section 8.4) because a wide range of materials can be deposited easily and these substrates are inexpensive relative to single crystals. Other applications, such as measurements of electron transport through organic molecules (section 8.2), benefit from substrates that are single crystals or polycrystalline films with minimal grain boundaries.

2.1.1. Preparation of Thin Metal Films as Substrates for SAMs

The most common planar substrates for SAMs formed from alkanethiols are thin films of metal supported on silicon wafers, glass, mica, or plastic substrates. These substrates are easy to prepare by physical vapor deposition (PVD) methods (thermal or electron beam (e-beam) evaporation),[177] electrodeposition,[178] or electroless deposition.[179−183] PVD and electrodeposition can generate thin films of a wide range of metals (including gold, silver, copper, palladium, platinum, and nickel) and alloys.

Thin Films on Glass or Silicon by PVD. A typical thin film deposited onto a silicon wafer or glass support consists of a thin primer or adhesion layer of titanium, chromium, or nickel (1−5 nm) and a layer of coinage or noble metal (10−200 nm). The primer improves the adhesion of metals that do not form oxides readily (especially gold) to substrates with an oxidized surface, e.g., silicon wafers with the native oxide, and glass slides. Metal films on glass or silicon are polycrystalline and composed of a continuous layer of contiguous islands or grains of metal that can range in size from ~10 to 1000 nm

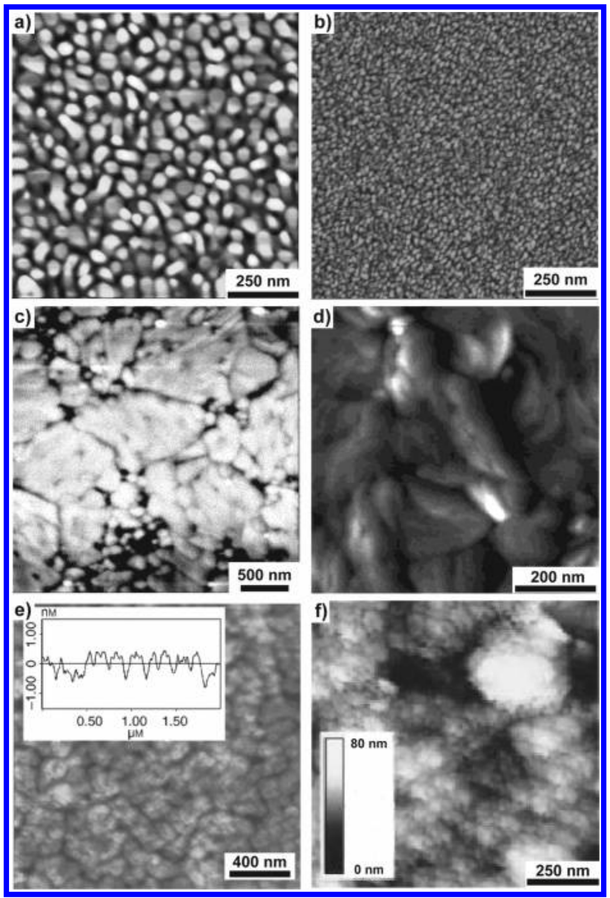


Figure 2. Scanning probe micrographs of metal thin films prepared by different techniques. AFM images of (a) a gold film (200 nm thick) deposited by electron-beam evaporation (note that the range of the topographical heights in the *z*-direction is expressed by the grayscale shading of the image, where white denotes the highest feature and black denotes the lowest one; the full range of the *z*-scale between these two extremes in (a) is 25 nm), (b) a palladium film (200 nm thick) deposited by electron-beam evaporation (range of *z*-scale = 10 nm), (c) a thermally evaporated gold film treated with dilute piranha and aqua regia solutions (range of *z*-scale = 15 nm), (d) a thermally annealed gold film (15 nm) deposited on a glass microscope slide functionalized with 3-aminopropyltrimethoxysilane (range of *z*-scale = 3.5 nm), and (e) a gold film prepared by the template-stripping method while immersed in a solution of octadecanethiol (range of *z*-scale = 3 nm). STM image of (f) a gold film prepared by electroless deposition on a glass microscope slide (range of *z*-scale = 80 nm). (c, d, and f) (Reprinted with permission from refs 188, 187, and 180. Copyright 2002, 2004, and 1998 American Chemical Society.) (e) (Reprinted with permission from ref 202. Copyright 2003 Wiley-VCH.)

(Figure 2a). As typically deposited, these films tend to have a dominant (111) texture—for fcc metals, a hexagonal presentation of the atoms at the surface—at the exposed interface.[22,26,30] The use of single-crystal substrates has allowed the study of SAMs forming on other low-index planes, particularly the (100) surface of gold.[27,184]

The morphology of the grains of thin films on glass or silicon can vary substantially depending on the experimental methods and conditions used in their formation. Semaltianos and Wilson have shown that changing the temperature of the substrate from room temperature to 400 °C during thermal deposition increases the average area of gold grains deposited on glass from ~200 to 10^6 nm^2.[185] The size and shape of the grains change from small and round to large and terraced. Abbott et al. demonstrated that deposition of metal films at oblique angles changes the grain size and roughness of the resulting metal films.[186] For example, at a particular rate of deposition the average grain size of gold can decrease from ~36 to ~14 nm as the angle of incidence onto glass substrates increases from 15° to 60°.

The composition of thin films also influences their topography. Metals with high melting points such as palladium (1552 °C) and platinum (1772 °C) tend to produce films with smaller grains than metals with lower melting points such as gold (1064 °C) when deposited at comparable deposition rates. For example, the grains in a thin film of palladium prepared on a silicon wafer by e-beam deposition are ~15−30 nm in diameter (Figure 2b); thin films of gold prepared in the same manner had grains of ~45−60 nm.[30] Differences in the sizes of grains can impact the utility of the materials in different applications of SAMs. Polycrystalline films with the smallest possible grains are desirable as substrates for microcontact printing and etching (section 8.1) structures with dimensions less than 100 nm because the small grain sizes minimize the roughness of the edges of the etched structures. Large grains are important in applications where the SAM provides an insulating barrier against electrochemical processes or biased electron transport (section 8.2). Glassy metal substrates, that is, ones with *no* grains and no long-range ordering, likely would be useful for many applications of SAMs, but there is no significant data available for SAMs on these types of materials, which typically are complex alloys of metals.

The primary method used to change the grain sizes of metal films after their preparation by PVD is thermal annealing.[180,187] Twardowski and Nuzzo demonstrated a chemical method for recrystallizing gold and gold/copper films.[188] Treatment of thick (180−200 nm) gold films with hot piranha solution (3:1 concentrated H_2SO_4:30% H_2O_2) followed by immersion in a dilute aqua regia solution (3:1:16 HCl:HNO_3:H_2O) led to coalescence of the grains and recrystallization of the surface that enhanced the (111) texture of the surface (Figure 2c).[189] Chemomechanical and electrochemical polishing can also generate flat surfaces on thick films of metal.[190]

Metal films that are optically transparent are important for applications of SAMs in biology because experiments in this field (and especially in cell biology) often require observation by transmission optical microscopy. The opacity of a thin film of metal depends on the electrical resistivity of the metal; the thickness of the film at the point where the transmission of light is nearly zero is referred to as its ‘skin depth’.[191] Partial transparency tends to be seen in films that are thick compared to their formal skin depth. For example, gold films less than ~15 nm thick are semitransparent and commonly used as substrates for SAMs in biology.[192] The morphology of the thin film also influences its optical properties: evaporation of gold or other noble metals onto bare glass tends to produce island-textured films when their thickness is less than ~100 nm. Deposition of a primer (e.g., Ti, Cr, Ni) promotes the formation of a mostly continuous metal film structure on a substrate such as glass for thicknesses >~5–10 nm, but the primers tend to diffuse through the overlying metal film to the surface over time.[193] "Blooming" of the primer is a problem because chromium and nickel are toxic to cells adherent to the SAM and bonding of sulfur to alloy surfaces is not understood. The presence of admetal impurities such as tin can also lead to cell death, and therefore, stringent cleaning of the glass substrates should be carried out for studies of this sort. Titanium does not seem to affect the viability of the cells and is the adhesion layer of choice for those systems. Chemical primers such as 3-aminopropyl-trimethoxysilane provide an alternative method for promoting the formation of continuous films of gold or other noble metals on substrates such as glass or silicon;[194] thermal annealing of films deposited on chemically modified substrates can increase the grain sizes (from ~50–100 to ~200–500 nm diameter) and the degree of crystallinity (Figure 2d).[187] Whatever the method of preparation, the optical properties of so-called "transparent" gold thin films are complex and depend sensitively on the nature and evolution of their granular structure during the course of an experiment.[195]

An excellent quartz-substrate-supported gold thin film for studies of SAMs by SPM is provided by a flame annealing protocol. The method uses brief exposure of a supported film to the flame of an oxygen–hydrogen torch.[196] This method is capable of producing exceptional quality—nearly single-crystalline, low step density—gold surfaces for the assembly of SAMs over areas as large as a few square micrometers.

Thin Films on Mica. Freshly cleaved mica supporting a thin film of metal is a common substrate used as a pseudo-"single crystal" for microscopic studies of SAMs by scanning tunneling microscopy (STM) or atomic force microscopy (AFM).[197,198] Gold films grow epitaxially with a strongly oriented (111) texture on the (100) surface of mica. The films usually are prepared by thermal evaporation of gold at a rate of ~0.1–0.2 nm/s onto a heated (400–650 °C) sample of mica. The grain sizes of these films are ~1000 nm with flat (111) terraces of ~100 nm in width.

A method called template stripping can generate surfaces with roughness <1 nm.[199] In this technique a glass slide or other solid support is glued to the exposed surface of a gold film deposited on mica, and then the gold film is peeled from the mica to expose the surface that had been in direct contact with the mica. Knarr et al. showed that the mechanical shear required to separate these surfaces is large (~1800 mN/m) and induces roughening of the gold surface.[200] Gooding et al. demonstrated that immersion of the mica–gold–support structure into liquid nitrogen cleaved the mica from the surface and produced films with roughness on the order of ~1 nm over areas of ~200 × 200 nm^2 (measured by STM).[201] Ulman et al. reported another method for reducing the mechanical stress imparted on the gold film during separation.[202] They removed the mica film in an ethanolic solution containing thiol (200 μM), and a SAM formed on the gold surface as it was exposed (Figure 2e). The roughness of these surfaces was ~0.3–0.7 nm (rms), and the advancing and receding contact angles of water on the SAMs were essentially indistinguishable, that is, there was almost no hysteresis (~1–5°). (The hysteresis measured for SAMs of alkanethiolates prepared on polycrystalline substrates with no additional treatments is ~10–20°.)[26,30]

Electroless Deposition of Thin Films. Processes for depositing thin films by chemical reduction of metal salts onto surfaces are known as "electroless" processes.[179] One advantage of these methods over PVD is that they do not require vacuum processing equipment; the chemical solutions are commercially available and only require mixing. Unlike conventional electrodeposition, electroless deposition does not require a conductive electrode and, therefore, can deposit films onto nonconductive materials.

Because electroless methods are solution-based, they are attractive for depositing thin films on nanostructures, such as colloids and nanopores, which are easily suspended or immersed in solutions, or on structures that have internal surfaces, e.g., pores.[181,183,203,204] Stroeve et al. investigated the morphology of electroless gold deposits and its implications for SAMs.[180–182] The roughness of electrolessly deposited gold on glass was greater than that for films prepared by thermal evaporation (by a factor of ~4) (Figure 2f). X-ray diffraction studies showed that the primary crystalline texture of the electroless deposits was (111) but that the surface orientation was more heterogeneous than that of films prepared by evaporation. Other highly expressed orientations included Au(200), (220), and (311).[180] Thiols form densely packed SAMs on these surfaces, but RAIR spectra for SAMs of *n*-alkanethiolates on these surfaces suggest that there is a mixture of structures present that result from the heterogeneity in surface orientations.[180,182]

Underpotential Deposition. One technique used to modify the composition at the surface of thin films is underpotential deposition (UPD). UPD is an electrochemical method for generating submonolayer coverage of one metal on another metal; the atomic adlayer forms epitaxially, that is, it adopts the ordering of the underlying surface.[205] The deposited metal can alter the nature of the surface and, therefore, influence the structure and properties of the resulting SAMs. Gold films modified by underpotential deposition with submonolayers of silver,[206,207] copper,[207,208] lead,[209] cadmium,[210] thallium,[210] and bismuth[210] can support SAMs of alkanethiolates.

2.1.2. Other Substrates for SAMs

Studies of the structure–property relationships of SAMs typically use thin films prepared on planar supports, but metal structures formed with other geometries also support SAMs. Substrates with topographical features defined by photolithography,[211,212] micromachining,[213] or replica molding also can support SAMs, albeit with structural defects in the SAM introduced at points where the topography changes abruptly.[212,214] Other common metallic structures used in nanoscience are those formed by patterned or templated deposition[203] and those (especially colloids) synthesized by the chemical reduction of metal salts in solution. Single-crystal metal substrates are another type of substrate that are useful for fundamental studies of SAMs by UHV methods such as low-energy electron diffraction (LEED), grazing incidence X-ray diffraction (GIXD),[215] and STM;[22] these substrates are more costly than those prepared by thin-film deposition and less practical for applications of SAMs under standard atmospheric conditions.

There have also been a number of reports that have examined the assembly of SAMs on the surface of liquid mercury.[69,71 70,216,217] These assemblies appear to have exceptional organization by some measures of quality (e.g., low densities of pinholes, as measured by electrochemistry)[33,218] but may lack the (semi)-crystalline order found for thiolate SAMs on gold.[69,71]

2.1.3. Why Is Gold the Standard?

The answer to this question has two parts: (1) gold forms good (but not *uniquely* good) SAMs and (2) it is historically the most studied. In fact, for many applications gold may *not* be the best substrate. There are five characteristics of gold that make it a good choice as a substrate for studying SAMs. First, gold is easy to obtain, both as a thin film and as a colloid. It is straightforward to prepare thin films of gold by physical vapor deposition, sputtering, or electrodeposition. Although expensive and not essential to most studies of SAMs, single crystals are available commercially. Second, gold is exceptionally easy to pattern by a combination of lithographic tools (photolithography, micromachining, others) and chemical etchants. Third, gold is a reasonably inert metal: it does not oxidize at temperatures below its melting point; it does not react with atmospheric O_2; it does not react with most chemicals. These properties make it possible to handle and manipulate samples under atmospheric conditions instead of under UHV—a great practical convenience for conducting experiments that require "dirty" conditions, e.g., microfabrication (outside of a clean room environment) and cell biology. Gold binds thiols with a high affinity,[20] and it does not undergo any unusual reactions with them, e.g., the formation of a substitutional sulfide interphase (see section 3.1.3). (Because thiols have a high affinity for gold, they also displace adventitious materials from the surface readily.) Fourth, thin films of gold are common substrates used for a number of existing spectroscopies and analytical techniques, including SPR spectroscopy, quartz crystal microbalances (QCM), RAIRS, and ellipsometry. This characteristic is particularly useful for applications of SAMs as interfaces for studies in biology. Fifth, gold is compatible with cells, that is, cells can adhere and function on gold surfaces without evidence of toxicity. SAMs formed from thiols on gold are stable for periods of days to weeks when in contact with the complex liquid media required for cell studies (see section 8.4).

Other materials offer similar properties, but the SAMs formed on these materials have been less studied than those on gold. Silver is the most studied substrate for SAMs of alkanethiolates next to gold, but it oxidizes readily in air and is toxic to cells.[219] It does, however, give high-quality SAMs with a simpler structure than gold (as a result of the smaller tilt angle; see section 3.1.4). Copper is interesting from a technological perspective because it is a common material for interconnects and seed layers for electroless deposits, but it is even more susceptible to oxidation than silver.[26]

Palladium seems to be a practical alternative to gold for some applications and is superior to gold for others. Although palladium is less studied than the coinage metals (Au, Ag, Cu) as a substrate for SAMs, it has a number of useful characteristics. First, thin films of palladium consist of grains 2−3 times smaller than those in gold films; this property is important for fabricating micro- and nanostructures with low density of defects and low edge roughness.[31,220] Second, it is compatible with complementary metal oxide semiconductor (CMOS) processing; gold is not.[221] Third, it offers catalytic properties that could be useful for microcatalytic structures. Fourth, it is biocompatible, and studies of SAMs on palladium as supports for adherent cells indicate that the long-term stabilities of these cell cultures are greater than those on gold.[222] Fifth, like gold, palladium does not oxidize readily at room temperature. Finally, the cost of palladium has been more volatile than that of gold historically but is, on average, equal to or less than the cost of gold.

2.2. Protocols for Preparing SAMs from Organosulfur Precursors

SAMs of organosulfur compounds (thiols, disulfides, sulfides) form on substrates by spontaneous adsorption from either the liquid or the vapor phase. Assembly from solution on the laboratory bench is convenient and sufficient for most applications of SAMs, especially for those requiring contact with other liquid phases in subsequent experiments (for example, supports for cell culture, wetting studies). Assembly from the gas phase is necessary when the SAM is prepared under UHV conditions for analysis by certain spectroscopies.

2.2.1. Adsorption of Alkanethiols from Solution

The most common protocol for preparing SAMs on gold, silver, palladium, mercury, and other materials (Table 1) is immersion of a freshly prepared or clean substrate (section 2.1) into a dilute (∼1−10 mM) ethanolic solution of thiols for ∼12−18 h at room temperature. This procedure is widely used and originates from early studies of SAMs; the experimental details resulted from a combination of studies designed to optimize the reproducibility of the SAMs produced and convenience.[223] Dense coverages of adsorbates are obtained quickly from millimolar solutions (milliseconds to minutes), but a slow reorganization process requires times on the order of hours to maximize the density of molecules and minimize the defects in the SAM. There are, however, a number of experimental factors that can affect the structure of the resulting SAM and the rate of formation: solvent, temperature, concentration of adsorbate, immersion time, purity of the adsorbate, concentration of oxygen in solution, cleanliness of the substrate, and chain length (or more generally, structure of the adsorbate).

In practice, most experimental conditions for the preparation of SAMs yield organic interfaces with reproducible and desired functional behaviors. These characteristics are acceptable for some applications of SAMs, but fundamental studies of certain materials properties such as wettability, corrosion, tribology, and charge-transfer processes (among others) require an understanding of how to minimize defects in SAMs and maximize order in these systems. The effects that some parameters, such as immersion time, concentration of adsorbate, and chain length, have on the structure and properties of SAMs are known to a small degree, but less is known about others (choice of solvent, temperature). We summarize below the present knowledge determined by specific experiments or empirical evidence about several of these factors.

Solvents. Ethanol is the solvent that is most widely used for preparing SAMs. The limiting mass coverage and wettability of SAMs formed from solutions of alkanethiols comprising solvents other than ethanol (tetrahydrofuran, dimethylformamide, acetonitrile, cyclooctane, toluene) do not vary significantly from those formed from ethanolic solutions.[223] At least four other factors also contributed to the widespread use of ethanol: it solvates a variety of alkanethiols with varying degrees of polar character and chain length; it is inexpensive; it is available in high purity; and it has low toxicity.

The effects of the choice of a solvent on the kinetics of formation and the mechanism of assembly are complex and poorly understood. Studies on this topic have led to some qualitative understanding of how solvent can affect the assembly process. The presence of a solvent adds additional parameters to the dynamic equilibrium governing the adsorption of thiols: solvent−substrate and solvent−adsorbate interactions complicate the thermodynamics and kinetics of assembly. Solvent−substrate interactions can hinder the rate of adsorption of thiols from solution because the solvent molecules must be displaced from the surface prior to the adsorption of thiols, which are less prevalent in solution than the solvating molecules.

Studies suggest that the rate of formation of SAMs of alkanethiolates is faster in certain nonpolar solvents (heptane, hexanes) than ethanol.[224,225] The use of long hydrocarbons, such as dodecane and hexadecane, as solvents reduces the rates of formation such that they are comparable to those for forming SAMs from ethanolic solutions.[225] Hydrocarbon solvents may improve the kinetics of formation in some cases, but the strong solvent−adsorbate interactions in these solutions impede the organization of SAMs formed from alkanethiols. Contact angle measurements and electrochemistry suggest that SAMs formed from solutions of thiols in nonpolar organic solvents are less organized than SAMs formed in ethanol.[223,226]

Polar liquids−poor solvents for *n*-alkanethiols−seem to reduce the quantity of some types of defects found in SAMs (conformational arrangements, regions of missing adsorbates, others; see section 3.4 for a discussion of intrinsic and extrinsic defects in SAMs) and promote densely packed monolayers.[226−228] The low solubility of thiols in such solvents and the low segmental heats of adsorption for these solvents (that is, the heat associated with each additional interaction of the solvent molecules with the surface, for example, the heat of adsorption per methylene or alcohol group) probably serve to segregate the thiols at the metal surface and thus more efficiently drive the assembly processes involving them. SAMs with few conformational and pinhole defects also can form from aqueous solutions containing micelles of ionic or nonionic surfactants.[229] Taken together, the studies of the effects of solvent on the prototypical example of SAMs of alkanethiolates on gold indicate that the choice of solvent clearly is an important parameter for determining the resulting quality of a SAM deposited from solution, but there remains significant challenges in developing a detailed understanding of the complex and dynamic interactions that occur between the solvent, surface, and adsorbates during the formation process.

Temperature. Forming SAMs at temperatures above 25 °C can improve the kinetics of formation and reduce the number of defects in them.[230,231] Elevated temperatures increase the rate of desorption for adventitious materials and solvent molecules physisorbed on the surface of the substrate and make it possible for the system to cross activation barriers for processes such as chain reorganization and lateral rearrangements of the adsorbates more easily than at room temperature. Uosaki and co-workers suggest that the effect of temperature is particularly relevant during the first few minutes of the formation of a SAM when most of the adsorption and reorganization of the SAM is taking place.[231]

Concentration and Immersion Time. These two parameters are inversely related: low concentrations of thiols in solution require long immersion times.[223,232] For SAMs formed from alkanethiols on gold, the typical surface density of molecules (when maximum coverage is obtained) is $\sim 4.5 \times 10^{14}$ molecules/cm^2;[22] thus, the minimum concentration for forming a dense SAM is $\sim 1\ \mu$M, or $\sim 6 \times 10^{14}$ molecules/cm^3. In practice, SAMs formed by immersion for a week in solutions with concentrations at or below 1 μM do not exhibit the same physical properties as those formed from more concentrated solutions.[223] The amount of impurities or other sulfur-containing compounds also can complicate the use of extremely dilute solutions to form SAMs.

Most spectroscopic and experimental evidence suggests that the *average* properties of SAMs formed from *n*-alkanethiols (wettability, mass coverage, and, to a large extent, the structure deduced by RAIRS) do not change significantly when exposed to ∼1 mM solutions of thiols for more than 12−18 h. Electrochemistry,[233] STM,[150] and RAIRS[234] indicate, however, that the structure of the SAM can continue to evolve over immersion times of ~7−10 days. These results imply that the coverage of the surface increases with extended immersion times and suggest that there are two consequences: (1) the number of pinhole defects in the SAMs decreases and (2) the conformational defects in the alkane chains decrease. The typical time allowed for formation (12−18 h) is convenient experimentally, but for some applications, formation over many days can improve the reproducibility of subsequent experiments that use the SAM, for example, studies of electron transfer through SAMs.[233]

Purity of Thiols. Common impurities derived from thiols are disulfides−an oxidation product. Experiments suggest that trace amounts of these materials (<5%) do not necessarily impede the formation or alter the structure of the SAM.[30,223] The disulfides usually are, however, less soluble than their thiol precursors; the reduced solubility can result in physisorption of these materials and alteration of the physical properties of the SAM.[30] Oxidized, polar contaminants (sulfonates, etc.) can be removed by percolating the thiols over activated, neutral alumina prior to use.[26,30]

Oxygen Content of Solution. There is little, if any, quantitative knowledge about the effects that oxygen can have on the rate of formation and the structure of SAMs formed when it is present in solution. Empirical evidence suggests that degassing the solvent with an inert gas, such as argon, prior to preparing the solution of thiols and maintaining an inert atmosphere over the solution during formation improve the reproducibility of the materials properties of the SAMs.[26,30] Reducing the concentration of oxygen in the solution limits the oxidation of the thiols to sulfonates and other oxygenated species. This precaution is more important for SAMs prepared on palladium, silver, copper, and (perhaps) platinum than on gold; the sulfur moieties in SAMs on palladium, silver, and copper undergo oxidation within 1−7 days upon exposure to the ambient atmosphere.[26,30]

Cleanliness of Substrate. The formation of SAMs on substrates that are handled in a laboratory atmosphere is essentially an exchange process: the thiols must displace whatever adventitious materials adsorb onto the substrate prior to immersion in a solution of thiols. The assumption supporting this statement is that the thiols are, in fact, able to displace the miscellaneous adsorbates already present. Displacement with thiols first requires desorption of the contaminants and impurities; the rate of desorption of the contaminants must, therefore, affect the kinetics of formation. SAMs have reproducible materials properties when formed on substrates that are immersed into solutions of thiols within ~1 h of preparation or cleaned with strongly oxidizing chemicals ("piranha" solution−H_2SO_4:H_2O_2) or oxygen plasmas. Exposure to ambient conditions for prolonged times seems to allow adsorption of materials that are not easily displaced in the typical time allowed for the formation of SAMs.

2.2.2. Adsorption of Disulfides and Sulfides from Solution

The available evidence on the formation of SAMs from either thiols (RSH) or analogous disulfide adsorbates (RSSR) on gold suggests that both yield monolayers of similar structure.[25,146,235,236] One factor that has led to the predominant use of thiols as the reagent of choice for the formation of SAMs is that thiols have much higher solubilities than disulfides. The low solubility of disulfides makes them difficult to use in solution, and their precipitation has been noted as a marked source of multilayer contamination of the substrate if the conditions of the sample preparation are not controlled carefully.[30] Still, disulfides remain a convenient adsorbate for assembling "mixed" SAMs (see section 2.2.3).

Dialkylsulfides. Dialkylsulfides form SAMs that are similar to those formed by thiols and disulfides but are less robust.[88,237] Sulfides do not adsorb to metals in the same manner as thiols and disulfides: electrochemistry,[238] XPS,[237,239] HREELS,[240] and mass spectrometry[241] data indicate that there is no cleavage of the C−S bond during formation, and STM studies suggest that the adsorbates are not as well ordered on the surface as SAMs derived from thiols or disulfides.[236,242] Formation of SAMs of sulfides at 60 °C seems, however, to improve the structural order of the adsorbates on gold.[243]

The spectroscopic data indicate that the sulfur interacts with the metal surface through a dative bond.[239] This interaction is weaker than the metal−thiolate bond formed by thiols and disulfides on metal surfaces (see section 3.1), and thus, the SAMs formed from sulfides are less stable than those formed from thiols and disulfides. Because there is not a strong energetic factor driving the adsorption of the sulfides, they do not displace adventitious impurities adsorbed on the substrates easily; similarly, small contaminants of thiols or disulfides (~0.1%) can dominate the assembly process.[88,235,244] One advantage of sulfides is that they are not as susceptible to oxidation as thiols or disulfides; a second is that dialkylsulfides of structure RSR′ provide convenient compounds with which to control local adjacency of different R groups in SAMs.

2.2.3. "Mixed" SAMs

Monolayers comprising a well-defined mixture of molecular structures are called "mixed" SAMs. There are three easy methods for synthesizing mixed SAMs: (1) coadsorption from solutions containing mixtures of thiols (RSH + R′SH), (2) adsorption of asymmetric disulfides (RSSR′), and (3) adsorption of asymmetric dialkylsulfides (RSR′). Mixed SAMs provide a useful methodology for incorporating into a SAM a molecular species whose own physical dimensions would preclude a direct, well-organized assembly. Two specific examples include the formation of SAMs that include ligands or proteins that retain their active/native conformations (see section 8.4) and the placement of electroactive species at precise distances from an electrode surface (see section 8.2). Mixed SAMs are also useful for defining gradients of interfacial composition that, in turn, are useful for studying the properties and biology of cells.

Coadsorption from Solutions Containing Mixtures of Thiols. The adsorption of mixtures of thiols (RSH + R′SH) allows the formation of SAMs with widely varying compositions.[245,246] The mole fraction of a specific adsorbate in the SAM reflects—but is not necessarily the same as—the mole fraction of the adsorbate in solution through all ranges of concentration. Experimental conditions can bias the relative ratio of the molecular components constituting the SAM: for example, the choice of solvent can modify the relative mole fractions of adsorbates in SAMs formed from a mixture of polar and nonpolar molecules.[146,223,247] Similarly, mixtures of *n*-alkanethiols with different chain lengths will form SAMs with a composition enriched with the longer alkanethiol; this bias increases over time.[246] There has been some attention given to the homogeneity of the local composition of SAMs formed from mixtures of thiols, notably those on gold. The data suggest that some degree of phase segregation can occur in model systems,[142,248] but the extent of phase separation present in the types of SAMs commonly used in applications remains largely unexamined.

Adsorption of Asymmetric Disulfides (RSSR′). Asymmetric dialkyl disulfides provide another precursor for synthesizing mixed SAMs. This approach appears, however, to suffer from some limitations. First, the nature of the precursor, in principle, limits the range of compositions accessible to mixtures of 1:1. In fact, the actual ratio of adsorbates constituting the SAM does not necessarily correspond to a ratio of 1:1.[249] The assembly process is a dynamic equilibrium that favors formation of the most energetically stable SAM, that is, the composition of the SAM can deviate from the initial ratio of components established by the stoichiometry of the precursors to favor one component over another. Second, the low solubility of the disulfides makes them operationally more difficult to use than the comparable thiols.[30] Third, the disulfides tend to generate structures that have more defects than those formed by thiols.[21]

Adsorption of Asymmetric Dialkylsulfides (RSR′). Asymmetric sulfides provide yet another approach for preparing an organic interface containing a mixture of functionalities.[88] The advantage of this approach is that, unlike disulfides, the molecules remain intact upon adsorption. The fairly weak bonding interactions with gold have limited the useful types of organic sulfides to classes of polydentate ligands with complex structures.[250]

2.2.4. Adsorption from Gas Phase

Adsorption of alkanethiols and dialkyl disulfides (with fewer than ~10 carbons) from the gas phase in UHV has proven useful for studying the early-stage dynamics of assembly and provided an easy method for preparing ordered structures that exist at submonolayer coverages (e.g., “striped” phases) (section 3.3.1).[22,251] The method suffers, however, in its generality: many SAMs of interest require chemical modifications after the deposition, and many precursors for SAMs of interest lack adequate vapor pressures. More significantly, assembly from the gas phase is frequently limited by kinetic bottlenecks—activated processes that limited fluxes, finite surface residence times, and other dynamical factors—that preclude the formation of the densely packed phases commonly formed by solution-based methods; these limitations are discussed in section 3.3.1.

3. Characterization of SAMs: Structure, Assembly, and Defects

The structures of SAMs and the mechanisms by which they assemble are subjects that have evolved considerably over the past two decades because there have been substantial advances made in methods suitable for characterizing them. The development of scanning probe microscopies (AFM, STM, etc.) provided powerful new capacities to study both the structural organization of SAMs and the assembly process at a molecular level. These techniques have greatly extended the initial structural understandings derived mainly from spectroscopic techniques (RAIRS, XPS, ellipsometry, etc.) and physical methods (most notably, studies of wetting). More recently, diffraction methods have come to play a very powerful role in shaping the understanding of structures exhibiting true 2D translational order.

The extensive literature on SAMs has established a common, though simple, point of view that SAMs naturally exhibit a high degree of structural order after assembly, that is, they are well-defined phases of organic groups organized in precisely understood lateral organizations on the underlying substrate. A point of fact, however, is that SAMs are dynamic materials that include significant forms of structural complexities, especially when immersed in fluids.[252−254] SAMs embed myriad forms of defects—both intrinsic and extrinsic types—that the thermodynamic nature of the assembly process does not serve to remove. Some of the dynamic aspects of SAMs that are serving to shape current discussions of structure in the field comprise coverage-driven ordering transitions, conformational isomerism, lateral diffusion, and environmentally responsive reconstructions of their surfaces.

The mechanisms of formation of SAMs and the limiting structures obtained by both solution and gas-phase adsorption have been studied extensively. The literature on the structural and physical characterization of SAMs and the evolution of structure during assembly has been described in several excellent reviews.[22,251,254,255] The general understandings provided in the extensive body of work on SAMs of thiols on metals are summarized here; in particular, we emphasize some of the unresolved questions regarding the structure and dynamics of SAMs and discuss the intrinsic and extrinsic elements that complicate the commonplace representation of SAMs. The discussion begins most naturally with the chemistry of the metal−sulfur bonding interactions.

3.1. Nature of the Metal–SAM Interface

Most SAMs of practical interest are formed at a reactive interface, that is, the adsorbate and the substrate are both transformed to some degree by the reactions that lead to the formation of the SAM. The chemistry involved for the chemisorption of thiols on gold is, in principle, the most straightforward but remains the most enigmatic. Because gold does not form a surface oxide (as, for example, does silver), the formation of SAMs from thiols is not complicated by chemistries that might be required to displace or reduce surface oxides, but the details regarding the nature of the metal–sulfur bond and the spatial arrangement of the sulfur groups on the underlying gold lattice are still controversial.

There is even less known about the reactions for forming SAMs from organosulfur compounds on other metals, such as palladium, silver, copper, and mercury. All of these systems have been studied in some detail, but each metal has a different structural surface chemistry and a different reactivity toward organosulfur compounds. These variations impact the assembly process in significant ways and lead to a variety of structural motifs that are distinct for each. The structural details of the interface between these metals and the monolayer are only understood in qualitative terms at a level that makes it possible to rationalize many of the details seen in the organizations of the organic groups they support.

Consideration of the bonding arrangements formed at the metal–sulfur interfaces for several representative examples does suggest, however, a common motif: the molecules comprising the SAM tend to adopt structural arrangements that are similar to simple adlayer structures formed by elemental sulfur on that metal.[256,257] We provide here an analysis of the stabilization energy for gold–sulfur bonds and a brief summary of the current knowledge regarding the structural ordering for SAMs of *n*-alkanethiolates on gold, palladium, silver, and copper. We also discuss what is known about the chemistry between organosulfur compounds and the surface of these metals.

3.1.1. Thermodynamic Analysis of Gold–Thiolate Bonds

The formation of a thiolate requires the chemical activation of the S–H bond of the thiol (or the S–S bond of the disulfide). The energetics involved in this bond activation—the bonding energy that directly anchors the adsorbate molecules of the SAM to the gold substrate—were first examined in studies carried out in 1987: using temperature-programmed desorption as a kinetic measure of the SAM binding energy, Dubois et al. established that the adsorption of dimethyl disulfide on Au(111) occurs dissociatively.[258] The reaction is fully reversible, and recombinative desorption of the disulfide is an activated process with a barrier lying near 30 kcal/mol. This energy suggests that a fairly significant degree of charge transfer to sulfur must occur in the thiolates—an inference that has been supported by the results of theoretical calculations.[259] Using different experimental protocols, Scoles and co-workers also investigated the bonding energies of various organosulfur adsorbates on Au, and their studies suggest, for the case of SAMs involving thiolate structures, bonding energies similar to those cited above.[260]

Other kinetic treatments reveal the complex nature of the thermodynamics of the metal–sulfur bonding interactions. For example, Whitesides et al. and Liu and co-workers both reported the results of desorption experiments that employed SAMs immersed in a solvent.[223,261] The kinetics of these processes can be modeled using conventional rate equations, and these models suggest barriers for the desorption process that are somewhat lower than the values obtained from desorption rate measurements made in UHV (~20–25 kcal/mol). Schlenoff et al. used electrochemical measurements to provide a detailed analysis of the thiol/thiolate/disulfide bond energies and desorption barriers for SAMs on gold.[262] Of particular interest was the estimation that the barrier for the bimolecular recombinative desorption of an alkanethiolate from a SAM on gold in the form of a dialkyl disulfide is ~15 kcal/mol. This value is approximately a factor of 2 less than that deduced in the gas-phase studies.

We note here, though, that the two energies are not directly comparable given that one also contains contributions from the heats of dissolution of the adsorbate as well as the heat of immersion of the substrate in the solvent. The latter energies can, in fact, be quite large; for example, the segmental heat of interaction of a hydrocarbon on gold is ~1.5 kcal/mol for a methylene group.[263] In this context, the range of reported values appears to be one that follows directly from the different forms of the measurements used to assess the strength of the Au–S bonding interaction. As the vacuum measurements are most easily interpreted, we believe it is reasonable to conclude that the Au–S bond that anchors the SAM is, in fact, a reasonably strong one—a homolytic Au–S bond strength on the order of ca. −50 kcal/mol—based on the known S–S homolytic bond strength of a typical dialkyl disulfide (~62 kcal/mol).[258]

Where Does the Hydrogen Go? The fate of the hydrogen of the S–H groups still has not been determined unambiguously.[264–266] It seems probable that adsorption in a vacuum leads to loss of the hydrogen in the form of dihydrogen—the reductive elimination of H_2 from Au(111) is a weakly activated process.[267] In solution, another possibility exists. If the thiol hydrogen is not lost in the form of H_2, the presence of oxygen in the reaction medium might also lead to its oxidative conversion to water. In either case, the Au–S bonding interaction in the thiolate is sufficient to retain the chains at the surface in a durable fashion and preclude a recombinative desorption of a disulfide product at room temperature. At more elevated temperatures the conversion of surface thiolates to disulfides does become kinetically feasible and has been seen for a variety of SAM structures.[268,269]

3.1.2. Surface Structure of Thiolates on Gold

The central bonding habit of the high-coverage thiol phases on Au(111) is generally accepted to be based on a $(\sqrt{3}\times\sqrt{3})R30°$ overlayer (R = rotated).[22,27,251,253] The literature also strongly confirms that this organization adopts a secondary ordering

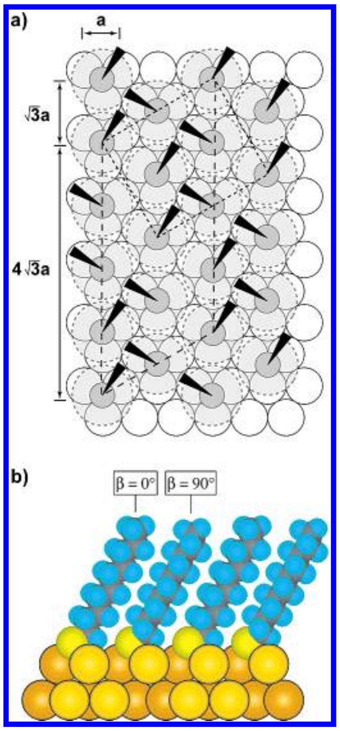


Figure 3. Schematic diagram depicting the arrangement of decanethiolates on Au(111) lattice when maximum coverage of the thiolates is attained. (a) Structural model of the commensurate adlayer formed by thiols on the gold lattice. The arrangement shown is a ($\sqrt{3}\times\sqrt{3}$)R30° structure where the sulfur atoms (dark gray circles) are positioned in the 3-fold hollows of the gold lattice (white circles, a = 2.88 Å). The light gray circles with the dashed lines indicate the approximate projected surface area occupied by each alkane chain; the dark wedges indicate the projection of the CCC plane of the alkane chain onto the surface. Note the alternating orientation of the alkane chains defines a c(4 × 2) superlattice structure. The formal c(4 × 2) unit cell is marked (long dashes); an equivalent $2\sqrt{3}\times 3$ unit cell is marked by lines with short dashes. The alkane chains tilt in the direction of their next-nearest neighbors. (b) Cross-section of the SAM formed from decanethiol. Note the alternating rotations of the carbon chains in this view. The chains are labeled with twist values (β) to indicate the relative orientations of the neighboring chains.

of the chains corresponding to a c(4 × 2) superlattice.[270,271] Figure 3a shows this structure schematically. The SAMs formed by n-alkanethiols were originally described as thiolate overlayers (chemisorbed structures formed by the activation of the S−H bond at the gold surface).[22,258] This structure had been called into question based on diffraction experiments and STM imaging that seemed to suggest a structure involving some degree of S−S bonding between pairs of adjacent adsorbates on the surface of the gold (a disulfide model).[161,272,273] Alternative interpretations have been presented, and this quasi-disulfide model has now been largely abandoned in favor of the original thiolate model.[259,266,274] The latter is a simple adlayer model of the Au−S bonding interactions. Within this model there has been considerable discussion of the surface sites involved in this bonding.[273,275] Bonding of the thiolates at both 3-fold hollows and bridge sites has been suggested on the basis of both experiment and theory.[276,277] This aspect of the structure appears to be unresolved as of this writing.

Most studies of SAMs on gold have employed substrates presenting a strong (111) texture to support the monolayer. Other studies have been directed at different crystallographic textures, although the structural literature available in these cases is far more limited. The SAMs formed on Au(100) appear to provide an enlightening example of the interplay between surface-directed and organic-directed assembly in the SAM. The adsorption of n-alkanethiols on Au(100) appears to give thiolate structures organized as a c(2 × 2) overlayer.[27] The packing density of chains in a structure of this sort could not support a structure canted to the same degree as that found on Au(111). Such inferences are supported by the results of direct experimental studies of the chain tilts adopted on the two metal surfaces (section 3.2).

3.1.3. Surface Structure of Thiolates on Palladium

The structure of SAMs formed by the assembly of n-alkanethiols on palladium surfaces has been described.[30] These monolayers form on top of a complex surface phase—a palladium sulfide interphase. XPS data reveal that the monolayer is bound in the form of a thiolate that terminates the metal−sulfide interlayer. For preparations carried out at room temperature, at least two sulfur atoms are present in the interface in the form of a palladium sulfide for every one bound as the thiolate that anchors the SAM. The sulfur atoms needed to construct this adlayer clearly derive from a relatively clean excision of heteroatoms from excess adsorbate molecules in solution. The thiolates form a dense and highly oriented presentation of chains—ones well described by a model based on all-trans chains oriented at a 14−18° angle with respect to the direction of the surface normal. This packing density correlates well with the expectations for a ($\sqrt{3}\times\sqrt{3}$)R30° hexagonal adlayer, a structure that has been observed in UHV studies of sulfur adlayers on Pd(111).[257] This point is, in fact, quite interesting given the presumption that the ($\sqrt{3}\times\sqrt{3}$)R30° structure of the elemental sulfur phase is a simple adlayer, that is, the coverage of sulfur is one-third that of the atomic density of the Pd(111) surface. The SAMs on Pd, however, clearly show that nearly two additional sulfur atoms are present in the form of a metal sulfide for every one bonded as a thiolate; this result suggests that the ($\sqrt{3}\times\sqrt{3}$)R30° structure may be substitutional in nature.

3.1.4. Surface Structure of Thiolates on Silver

Most thiol-derived SAMs supported on silver and copper show qualitative resemblances to properties seen in assembly on either gold or palladium.[26,29,215,278] The case of SAMs on silver is instructive: the available data again indicate the bonding of the monolayer in the form of a thiolate.[26] This observation is particularly important given that, under the methods of preparation typically used, the silver surface is generally present in the form of a complex oxide—one that can carry fairly significant amounts of environmentally sorbed contaminants. The interactions of thiols with Ag samples immersed promptly in a solution containing thiol rapidly strips these contaminating layers from the surface; XPS data confirms the removal of the surface oxide in most cases.[26] The chain organizations seen in these SAMs—ones forming atop a film with a dominant (111)-texture—are consistent with an organizational habit involving a $(\sqrt{7}\times\sqrt{7})R10.9°$ overlayer of the thiolate sulfur atoms, a structure characterized in LEED studies of elemental sulfur on Ag(111).[279]

The silver–sulfur bonding can, however, vary with the conditions of preparation. Short immersions, or adsorption from the gas phase on an atomically clean metal surface, give a simple thiolate adlayer. The chains in this layer are densely packed. Prolonged exposures in solution, however, lead to somewhat different chemistry—one characterized by the build-up of an excess of metal sulfide species at the interface.[26] These latter phases have not been fully characterized, but they do not seem to impact the structures or chain organizations of the SAM based on metrics such as the degree of conformational ordering, the tilt, and other organizational properties of the chains.

3.1.5. Surface Structure of Thiolates on Copper

Copper presents an enigmatic case in the chemistry of SAMs. The adsorption of an organosulfur adlayer can overcome the tendencies of copper to oxidize and strongly adsorb contaminants picked up from the laboratory ambient at its surface. The chemistry is, however, not as forgiving in our experience as it is for silver, and considerable care is needed to prepare high-quality SAMs on copper. As a result of these experimental difficulties, the structures formed on this metal remain incompletely understood.[26]

3.2. Organization of the Organic Layer

The geometric arrangement of the sulfur moieties on the surface and the nearest-neighbor distances between the metal atoms at the surface are factors that determine the upper limit on the density of molecules on the surface. This two-dimensional density of molecules may not correspond, however, to the density that the same molecules could attain in a crystalline form, that is, the arrangement of molecules that is dictated by the placement of the sulfur moieties on the surface may not maximize the lateral interactions between the organic components of the SAMs. To minimize the free energy of the organic layer, the molecules adopt conformations that allow high degrees of van der Waals interactions[280] (and in some cases hydrogen bonds[281–283]) with the neighboring molecules; these arrangements yield a secondary level of organization in the monolayer that is important in determining macroscopic materials properties, such as wetting, of the SAMs.

3.2.1. Single-Chain Model for Describing the Average Organization of the Organic Layer in SAMs

A simple single-chain model is sufficient to facilitate comparisons of the organization adopted by different organosulfur compounds with (mostly) linear conformations on different types of substrates (Figure 4a). Two parameters describe the variations in the orientation of the organic molecules in the SAM: the angle of tilt for the linear backbone of the molecule away from the surface normal (α) and the angle of rotation about the long axis of the molecule (β). As defined in Figure 4, α can assume both positive and negative values; values of β range from 0° to 90°. Table 2 summarizes the chain organizations adopted by SAMs for which the available data have confirmed the formation of an assembly possessing significant orientational (or higher translational) order in the adsorbate adlayer.

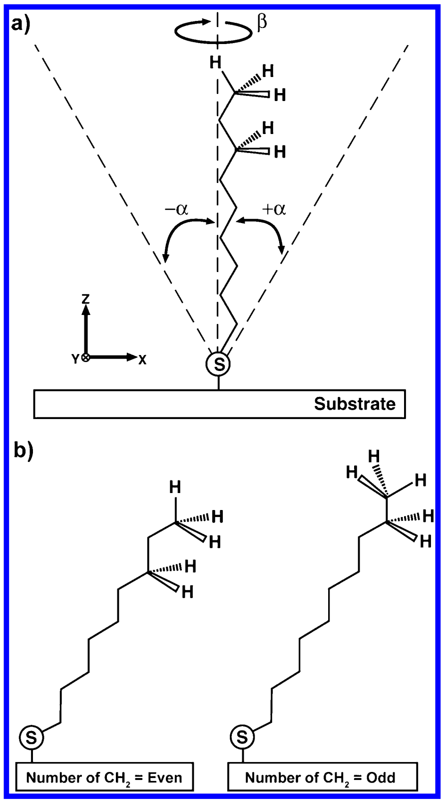
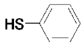
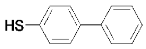
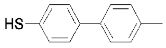
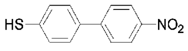
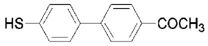
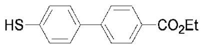
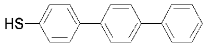
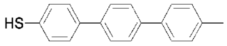
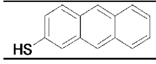
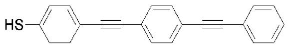
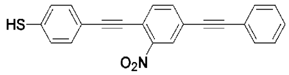


Figure 4. (a) Schematic view of an all-trans conformer of a single, long-chain alkanethiolate adsorbed on a surface. The tilt angle (α) is defined with respect to the surface normal direction. The twist angle (β) describes the rotation of the CCC bond plane relative to the plane of the surface normal and the tilted chain. (b) Schematic views of single, long-chain alkanethiolates (with even and odd numbers of methylene groups) adsorbed on gold. The conserved value of α for each produces different projections of the terminal methyl group on the surface.

For SAMs formed from *n*-alkanethiols on gold, palladium, silver, copper, mercury, platinum, and other materials, the alkane chains adopt a quasi-crystalline structure where the chains are fully extended in a nearly all-trans conformation. The tilts of these chains vary for the various metals: the largest cants, α (with an absolute value near 30°), are found on gold, while the structures most highly oriented along the surface normal direction arise on silver ($\alpha \approx 10°$) and mercury ($\alpha \approx 0°$). The average β for gold lies near 50°, while for other metals, the data, where available, indicates values generally clustered near 45°. These data are consistent with space-filling models involving (at least for the case of gold) chain tilts lying along the direction of the next-nearest neighbor, that is, an ordered structure involving a hexagonal arrangement of the sulfur atoms. These

Table 2. Values of α and *β* for Different Thiolates Adsorbed on a Variety of Materials

Molecular Constituent of SAM	Substrate	Cant Angle (|α|)	Chain/Plane Rotation (β)	Characterization Method	Reference
n-alkanethiols	Au(111)	28°	53°	RAIRS	26
	Au(100)	14°	70°	RAIRS	27
	Ag	11-14°	45°	RAIRS	26
		13±2°	44±6°	RAIRS	28
		15°	45°	Surface Raman Scattering	151
	Cu	12°	45°	RAIRS	26
	Pd	16±2°	45°	RAIRS	30
	Pt	< 15°	n.a.	RAIRS	32
	Hg	0°	n.a.	X-ray scattering	69
		0°	n.a.	Electrochemistry	284
	GaAs(100)	57±3°	45±5°	RAIRS	285
	InP(100)	55±6°	n.a.	XPS	286
$HS(CH_2)_{21}OH$	Ag	5±5°	n.a.	Raman Spectroscopy	287
	Cu	5±5°	n.a.	Raman Spectroscopy	287
	Au(111)	49±5°	32°	NEXAFS	288
	Ag(111)	24±5°	32°	NEXAFS	288
	Au(111)	15±5°	n.a.	NEXAFS	289
		23±5°	32°	NEXAFS	288
	Ag(111)	18±5°	32°	NEXAFS	288
	Au(111)	≤19°	n.a.	GIXD	290
	Au(111)	14±2°	30°	RAIRS	291
	Ag(111)	8±2°	32°	RAIRS	291
	Au(111)	20±2°	15°	RAIRS	291
	Ag(111)	21±2°	10°	RAIRS	291
	Au(111)	12±2°	30°	RAIRS	291
	Ag(111)	11±2°	31°	RAIRS	291
	Au(111)	20±5°	32°	NEXAFS	288
		27±5°	n.a.	NEXAFS	292,293
	Ag(111)	16±5°	32°	NEXAFS	288
	Au(111)	17±8°	n.a.	Ellipsometry	294
	Au(111)	23±5°	26°	NEXAFS	288
	Ag(111)	14±5°	26°	NEXAFS	288
	Au(111)	<5°	n.a.	STM/AFM	295
		33±18°	31±6°	RAIRS	296
	Au(111)	39±8°	51±13°	RAIRS	296

[a] n.a. = not available.

assumptions have been largely confirmed by the results of diffraction studies.[161,297]

Table 2 suggests that not all thiols adopt the same orientations as *n*-alkanethiols. The behaviors seen on gold are instructive. For cases where the steric requirements of the adsorbate preclude the ordering found for the *n*-alkanethiolate structures, other organizations have been seen. For example, aromatic compounds such as *p*-biphenylthiols, *p*-terphenylthiols, and oligo(phenylene ethynylene) thiols seem to adopt orientations on Au(111) that are slightly less canted than those for *n*-alkanethiols.[288,289,292,296,298] These structures, however, seem to exhibit the same structural arrangement on the Au(111) surface as SAMs of *n*-alkanethiolates when a limiting mass coverage is achieved, that is, they adopt either a $(\sqrt{3}\times\sqrt{3})R30°$ ordering or, in some cases, one that may be incommensurate with the underlying Au(111) lattice. These data suggest that the assembly chemistries are ones that involve significant contributions from the interplay between the metal−sulfur bonding and (stabilizing) lateral interactions of the organic groups. For the structures summarized in Table 2, neither contributor seems to predominate clearly and the design rules for SAMs, in this sense, reflect chemistry that still continues to surprise us.

3.2.2. "Odd–Even" Effect for SAMs on Gold

The values of α for SAMs formed by *n*-alkanethiols on Au(111) appear to be unique. The tilt of the chain projects an orientation of the average chain in which the sign of the tilt angle is conserved regardless of the number of carbons in the alkane chain. All the available data suggest that the structures exhibited by thiolate SAMs on gold adopt a value of $\alpha \approx +30°$.[26,299a] This feature of the assembly leads to very different surface projections of the methyl groups for SAMs with odd and even numbers of methylene groups (Figure 4b) and correlates strongly with the unique wetting behaviors of SAMs on gold; SAMs of thiolates with an odd number of methylene groups produce surfaces whose free energies are systematically slightly larger than those with an even number of methylenes.[299b−d] This "odd−even" effect also underpins the chain-length-dependent anchoring interactions of liquid crystals contacting them (see section 8.3.2).[300−302]

3.2.3. Multichain Unit Cells

The adoption of a single-chain model facilitates a comparison of the structural motifs seen in various SAMs, but loses certain relevant aspects of the information that might be known about their structure. Thiolate SAMs on Au(111), for example, form a c(4 × 2) superlattice structure that involves four chains within the unit cell (Figure 3a).[22,303] A single-chain model of this structure simply averages all the values of cant (α) and twist (β) for the individual chains. The high symmetry of the order superlattice, however, makes the reference between the simplified model and the more detailed structure a facile one.

The tendency for the twist angles for SAMs of alkanethiolates on other metals (palladium, silver, copper) to lie around 45° suggests that these SAMs also may adopt an ordered structure based on a multichain unit cell−one reminiscent of that on gold. An orthorhombic sublattice of all-trans chains would dictate an orthogonal arrangement of the CCC planes of the chains in the lattice, that is, the CCC planes of adjacent alkane chains would be rotated 90° with respect to one another (Figure 3b). Orientation of the chains in this manner yields an *average* chain representation in the single-chain model with a twist angle of $\beta \approx 45°$ regardless of the tilt angle or direction. This model suggests that the organization of the organic layer in SAMs on palladium, silver, and copper are very similar, with only slight differences in the setting angles and magnitudes of the cants of the chains present in a multichain unit cell.

The single-chain and multichain models developed for SAMs of *n*-alkanethiolates on different metals provide a rational picture of the organization of the chains in these systems and are useful for understanding certain chain-length-dependent trends observed in the macroscopic properties of these materials (wetting, liquid-crystal orientation). These models seem suitable for describing the organization of other SAMs comprising molecules with linear geometries, such as oligo(phenylene) compounds. It is not clear, however, that they can adequately describe the organization of monolayers formed from molecules with complex (not rodlike) geometries.

3.2.4. Effect of the Organic Component on the Stability of the SAM

The thermodynamic stability of organosulfur adsorbates bonded to a gold surface does show sensitivities to the structural nature of the organic substituents. Long-chain adsorbates are somewhat more robust in their applications than are short-chain adsorbates ($n < 10$) for reasons that are probably both kinetic and thermodynamic. Chain organizations within the SAM arise in part as a consequence of attractive lateral interactions; a subject discussed in more detail below. Longer chains are strongly driven to order by these contributions to the energetics, an effect that is further correlated with improvements in stability (thermal, chemical, etc.). These issues have been discussed in a recent review.[251]

3.3. Mechanisms of Assembly

Developing a comprehensive understanding of the assembly of SAMs requires careful considerations of both kinetic and thermodynamic factors. Although the dynamics of the assembly remain incompletely understood, it is clear that the process leading to the formation of SAMs involves a subtle interplay of the energetics of the metal−sulfur bonds and (typically) noncovalent lateral interactions among the organic groups. In most cases, the specific ordering of the sulfur moieties on the metal lattice defines the free space available to the organic components. The organization of the organic layer results from maximizing the attractive lateral interactions (van der Waals, hydrogen bonding) within the geometric constraints imposed by the structure of the adlayer. The organic groups, however, can also restrict the density of coverage: steric crowding of the organic groups can limit the arrangement of the sulfur atoms to one that is less dense than that exhibited by elemental sulfur on a given substrate (for example, the $(\sqrt{3}\times\sqrt{3})$R30° structure for sulfur on gold).

The prototypical example of SAMs of *n*-alkanethiolates on Au(111) demonstrates the balance between the structure of the adlayer and the lateral interactions that stabilize the assembly: the metal−sulfur interaction drives the assembly to the limiting case where the gold surface is covered by a $(\sqrt{3}\times\sqrt{3})$-R30° overlayer of thiolates, but the attractive lateral interactions promote the secondary organization of the alkane chains that defines the fine details of the c(4 × 2) superlattice structure (Figure 3a). The chain−chain interactions contribute ~1.0 kcal/mol of stabilization to the SAM for each methylene group in the chain.[22] The remaining energy dictating the organization of the SAM results from the metal−sulfur bonding.

This section discusses the evolution of the structure of SAMs formed by adsorption of organosulfur compounds from the gas phase and solution. Several recent reviews have examined these issues in depth.[251,254,255] We focus the discussion here on a summary of the general understanding of the mechanism of formation of SAMs of *n*-alkanethiolates and some of the key thermodynamic and kinetic factors in the process.

3.3.1. Assembly of SAMs from the Gas Phase

The assembly of SAMs of thiolates on gold from the gas phase proceeds by complex growth kinetics that involve the intermediacy of one or more low-coverage phases. Of the multiple variations of low-coverage phases that have been described in the literature, the so-called striped phases−an ordered assembly of alkanethiol molecules lying flat on the surface−have

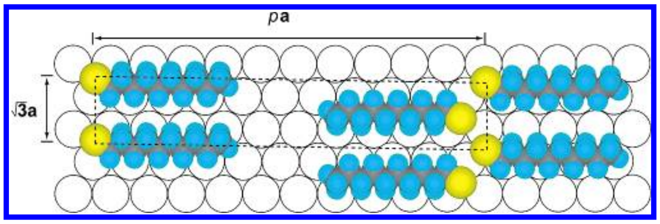


Figure 5. Schematic diagram depicting a representative striped phase that can form at submonolayer coverages of thiol on Au(111) (a = 2.88 Å). In this example, the periodicity of the rectangular unit cell (p) is 11.5.

been studied the most extensively (Figure 5).[253] They are believed to be an intermediate phase that forms prior to nucleation and subsequent growth of the higher coverage (upright) structures that make up SAMs. The phase transitions from the striped phases to the dense, upright-oriented thiolate phases constitute a significant kinetic bottleneck for long-chain adsorbates.

The assembly of SAMs of alkanethiolates on gold surfaces from the gas phase probably involves a precursor, that is, a physisorbed and mobile thiol, and may also involve chemisorbed thiolates with noncrystalline geometry. The progression of this chemistry is reasonably well understood and has been reviewed in considerable depth by Schreiber et al.[251] The picture of the chemistry that converts molecular thiol adsorbates to the thiolate species of the familiar SAM structures is an intriguing one. It is understood, for example, that the thiols first deposit onto the substrate in a low-coverage molecular phase. This structure retains an intact S−H bond, but ultimately the thiols are converted, via a dissociative adsorption pathway, to thiolates. (As noted above, the hydrogen is probably lost−via a recombinative desorption−as H_2 in this process.)

The low-coverage phase is one that exhibits a distinct ordered motif−the striped phase (shown schematically in Figure 5). This phase is a durable one that requires significant fluxes of adsorbates and temperatures above 200 K to convert to the high-coverage thiolate form of the SAM. The progression of this chemistry for n-alkanethiols is exceptionally sensitive to their chain length. Steric preclusion effects and strong metal−chain interactions tend to limit the kinetics for the assembly of long-chain adsorbates from the gas phase. More fundamental chain-length-dependent kinetic effects−ones related to the activation of the S−H bond by the gold surface−are also seen. It has been shown that the kinetics for the dissociation of this bond on the gold surface under UHV conditions are, in fact, strongly chain dependent. Short-chain n-alkanethiols have lower reactive sticking probabilities on gold surfaces than do long chains.[27] For the case of methane thiol, the weak physisorption of the molecular precursor kinetically precludes the dissociative adsorption of the S−H bond. The heats of adsorption for the physisorbed precursor states of longer n-alkanethiols are, however, large enough to allow a facile barrier crossing of the gold-mediated S−H bond dissociation reaction; the large reactive sticking probabilities make it possible to form thiolate-based structures with even relatively limited exposures.

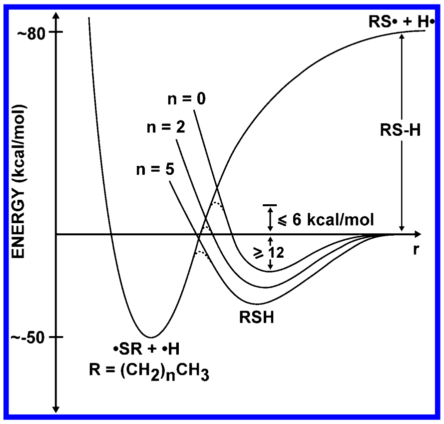


Figure 6. Schematic one-dimensional energy diagram showing the effect of chain length on the barrier for activation of the S−H bond of n-alkanethiols on gold. For short chain lengths ($n \approx 0-2$), the transition from a physisorbed state to a chemisorbed state is an activated process. (Reprinted with permission from ref 27. Copyright 1993, American Institute of Physics.)

Figure 6 schematically shows the relative scaling of the energy barriers that contribute to the substantial chain-length dependence of the activation of the S−H bond by the gold surface. This simple parabolic model of the energy surface suggests that increasing the length of the alkanethiol increases the thermodynamic stability of the physisorbed state and decreases the activation barriers for the S−H bond dissociation process. For alkanethiols with more than a certain number of carbons (~6), the activation barrier for the dissociation process actually lies below the energy required for molecular desorption. Reactive sticking probabilities of dialkyl disulfides are uniformly large: for example, the reactive sticking probability of dimethyl disulfide on Au(111) at zero coverage is near unity, and its reaction yields a well-defined ($\sqrt{3}\times\sqrt{3}$)R30° thiolate overlayer structure on that surface.[258]

It is useful to consider the chemistry seen for a model adsorbate structure in more detail. The assembly kinetics of n-hexanethiol is instructive in this regard.[251] Adsorption below 200 K yields a physisorbed monolayer of flat-lying adsorbate molecules. Warming the substrate to 208 K leads to a substantial change of bonding in the adsorbed overlayer−one related to the activated dissociation of the S−H bond by the gold surface. For this adsorbate, the significant adsorption interaction allows an efficient barrier crossing to the chemisorbed form of the adsorbate. A simple first-order kinetic analysis suggests the barrier is ~7 kcal/mol. When additional adsorbate molecules impinge on the surface at this temperature, the system begins to nucleate the formation of domains of the dense SAM phase. The kinetics of this process remain poorly understood in many regards, and its study continues to attract attention in current research.

Some of the trends seen in the chemistry controlling the gas-phase assembly do not appear to be unique to the formation of SAMs on gold. Yates and co-workers reported what appears to be a similar chain-length-dependent kinetic constraint to the activation of the S−H bond on silver.[265] Methanethiol

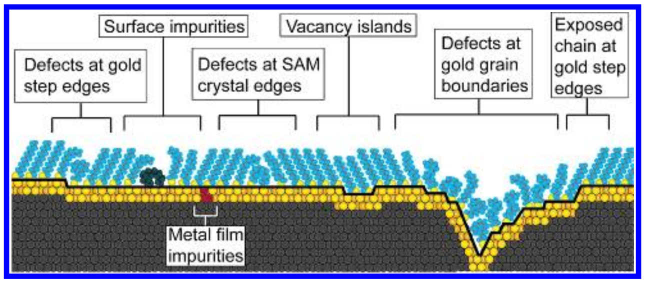


Figure 7. Schematic illustration of some of the intrinsic and extrinsic defects found in SAMs formed on polycrystalline substrates. The dark line at the metal−sulfur interface is a visual guide for the reader and indicates the changing topography of the substrate itself.

does not dissociate on Ag(110)—an absence of reactivity similar to that seen on Au(111). Longer chain alkanethiols are known to form thiolate adlayers on Ag(111), and it seems clear that further work will be needed to describe this dynamical aspect of the chemistry involved in the assembly process more fully.

3.3.2. Assembly of SAMs from Solution

The complexity of the solution environment has made it difficult to characterize the dynamic aspects of this form of assembly in the same detail as has been possible for the case of gas-phase studies. The assembly from solution follows a kinetic progression that has a functional form approximated *qualitatively* by a Langmuir adsorption model (although the assumptions of this treatment of the kinetics are likely to be inaccurate in quantitative detail).[251,304] The evolution of the structural phases formed during the assembly is believed to be similar to that for assembly from the gas phase, but the involvement of low-coverage intermediate phases (such as the striped phases commonly seen in gas-phase adsorption studies) has not been demonstrated definitively.[251] Detailed electrochemical studies of the assembly of thiolates on mercury indicate the formation of distinct low-coverage phases.[305] These phases may be reminiscent of the low-coverage phases seen in the gold system, but the extent of long-range order in the low-coverage phases on mercury probably differs significantly from those on gold.

3.4. Defects in SAMs

Because they form by self-assembly, that is, because they adopt adsorbed structures that are directed by the thermodynamics of a reasonably complex chemisorption process, SAMs provide, in theory, convenient access to highly ordered organic interfaces whose molecular and aggregate structures can be varied by principles of rational design. The structures of SAMs are generally regarded as if they contained few defects. A point of fact, they are substantially more complex than the highly ordered arrangements that are commonly assumed (Figure 7). The causes of defects in SAMs are both intrinsic and extrinsic: external factors, such as cleanliness of the substrate, methods for preparing the substrates, and purity of the solution of adsorbates, are responsible for some defects in SAMs, but some result simply because SAMs are, in fact, *dynamic* systems with complex phase behaviors.

3.4.1. Defects Caused by Variations in the Surface of the Substrate

The substrates on which SAMs form are replete with many structural defects. Polycrystalline gold substrates—a system that has been a benchmark choice for much of the published work in the field—present a grain structure characterized by dense arrangements of intergrain boundaries, faceting, occlusions, twins, and other gross structural irregularities. Even for samples that present a strong (111) texture misalignments are common as are other low-index crystallographic textures. All metal substrates also have a varying density of atomic steps, and these in turn impact the structures and defect content of SAMs as judged by numerous STM studies.[253,270,276,306]

3.4.2. Reconstruction of the Surface during Assembly

One type of defect inherent to the formation of SAMs on gold is monatomic vacancies, that is, regions of the SAM offset in height by one (gold) atomic diameter from the surrounding regions. The probable origins of these pit-like defect structures are easily understood by considering the structure of the gold surface prior to adsorption of the SAM. A clean Au(111) surface normally exhibits a $(23\times\sqrt{3})$ reconstruction; the surface density of gold atoms in this reconstruction is greater than that on the ideal (111) plane.[254] The adsorption of thiols onto the bare gold surface lifts the reconstruction and induces a change in the atom density at the surface. The relaxation of the surface is achieved via the formation of single-atom vacancies; these defects subsequently nucleate and grow into large vacancy “islands” that are seen in STM studies.[253,254] The topography of SAMs faithfully replicate the topography of these defects and, for interfacial properties that are sensitive to them, cannot fully obviate their impacts. Such effects, for example, are strongly evident in electrochemical studies and probably complicate the structures used in studies of molecular electronics as well.

3.4.3. Composition of SAMs

In simple terms, the formation of a SAM is a form of chemical selection. The assembly process involves a thermodynamic equilibrium between adsorbates on the surface and their precursors free in solution. The composition of a SAM must reflect, therefore, a concentration-dependent binding of the most strongly interacting adsorbate species present in the solution (or gas vapor) used to prepare it. Impurities in solvents and reagents can thus complicate both the kinetics of formation and the final structure of a SAM. These defects are extrinsic, and careful control of experimental methods can minimize them.

3.4.4. Structural Dynamics of SAMs Induce Defects

SAMs present other types of defects that are less well appreciated than are those related to the characteristics of the substrates or the purity of the adsorbates used to prepare them. These are the defects that are intrinsic to the dynamic nature of the SAM itself.[149,307] In this regard, one must consider both the intrinsic structural (i.e., phase) dynamics of the SAM and the thermodynamically imposed constraints to its stability. The latter issue is one that is easily understood. SAMs form via a thermodynamically driven assembly of an adsorbate at a surface/interface. Where the adsorbate−substrate interaction is sufficiently strong (as for the case of the prototypical layers formed by alkanethiols on gold), the SAM may be safely removed from the solution used to prepare it and studied or used further. Although these SAMs may be kinetically stable in the absence of a flux of adsorbate, the high coverage of the adsorbate present in the SAM is, in fact, thermodynamically unstable. Only in a case where the rate of desorption is rigorously zero would the SAM be expected to exist for an indeterminate period outside the solution used to prepare it.

The unique aspects of the systems that have attracted wide attention in studies of SAMs are the essential abilities of the best adsorbate−substrate pairings to resist the competitive binding of impurities at the interface and their substantial stabilities with respect to thermal desorption or displacement by other chemical species. This stability is, however, one that is limited by the finite strength of the M−S bond and by the susceptibility of the simplest thiolate systems toward decomposition (whether via oxidative degradation or other dissociative pathways) reactions that are sensitive to the ambients in which the SAMs are used. Still, the main concern for stability remains desorption. For simple SAMs of thiolates on gold, the limit of thermal stability due to desorption is modest but quite useful (especially at room temperature).[308]

One also encounters classes of defects that are related to intrinsic dynamics of the organic component of the SAM. The chain dynamics of alkanethiolate SAMs on gold provide an instructive example. First, because the chains of these SAMs are canted (reflecting the gold−sulfur spacings), the chains are subject to a variety of complex phase transitions—thermally driven population of gauche conformers and tilt-order phase transitions are among some of the phase dynamics that have been investigated and used to rationalize aspects of their interfacial properties.[149,307] Order−order phase transitions—such as those involving a posited thermal coexistence of the $c(4 \times 2)$ and $(\sqrt{3}\times\sqrt{3})R30°$ phases—constitute another example. In yet another example, Grunze interpreted the relative protein-binding affinities of oligo(ethylene glycol) (OEG)-modified SAMs on gold as arising from a coverage-dependent rod−helix ordering transition of the OEG chain end segments (see section 8.4.1).[309,310] This last example illustrates the subtle interplay of physical features that might serve to modulate the properties of SAMs in a specific application.

4. Removing SAMs from Surfaces

There are a number of different techniques for removing SAMs from gold, silver, and other substrates. Thermal desorption[311] or ion sputtering[312] are convenient techniques for removing SAMs from single-crystal substrates in UHV environments. SAMs are mechanically fragile surfaces, and thus, techniques for polishing or roughening surfaces of metals can remove the SAM and expose a clean surface on bulk metal substrates.[313] Chemical oxidants or reductants such as concentrated acids or bases or "piranha" solutions (H_2O_2:H_2SO_4)[227] also are effective for cleaning substrates. Another method for removing SAMs from metal substrates is plasma oxidation.[314]

Some substrates such as patterned thin films or suspensions of nanoparticles (colloids, rods, other structures) can be damaged by harsh mechanical or chemical treatments. We discuss three mild chemical methods that are used to remove or exchange SAMs on surfaces; these methods offer mild conditions and chemical selectivity.

4.1. Electrochemical Desorption of SAMs

Thiols undergo reductive desorption when a negative potential is applied to the supporting metallic film.[197,227,315] For electrochemical desorption SAMs typically are immersed in an aqueous or ethanolic solution with an electrolyte at a neutral or basic pH.[316] The electrochemical half-reaction for alkanethiolates adsorbed on metals is

$$\mathrm{RS{-}M} + e^- \rightarrow \mathrm{RS}^- + \mathrm{M}^0 \qquad (1)$$

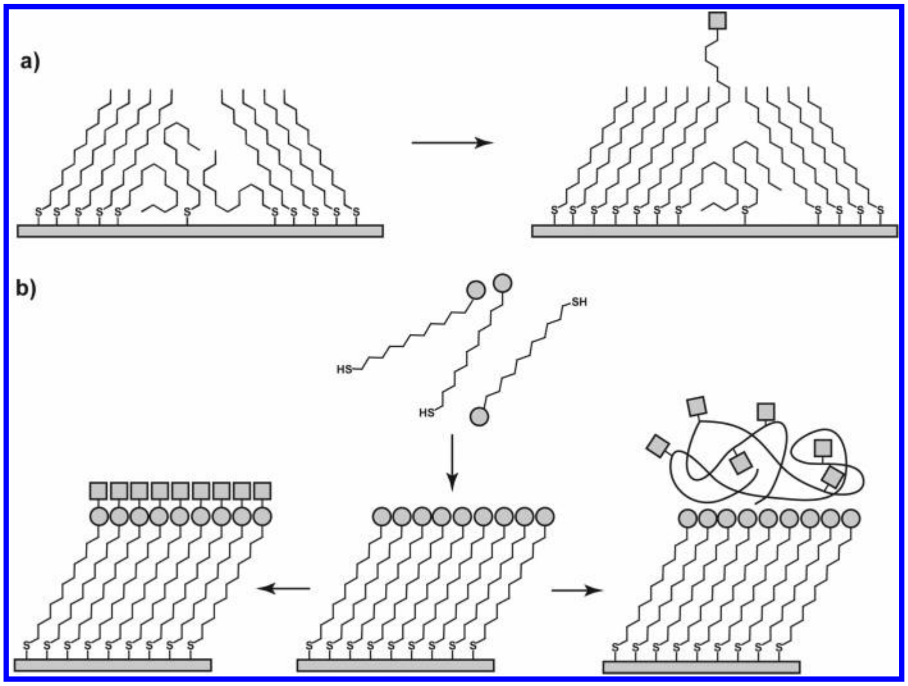
Both the thiolate and the bare metal surface become solvated, and the thiolate diffuses away from the surface. The process is reversible: removing the applied negative potential can result in readsorption of the thiolates onto the metal surface.[317]

Studies of the mechanism of this process suggest that desorption occurs first at defect sites and grain boundaries in the SAM and then at apparently random nucleation sites within the well-organized, crystalline regions of the SAM.[318] The electric field-induced rate of desorption seems to be highest for the adsorbate molecules at edges and defects. The potential at which the desorption of alkanethiolates occurs depends on a number of factors, including the chain length, degree of ordering and number of intermolecular interactions (hydrogen bonding) within the organic film, and crystallinity of the substrate.[319] A typical desorption potential for n-alkanethiolates is −1.0 V with respect to a Ag/AgCl (satd KCl) reference electrode, but the value can vary for different structures by ±0.25 V. This range makes it possible to desorb one component of a mixed SAM selectively by controlling the applied potential.[320]

4.2. Displacement of SAMs by Exchange

The molecules comprising a SAM exchange gradually (minutes to hours) when exposed to solutions containing other thiols or disulfides. This replacement reaction generally does not yield a homogeneous or uniform SAM nor does it provide a bare substrate, but it does offer a route to generate a new organic surface on a substrate already supporting a SAM. The mechanism of this reaction has been studied on SAMs supported on thin films by a number of techniques, including contact angle goni-

Scheme 1. General Strategies for Modifying the Interfacial Composition of SAMs after Formation[a]



[a] (a) Insertion of a functional adsorbate at a defect site in a preformed SAM. (b) Transformation of a SAM with exposed functional groups (circles) by either chemical reaction or adsorption of another material.

ometry,[23,246] electrochemistry,[321−323] radioactive labeling,[262] SPM,[261,269] temperature programmed desorption (TPD),[269] attenuated total reflection,[324] and FT-IR.[325]

Replacement occurs rapidly (hours) at grain boundaries, defects, and regions of disorder in the SAM and is similar, in this sense, to the electrochemical desorption of thiolates; the replacement of molecules in dense, crystalline regions is slow (days).[261,321,322] Because SAMs prepared on rough metallic films (e.g., electroless deposits) have less order and, consequently, more defects than those on smooth surfaces, they undergo exchange more easily than those on surfaces generated by physical vapor deposition.[326]

Pseudo-first-order kinetics can describe the exchange reaction,[262] but the rate of replacement of alkanethiolates depends on a number of parameters, including the chain length, degree of order, and topography/roughness of the substrate. For n-alkanethiols, a general guideline is that short chains ($n < 12$) are more rapidly displaced than long ones ($n > 14$).[246] This characteristic makes it possible to exchange one component in a mixed or patterned SAM selectively. Intermolecular interactions between molecules in the SAM (e.g., hydrogen bonds[327]) or molecules bearing multiple thiols[328] for chelating metallic surfaces can improve the stability of SAMs against displacement by other thiols.

4.3. Photooxidation of SAMs

SAMs of thiolates on gold undergo oxidation upon exposure to ultraviolet (UV) irradiation in air.[329] The thiolates convert to sulfonate groups, and the oxidized SAM washes away easily from the surface with a polar solvent, such as ethanol or water. The mechanism for this process has been studied by mass spectrometry,[330−332] XPS,[331,333] surface-extended X-ray absorption fine structure,[334] surface-enhanced Raman spectroscopy,[335] SPR spectroscopy,[336] and IR,[336] but the elementary steps of the mechanism are not completely understood. The species responsible for the oxidation seems to be ozone produced by UV photolysis of O_2.[335,336] Whether the ozone itself or singlet oxygen atoms/molecules (generated by degradation of ozone at the metal surface) leads to oxidation is not known. The rate of oxidation decreases as the number of carbons in the alkanethiols that form the SAM increase.[330,337] Raman spectroscopy studies suggest that scission of C−S bonds may also contribute to the photooxidation process.[335]

5. Tailoring the Composition and Structure of SAMs

SAMs formed from alkanethiols make it possible to generate organic surfaces that present a wide range of organic functionalities (nonpolar, polar, electroactive, biologically active). There are three general strategies for engineering the composition of the exposed surface: (1) synthesis of functionalized thiols for forming single-component or mixed SAMs by (co-)adsorption;[24,245,338] (2) insertion of synthesized thiols into defect sites of preformed SAMs (Scheme 1a);[339] and (3) modification of the surface composition of a preformed SAM (Scheme 1b). Both covalent reactions and noncovalent interactions (van der Waals forces, hydrogen bonding, metal−ligand bonding) can generate new interfaces for SAMs.

5.1. Why Modify SAMs after Formation?

Simple, small functional groups (−OH, −COOH) are often adequate for studies of properties relevant to materials science such as wettability,[154,340] friction,[341] adhesion,[342] and corrosion resistance,[343] but methods for modifying SAMs *after* their formation are critical for the development of surfaces that present the large, complex ligands and molecules needed for biology and biochemistry. The synthesis of functionalized thiols is usually laborious and difficult even for “simple” molecules, and for SAMs comprising alkanethiols linked to a peptide, protein, carbohydrate, or other biomolecules, synthesis can provide a major challenge. Many of the strategies adopted for modifying SAMs after their formation derive from precedents established in the 1970s and early 1980s for functionalizing organic films supported on electrodes used for electrochemistry[344] and on solid-phase materials used for chromatography.[345] Some of the methods developed for those systems, such as amide-bond formation (section 5.2.1) and nonspecific adsorption of polymers (section 5.3), remain important techniques for modifying SAMs. Modification of the exposed surface of a SAM after formation offers four advantages: (1) it uses common synthetic procedures and thus simplifies the preparation of functionalized surfaces (section 5.2); (2) it enables the incorporation of ligands into SAMs that are not compatible with thiols or the synthetic methods for preparing them; (3) it can generate multiple samples with different types of ligands in a short period of time (because the SAMs are easy to prepare); and (4) it preserves the ordered underlying structure of the SAM. An important economic advantage of modifying the SAM after formation is that the amount of ligand required for immobilization is very small ($<10^{14}$ or ~nanomoles): this characteristic is especially important for linking biological ligands that may be in short supply to surfaces. The disadvantages of modifying the composition of the SAM after formation are that (1) the extent of surface coverage is unknown, (2) the reactions can produce a mixture of functional groups on the surface, and (3) the structure of the resulting surface is unknown (but it is usually unknown with other procedures as well.)

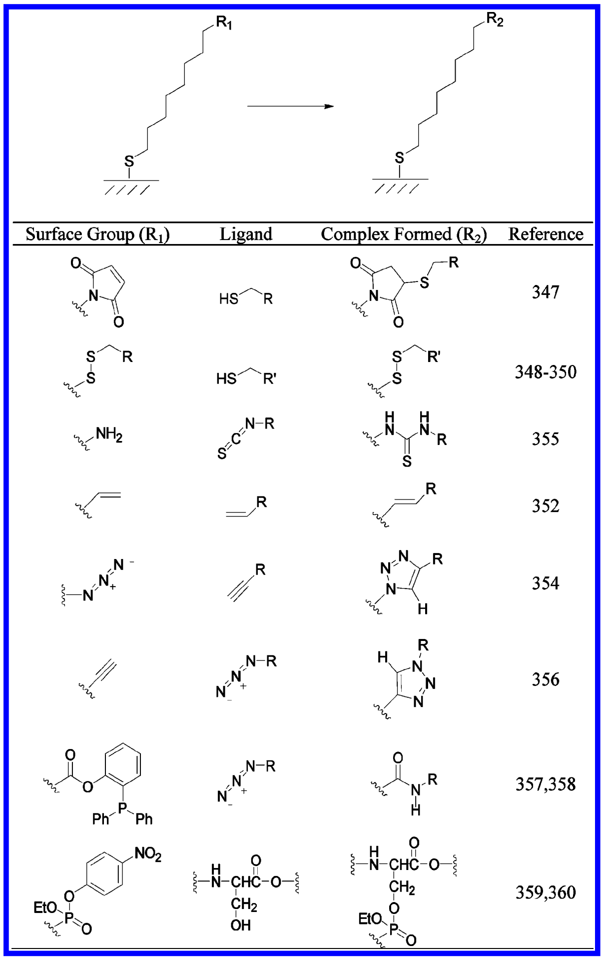
5.2. Strategies for Covalent Coupling on SAMs

A number of different classes of organic reactions have been explored for modifying the surfaces of SAMs, including nucleophilic substitutions, esterification, acylation, and nucleophilic addition. Sullivan and Huck reviewed these reaction types for organic surfaces derived from thiols and siloxanes that present terminal amines, hydroxyls, carboxylic acids, aldehydes, and halogens.[346] Here we highlight important reactions used to modify the exposed surfaces of SAMs formed from thiols and new developments in this area.

5.2.1. Direct Reactions with Exposed Functional Groups

Under appropriate reaction conditions, terminal functional groups exposed on the surface of a SAM immersed in a solution of ligands can react directly with the molecules present in solution. Many direct immobilization techniques have been adapted from methods for immobilizing DNA, polypeptides, and proteins on glass surfaces (Scheme 2). Mrksich et al. have shown that SAMs presenting maleimide functional groups react in good yield with biologically active ligands (peptides and carbohydrates) having thiols.[347]

Scheme 2. Direct Interfacial Reactions of Exposed Functional Groups



Disulfide−thiol exchange is another method used to attach thiol-modified DNA,[348] peptides,[349] and carbohydrates[350] to SAMs on gold. The exchange process appears to occur more readily than displacement of the thiols on the surface. The steric bulk of the thiol-modified biomolecules may hinder their transport into defect sites on the surface.

Ruthenium-catalyzed olefin cross-metathesis is a versatile method for forming carbon−carbon bonds under mild reaction conditions.[351] Choi et al. demonstrated the usefulness of cross-metathesis reactions for attaching acrylamide, acrylic acid, and methyl acrylate to vinyl-terminated SAMs.[352] Intra-SAM cross-coupling reactions between adjacent vinyl groups and reaction temperatures of 50 °C may, however, limit the usefulness of this method for linking proteins or carbohydrates to surfaces.

Triazoles formed by 1,3-dipolar cycloadditions of acetyl groups to azides (so-called ‘click’ chemistry[353]) provide a thermally and hydrolytically stable linkage between two molecules. Collman et al. showed that azides attached to undecanethiolates (diluted in a SAM of decanethiolates) reacted readily with ferrocene molecules modified with acetylenes.[354] The reaction proceeded in water and aqueous alcohol, but the reaction times varied with the electrophilicity of the acetylene acceptor. Acetylenyl-terminated SAMs also form triazoles upon reaction with azide compounds.[356] Both methods require at least 3 h for completion of the reaction as well as manipulation of potentially explosive azides and acetylenes. (The presence of copper ion increases the sensitivity of both classes of compounds to explosion.)

Another type of reaction that uses terminal azides is the Staudinger reaction: substituted phosphanes react with azides to form amide bonds. This reaction can modify the surfaces of cells[357] and immobilize small molecules on glass slides.[358] To the best of our knowledge this ligation has not been used to modify SAMs on gold but has proved useful in other types of biological surface chemistry. One advantage of both 'click' chemistry and the Staudinger ligation is that the reactions are highly selective, that is, the reaction is not sensitive to the presence of other functional groups, such as amines, hydroxyls, or thiols, in solution or on the surface.

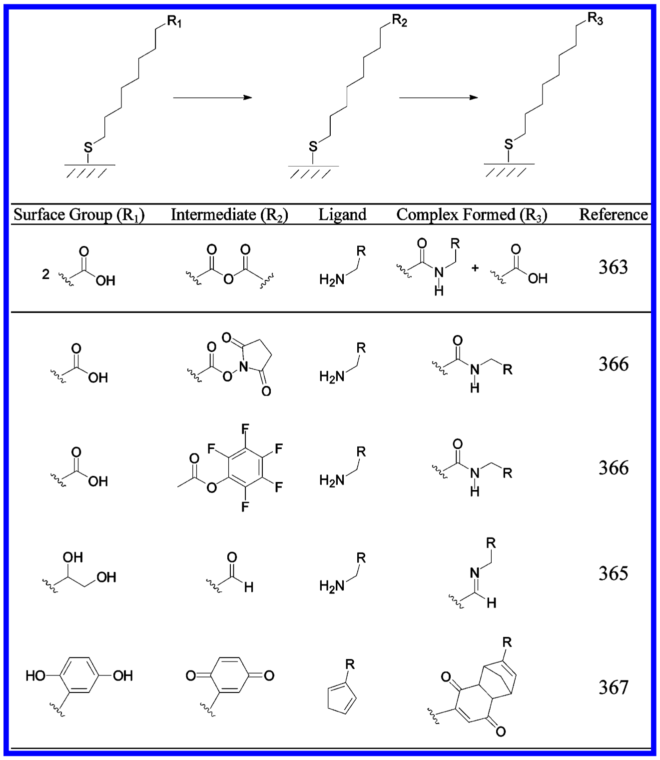
An approach for selectively immobilizing proteins is to use SAMs that present ligands that only react when bound to the active site of an enzyme. Mrksich et al. have shown that SAMs presenting phosphonates form covalent adducts with an engineered fusion protein comprising cutinase and a protein of interest such as calmodulin or sections of fibronectin.[359,360] This strategy leaves the enzyme (cutinase) bound to the surface, but the attached protein extends into the ambient solution with a defined orientation. Enzymatic processing of ligands presented on SAMs has not been widely explored;[361] further studies should enable a range of selective chemical transformations on surfaces.

5.2.2. Activation of Surfaces for Reactions

An operationally different approach to the functionalization of the surfaces of SAMs is to form a reactive intermediate, which is then coupled to a ligand (Scheme 3). There are two primary advantages of this strategy: (1) the common intermediate can react with a variety of ligands and (2) it allows, in principle, spatial discrimination of active and inactive regions, that is, the reactivity of regions on the surface can be turned 'on' or 'off'. The combination of activated intermediates with methods for spatial patterning, e.g., microcontact printing (μCP) (see section 7.1) and scanning probe lithography,[133,362] make it possible to attach ligands in specified locations.[363−365]

One of the experimentally simplest and most broadly applicable methods developed for modifying SAMs is the formation of amide linkages via an interchain anhydride intermediate.[363] In this method, a SAM terminated with carboxylic acids is dehydrated with trifluoroacetic anhydride to yield an interchain anhydride. Exposure of this activated surface to amines generates amide bonds. This so-called "anhydride method" produces a SAM (for the best defined cases) with a 1:1 mixture of functional groups on the surface (−COOH and −CONHR). Three factors make this reaction very useful for screening structure−property relations for surfaces: (1) the simplicity and rapidity of the method, (2) the large number of amine-containing organic and organometallic ligands that are available commercially or that can be synthesized easily, and (3) the high yield normally observed for the coupling reaction.

Scheme 3. Interfacial Reactions That Involve an Intermediate Functional Group



A method familiar to biochemists for modifying free carboxylic acid groups is the activation of a free carboxylic acid by *N*-hydroxysuccinimidyl (NHS) esters and the subsequent reaction with an amine; the reaction yields amide bonds.[366,368] Substituting pentafluorophenol for NHS increases the reactivity of the activated ester on the surface by approximately an order of magnitude.[366] Using this method, ligands and proteins have been immobilized on mixed SAMs derived from tri(ethylene glycol)-terminated thiols and hexa(ethylene glycol)-carboxylic-acid-terminated thiols. For mixed SAMs with a low fraction of acid functional groups (~10% surface coverage), RAIR spectroscopy indicated that the conversion of free acids to NHS esters was nearly quantitative and that the reaction of amines with the activated ester generated amides in better than 80% yield.

Other approaches for activating the functional surfaces of SAMs use external stimuli, such as electrochemical potentials and photoradiation,[369] to transform unreactive functional groups into reactive ones for the subsequent attachment of ligands. Mrksich et al. have shown that the electrochemical oxidation of SAMs terminated with hydroquinone yields a quinone, which subsequently can react with a diene, e.g., cyclopentadiene, via a Diels−Alder reaction.[367] Cyclic voltammetry can control the degree of oxidation/reduction of the quinone groups and alter the reactivity of the surface dynamically. Koberstein et al. developed a SAM terminated with a *tert*-butyl ester azobenzene group that undergoes de-esterification photochemically in the presence of a photoacid generator (triphenylsulfonium triflate); this reaction

Table 3. Examples of Polymers Grafted to SAMs via Surface Initiation

polymer	mechanism	ref
polystyrene	photoinitiated radical polymerization	379
	thermal radical polymerization	380
	living anionic polymerization	381
polyacrylonitrile	photoinitiated radical polymerization	382
polyacrylamide	ATRP	383
poly(norbornene)	ring-opening metathesis	384
poly(methyl methacrylate)	ATRP	385
poly(glycidyl methacrylate)	ATRP	385
poly(butyl methacrylate)	ATRP	385
poly(2-hydroxyethyl methacrylate)	ATRP	385
polylactide	ring-opening polymerization	386
poly(*p*-dioxanone)	ring-opening polymerization	387
	enzymatic polymerization	388
poly(3-hydroxybutyrate)	enzymatic polymerization	389
poly(ethylene glycol dimethacrylate)	ATRP	390
poly(ϵ-caprolactone)	enzymatic	388
	ring-opening polymerization	386

[a] ATRP = Atom transfer radical polymerization.

yields a free carboxylic acid terminus.[370] This reaction does not generate a reactive intermediate directly, but the free acid is useful for attaching ligands by the methods described above.

5.2.3. Reactions that Break Covalent Bonds

A third strategy for modifying the interfacial composition of a SAM is the cleavage of covalent bonds of a terminal surface group.[371] Mrksich et al. demonstrated that quinones modified with propionic esters can undergo an intramolecular cyclization upon electrochemical reduction; ligands bound to the propionic ester moiety are released with the formation of a lactone.[372] Similarly, *O*-silyl hydroquinones will release the silyl group via electrochemical oxidation and hydrolysis.[373] This approach can release a bound molecule into solution and generate a new organic surface for subsequent reactions. Sortino and co-workers have shown that SAMs presenting an anti-cancer drug, flutamide, can release nitric oxide when the surface is irradiated with ultraviolet (UV) light.[374]

5.2.4. Surface-Initiated Polymerizations

Polymer coatings can contribute durability and toughness to SAMs. Two methods for attaching, or grafting, polymers to SAMs are (1) covalently linking preformed polymer chains to reactive SAM surfaces and (2) growth of the polymer directly on the SAM from a terminal functional group that can act as an initiation site. Examples of polymers attached to SAMs by the first method include polyethyleneimine/poly(ethylene-*alt*-maleic anhydride)[375] and poly(acrylic acid)/poly(ethylene glycol).[376] A number of polymers also have been formed by surface-initiated growth processes on SAMs of alkanethiolates (Table 3); it also is possible to grow block copolymers on surfaces by this method.[377] These methods, the types of polymers grafted, and the mechanisms for growth have been reviewed.[378]

5.2.5. How Does the Structure of the SAM Influence Reactivity on Surfaces?

Reactions that involve functional groups immobilized at a surface are subject to certain geometric constraints and environmental variations that are not present in solution. The surface can limit the accessibility of interfacial functional groups, and there is evidence that the nature of the solution (solvent density, viscosity, pH, ion concentrations) at interfaces can differ significantly from the bulk solution.[282,391,392] Other factors also can influence the kinetics of reactions on a SAM: (1) the organization of the chains in the monolayer (crystalline, disordered), (2) the density and orientation of the functional groups on the surface, (3) lateral steric effects, (4) the partitioning of the free reactants at the interface, and (5) the distance of the functional group from the interface between the SAM and the solution.

Effects of the Organization and Density of Molecules. The crystallinity of a SAM can influence the kinetics of reactions on its functional groups. Schönherr et al. used ex-situ RAIRS to measure the effect of chain organization on the rate constants of the base-catalyzed hydrolysis of NHS esters.[393] NHS esters at the termini of SAMs of undecanethiolates hydrolyzed more rapidly than those on SAMs of hexadecanethiolates. Both reactions progressed more slowly (by as much as 2 orders of magnitude) than the hydrolysis reaction of the precursor molecules in solution. In a similar set of experiments, Vaidya et al. demonstrated that the rate of hydrolysis for terminal ester groups on SAMs formed from structural isomers depends on the density and orientation of the organic components;[394] these monolayers were also less reactive than the corresponding hydrolysis reactions in solution. These results suggest that functional groups positioned within highly ordered organic interfaces can have poor reactivities and that conformational and steric effects are important factors in determining the reactivity of a surface.

Lateral Steric Effects. In some cases, steric crowding between reactive sites adjacent to one another within a SAM also can influence interfacial reactions. Houseman and Mrksich observed that the enzymatic activity of bovine β-1,4-galactosyltransferase increased linearly when molecules presenting an appropriate reactant (*N*-acetylglucosamine) constituted ≤70% of a mixed SAM; the activity decreased rapidly, however, when the surface concentration exceeded 70%.[361] In a contrasting study, Huck and co-workers observed that the rate of growth for poly(methyl methacrylate) and poly(glycidyl methacrylate) in water increased with the concentration of initiation sites on the surface for all concentrations.[395] Whether lateral steric crowding affects a reaction and how the rates of interfacial reactions change with increasing concentrations of reactive sites in the SAM seem to depend strongly on the type of reaction.

Position of Reactive Sites. The position of the reactive sites relative to the surface of the substrate supporting a SAM is another important factor that can influence the kinetics of interfacial reactions. Reactive sites positioned below the surface of the SAM—or "embedded" in the SAM—can be less accessible to reactants in the surrounding medium than ones positioned at the termini of the SAM.[396] Steric effects also are reduced when the reactive site is tethered to a molecular component of a mixed SAM that is longer than those comprising the surrounding organic background, for example, alkanethiols terminated with hexa(ethylene glycol) are useful for presenting reactive sites away from a background of a tri(ethylene glycol)-terminated SAM.[366]

Partitioning of Reactants in the Organic Interface. Solvation of reactants from solution by the organic interface can affect the apparent rate of reactions at the interface. Some studies suggest that association of solvated reactants with the organic interface increases the local concentration of the reagent at that interface and can improve rates of reaction.[397] Others indicate that partitioning of reagents in the monolayer or adsorption of reagents onto vacant sites of the surface can hinder the reaction.[398] The composition of the SAM also can affect the degree to which solvated reagents associate with the organic interface and thus the rates of reaction.[399]

There are not enough experimental data to establish detailed structure—reactivity relationships for interfacial reactions on SAMs, especially on mixed SAMs. There remain several outstanding questions regarding the structure of the SAMs that are relevant to the kinetics of interfacial reactions: what is the structure and composition of the SAM near defects? What is the degree of heterogeneity in the SAM—that is, is there significant phase separation of the components? How does increasing the concentration of reactive sites influence the density of molecules on the surface or the conformation adopted by the organic components? The common assumption that reactive sites are isolated from one another may be reasonable for SAMs where less than 1% of the molecules are reactive, but it is not clear that this hypothesis holds for SAMs containing higher percentages of reactive sites. The relationships between the mechanisms of reactivity and mass transfer also require a closer inspection in our view. In cases where systems strongly segregate reactants at the immersed interface—a feature common to reactions involving proteins—accurately measuring rates of true covalent modification can be hard to quantify.

5.3. Noncovalent Modifications

Another set of methods for modifying the composition of preformed SAMs use either the intrinsic properties of the surface (hydrophobicity, electrostatics) or selective interactions with the preformed chemical functional groups on the surface to promote adsorption of materials from solution. These methods use noncovalent interactions rather than covalent reactions to stabilize the adsorbed materials.

5.3.1. Nonspecific Adsorption of Molecules from Solution onto SAMs

A practical and operationally simple method for altering the composition of the exposed surface of a SAM is the adsorption of materials from solution. Surfactants,[400,401] polymers,[402] polyelectrolytes,[403] proteins,[404] organic dyes,[405] and colloidal particles[406] are examples of the types of materials that can adsorb onto SAMs. The attractive interactions between the adsorbate and surface are primarily van der Waals forces, electrostatic forces, or combinations of the two. Hydrophobic SAMs, such as ones formed from *n*-alkanethiols, readily adsorb amphiphilic molecules (surfactants),[400] some polymers,[402] and most proteins.[407−410]

One disadvantage of this method is that there is limited control over the thickness of the adsorbed layer and the orientation of the functionalities of the adsorbed material. This characteristic is less important for certain applications such as the preparation of surfaces that promote or resist cell adhesion[402,404] than it is for applications such as sensors for biological agents, where the activity of immobilized biomolecules may depend on their orientation and conformation.

5.3.2. Fusion of Vesicles on SAMs

Vesicles of phospholipids can adsorb on SAMs and yield either supported bilayers[411,412] or hybrid bilayers comprising the SAM and a single layer of phospholipids.[413,414] The nature of the organization of the adsorbed lipids depends on the functional groups presented at the exposed surface: SAMs terminated with hydrophilic functional groups such as alcohols promote the adsorption and rupture of vesicles to generate patches (or more extensive coverages) of bilayers supported by the underlying SAM, and hydrophobic SAMs formed from *n*-alkanethiols promote the formation of hybrid bilayers.[415] Large unilamellar vesicles typically fuse to generate high-coverage phases in either case.

Characterization of the supported bilayers by AFM and electrochemistry suggests that these adlayers are complex structures and contain a number of defects.[411,416] In contrast, the hybrid bilayers are excellent dielectric barriers with few pinhole defects.[414,416] These structures provide a useful model system for studying the structure and function of cell membranes: they can incorporate proteins found in the membrane, and they are accessible by a number of analytical techniques including SPR, optical ellipsometry, electrochemistry, QCM, AFM, and RAIRS.[414,416]

5.3.3. Selective Deposition onto SAMs

The degree of hydrophobicity and the surface density of electrostatic charge presented by a SAM can determine the nature and extent of materials adsorbed on SAMs. Hammond and co-workers demonstrated that pH can control the adsorption of polyallylamine and polyethyleneimine onto SAMs terminated with carboxylic acids and oligo(ethylene glycol) (OEG) groups.[417] At a pH of 4.8 polyallylamine adsorbs predominantly onto EG-terminated SAMs while polyethyleneimine deposits primarily onto carboxylic-acid-terminated SAMs. This selectivity makes it possible to generate patterns of multilayers of polyelectrolytes with micrometer-scale dimensions using templates of patterned SAMs.[418] Changing the pH of the system alters the relative contributions of the hydrophobicity and electrostatics to the attractive forces experienced by the polyelectrolytes.

SAMs presenting different electrostatic charges also provide a sensitive means to control the orientation of adsorbates. For example, cytochrome *c* adsorbs to positively charged SAMs in a manner that maintains its native structure and orients it favorably for electron transfer; the protein also adsorbs to negatively charged SAMs, but the orientation of the protein on these SAMS is such that electron transfer is hindered.[419] Similarly, Jiang and co-workers have shown that positively charged surfaces adsorbed antibodies in an orientation that allowed better responses to antigens than either negatively charged surfaces or neutral, hydrophobic surfaces.[420]

5.3.4. Modifications via Molecular Recognition

The strategy for modifying the composition of a surface through noncovalent interactions that provides the highest degree of specificity is the use of designed supramolecular interactions to control adsorption. These systems comprise two molecules or functional groups that bind through a network of hydrogen bonds,[421] metal–ligand interactions,[422] electrostatic interactions,[423] or hydrophobic interactions;[424] one molecule is present at the surface, and the second adsorbs from solution. Multiple “host–guest” interactions can stabilize the noncovalent assembly,[424] but it is possible to dissociate the adsorbate from the surface by adding excess ligands that can compete for the available binding sites.[425] Two advantages of this method are as follows: (1) the modification is reversible and (2) the selectivity of the interactions suggests that, in principle, it is possible to position two ligands close together on a surface. Such a degree of precision could be useful for applications in biology or organic/molecular electronics.

6. SAMs as Surface Layers on Nanoparticles

An important class of nanometer-scale materials is colloids and nanocrystals—structures that typically are 1–20 nm in diameter and composed of metals, metal oxides, or semiconductors. The small dimensions of these materials give them unique physical properties such as superparamagnetism, fluorescence with high quantum yields (>80%), and depressed melting points. These properties make nanoparticles useful as stains for analyzing biological samples by electron and optical microscopies,[426] as catalysts for the synthesis of carbon nanotubes and inorganic nanowires,[427] as ultrafine magnetic particulates for information storage,[428] and as MRI contrast agents.[429]

One aspect of nanoparticles that is different than bulk materials is the percentage of the total number of atoms in the nanoparticle that are interfacial. For example, if gold nanoparticles are assumed to be spherical, a 1.3 nm diameter gold particle has 88% of its atoms on the surface; a 2.0 nm particle has 58% surface atoms; a 5 nm particles has 23% surface atoms; a 10 nm particle has 11.5% surface atoms; a 50 nm particle has 2.3% surface atoms; a 100 nm particle has 1.2% surface atoms; and a 1000 nm particle has 0.2% surface atoms. The electronic states of the interfacial atoms of nanoparticles influence their chemical, electronic, and optical properties. Similarly, the finite size of the cluster can affect its electronic structure.

The majority of atoms that constitute nanoparticles smaller than 2 nm are located at the interface between the particle and the surrounding environment, that is, at the surface. For this reason, there is a strong synergy between nanoparticles and SAMs. Since SAMs form by self-assembly, it does not matter what the size of the particles are—that is, chemistry controls the process. The structure of SAMs, however, differs greatly depending on the curvature and defect rate of a given surface. SAMs on nanoparticles simultaneously stabilize the reactive surface of the particle and present organic functional groups at the particle–solvent interface.[57] Tailored organic surfaces on nanoparticles are useful for applications in nanotechnology that depend on chemical composition of the surface; one example is immunoassays.

6.1. Formation of Monolayer-Protected Clusters (MPCs)

There are two principal strategies for forming metallic and semiconductor nanoparticles: (1) reduction of metal salts (usually in aqueous solutions) and (2) controlled aggregation of zerovalent metals (usually in organic solvents).[9,430,431] To get highly monodisperse particles, there needs to be rapid nucleation that brings the solution below saturation and then slow, controlled growth until all precursors are consumed.[431] There are two common approaches used to achieve rapid nucleation: decomposition of metal precursors at high temperatures and rapid addition of the reductant. To control the rate of growth and limit aggregation, surfactants are added to the reaction vessel during nanoparticle formation.[60,85,102,106,432,433]

What is the role of surfactants on nanoparticles? The adsorption of surfactant-like molecules to nucleated nanocrystals lowers the free energy of the surface and, therefore, the reactivity of the particles. The ratio of surfactant to metal precursor can control the size distribution of the nanoparticles. The mechanism by which this ratio controls the nucleation events and limits the growth of the particles is understood in general qualitative terms. The steric bulk of the surfactants provides a physical barrier that prevents the metal surfaces from contacting each other directly. They can also change the surface charge of a cluster and thus change its stability toward aggregation.[434,435] The combination of the energetic stabilization of the metal surface by the surfactant, the consequences of charge−charge interactions, and the steric repulsion between particles prevents the system from forming aggregates.[436]

During the formation of nanoparticles, surfactants interact with the surfaces of the particles in a dynamic equilibrium process—that is, the amount of surfactant on the surface of the particle depends on the relative rates of adsorption and desorption. Surfactants that are chemisorbed to the surface of the particle are less prone to desorption than are physisorbed species. One consequence of a low desorption rate is that particles do not grow rapidly after nucleation. For example, thiols bind via chemisorption to gold nanoparticles and typically limit their sizes to ≤ 5 nm (though extremely large particles are also observed in the preparation of small particles).[437−439] In contrast, the majority of surfactants used to stabilize nanoparticles of semiconductors, metal oxides, and some metals (e.g., long-chain acids, amines, phosphines, phosphine oxides, and diols) associate with the surface of particles through van der Waals contacts or weak electronic interactions. These interactions are sufficiently weak that the species readily adsorb and desorb throughout the nucleation and growth processes. The dynamic process allows control over the size and shape of nanocrystals.[145] Some classes of surfactants (thiols and diols) also can act as reductants in the formation of nanoparticles.[74,440−442]

6.1.1. Thiols Are a Special Subclass of Surfactants

Their chemical reactivity makes thiols different from other surfactants. They associate specifically with transition metals to form metal chalcogenides. Although alkanethiols are used most commonly in the synthesis of gold MPCs,[57,443] they are also used in the formation of nanoparticles of many other materials (see Table 1). For gold nanoclusters, the assembly of thiols on their surfaces also can be accompanied by metal etching processes.[444]

One of the most common routes to gold nanoparticles functionalized with thiols is the Brust−Schiffrin method.[437,445] The thiols in this reaction and other related routes are involved in the reduction of gold precursor salts to a Au(I)−thiol polymer (eqs 2 and 3).[74,441]

$$\mathrm{AuCl_4^-\ (toluene) + RSH \rightarrow (-Au^{I}SR-)_{\mathit{n}}(polymer)} \tag{2}$$

$$\mathrm{(-Au^{I}SR-)_{\mathit{n}} + BH_4^- \rightarrow Au_{\mathit{x}}(SR)_y} \tag{3}$$

The Au(I)−thiol intermediates are also useful for forming bimetallic nanoparticles (Au−Pd, Au−Cu, and Au−Ag) via galvanic exchange reactions with thiol-protected metallic nanoparticles.[58,446] If dithiols, such as dimercaptosuccinic acid, are used instead of monothiols, Au(III) is reduced completely to Au(0), eliminating the need for any additional reductants in the formation of small (1−2 nm) gold nanoparticles.[442]

An excellent review by Daniel and Astruc has covered many aspects of gold nanoparticles, including their formation and characterization as well as uses in studies of molecular recognition, biology, and catalysis.[443] In the following sections, therefore, we only highlight the important roles of thiols in the formation, stabilization, and assembly of nanoparticles of gold and other materials. Section 9.6 addresses some applications of nanoparticles protected with SAMs.

6.1.2. Thiols Can Influence the Size and Shape of Nanoparticles

The ratio of alkanethiol to Au(III) controls the size of the resulting nanoparticles by adjusting the relative rates of particle nucleation and growth (higher ratios yield smaller particles).[166,447] Methods of forming gold nanoparticles in the presence of thiols can only be used to form small (<5 nm in diameter) particles. The formation of particles with diameters >5 nm requires the use of surfactants that have a faster desorption rate than thiols (e.g., phosphines and cetyltrimethylammonium bromide (CTAB) or stabilization by electrostatic charges (citric acid synthesis)).[438,448] These larger particles can be functionalized with thiols via “ligand-exchange” methods to displace the weakly bound surfactants (see section 6.2.2).

Effect of Thiols on the Shape of Nanoparticles. Micrometer-sized crystals grown in the presence of an organic additive (e.g., a surfactant) that preferentially binds to a certain set of crystalline faces will have a morphology that expresses these faces.[449] The organic additives lower the free energy of the crystalline faces to which they bind and retard the growth of those faces; these interactions control the resulting morphologies of crystals by selecting the crystalline planes that are expressed at the surface of the crystal. The same principles may apply at the nanometer-scale, where the differential binding of surfactants to selected crystalline faces and polymorphs has been shown to influence the size, shape, and polymorph of nanocrystals.[117,145,433,450] Because of their decidedly non-bulk-like characteristics, thermodynamic arguments must be applied thoughtfully to nanoscale processes and particles.[451]

Alkanethiols are not well-suited for controlling the shape of gold nanoparticles because thiols presumably have similar affinities for all crystalline faces; gold nanoparticles formed in the presence of thiols adopt a roughly spherical shape.[452] This geometry indicates isotropic growth, but the weak ability of thiols to etch gold also influences the symmetry of the particles. Materials with slightly more complex crystal structures than gold have crystalline faces with different surface energies that will bind thiols with different affinities; this difference makes it possible to control the morphology of the resulting particles.

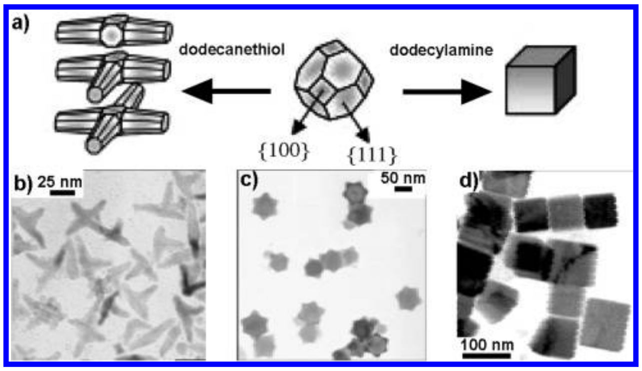
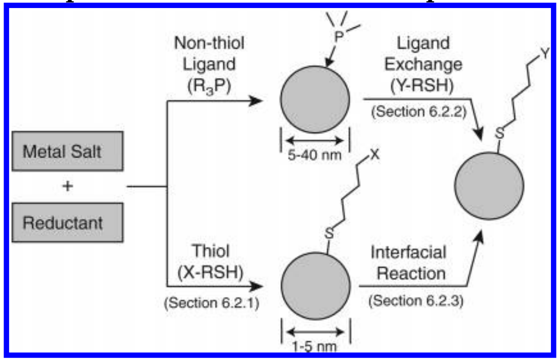


Figure 8. (a) Schematic representation of the different growth modes of PbS nanocrystals in the presence of different surfactants. (Reprinted with permission from ref 78. Copyright 2003 Wiley-VCH.) (b) TEM image of rod-based PbS multipods formed in the presence of dodecanethiol at 140 °C for 5 min. (c) TEM image of star-shaped nanocrystals of PbS formed in the presence of dodecanethiol at 230 °C. (d) TEM image of cubic PbS nanocrystals formed in the presence of dodecylamine. (b−d) (Reprinted with permission from ref 77. Copyright 2002 American Chemical Society.)

Scheme 4. Three Common Strategies for Tailoring the Composition of the SAM on Nanoparticles[a]



[a] Each one is discussed in the text in the section indicated in the scheme.

For example, depending on the concentration of dodecanethiol present during formation and on the temperature of the reaction, the shape of PbS (a semiconductor) nanocrystals changes from the equilibrium cubic habit (bounded by six {100} faces), to starlike crystals, to elongated rods and branched structures (bounded by {111} faces) (Figure 8).[77,78] This effect is specific to thiols: growth in the presence of dodecylamine, a ligand with lower affinity for PbS, yields only PbS cubes. These results suggest that the thiols have a higher affinity for the {111} faces, where the sulfur can be positioned equidistant from three Pb(II) atoms, than for the {100} faces, where the sulfur can only be positioned equidistant from two Pb(II) atoms.

6.2. Strategies for Functionalizing Nanoparticles with Ligands

There are three common strategies for tailoring the composition of the SAM on nanoparticles and the functional groups exposed at the SAM−solvent interface (Scheme 4). They are (1) forming the nanoparticles directly in the presence of ω-functionalized thiols, (2) exchanging an existing ligand for an ω-functionalized thiol, and (3) modifying the original thiol covalently by an interfacial reaction. We address each of these approaches in the following sections.

6.2.1. Formation of Nanoparticles in the Presence of Thiols

The ω-functionalities of the thiols used to protect nanoparticles determine what solvents (aqueous or organic) can disperse the particles. Some alkanethiols can tolerate the reductive conditions used to prepare nanoparticles and, therefore, can be used to protect the nanoparticles during formation (Scheme 4). For example, in the two-phase Brust−Schiffrin method, *n*-alkanethiols and other organic soluble thiols, including a BINOL (1,1′-bi-2-naphthol) derivative,[453] have been used.[57,92,454]

Water-soluble nanoparticles are desirable for biological applications, and many preparations have been developed that use thiols with hydrophilic, polar headgroups. For example, mercaptosuccinic acid can serve as a stabilizer during borohydride reduction of $HAuCl_4$ to give 1−3 nm, water-dispersible gold nanoparticles that are stabilized by the charge−charge repulsion of the carboxylate ions.[447] Glutathione,[455] tiopronin (*N*-2-mercaptopropionyl-glycine),[456] coenzyme A (CoA),[456] trimethyl (mercaptoundecyl)ammonium,[457] and thiolated derivatives of PEG [458] have all been used as thiol-based water-soluble stabilizers during the formation of gold nanoparticles with a variety of reductants.

6.2.2. Ligand-Exchange Methods

Displacement of one ligand for another is a second strategy for modifying the organic surface of nanoparticles after their formation (Scheme 4).[459,460] These so-called "ligand-exchange" methods are particularly useful if the desired ligand is not compatible with the highly reductive environment required for forming nanoparticles or if the desired ligand is particularly valuable (or simply not commercially available) and cannot be used in the excess necessary for stabilization during synthesis. Simple thiols can be exchanged for more complex thiols[459] or disulfides.[91,461] Ligand exchange is often used to synthesize poly-hetero-ω-functionalized alkanethiol gold nanoparticles via either simultaneous or stepwise exchange.[462,463] There are also several recent reports of solid-phase place-exchange reactions with thiol ligands displayed on Wang resin beads.[464,465]

Thiols can displace other ligands weakly bound to gold (e.g., phosphines and citrate ions); procedures based on exchange are used to functionalize large gold nanoparticles (>5 nm) that cannot be formed directly with a protective layer of thiols.[466] For example, dodecanethiol has been used to extract gold nanoparticles from water (where they were formed via ascorbic acid reduction in the presence of CTAB) into organic solvents. [438,446] Caruso and co-workers also demonstrated the extraction of gold nanoparticles from toluene into aqueous solutions; this method relies on the displacement of hydrophobic *n*-alkanethiols with water-soluble thiols.[435,446]

6.2.3. Covalent Modification

Murray and co-workers demonstrated the use of chemical reactions to modify the terminal functional groups of alkanethiolates on nanoparticles (Scheme 4).[467] Many of the same reactions discussed in section 5.2 have been used to functionalize nanoparticles, including cross-metathesis,[468] peptide coupling reactions,[463,465,467,469] and nucleophilic substitution reactions.[470] The chemical reactivities of thiols are, however, different on nanoparticles than on thin films (section 6.3.2) because the structure of SAMs on highly curved surfaces (nanoparticles) are different than that for SAMs on planar surfaces (section 6.3). These differences make it possible to use other classes of organic reactions that typically are precluded by steric effects on planar surfaces, for example, S_N2 reactions.[470]

6.3. Structure of SAMs on Highly Curved Surfaces

Much of the research involving gold nanoparticles has been carried out without a detailed understanding of the structure of the organic films formed by SAMs on the surfaces of nanoparticles.[235] Two experimental approaches are used to investigate the structure of SAMs on nanoparticles: physical analytical techniques (IR, NMR, differential scanning calorimetry (DSC), HRTEM, AFM[167]) and chemical methods (reactivities). Before summarizing experimental results, we will discuss two physical characteristics of nanocrystals (geometric shape and radius of curvature) that are important in determining the structure of SAMs supported on them.

Gold nanocrystals larger than 0.8 nm are believed to have a truncated octahedral or cubooctahedral shape, depending on the number of gold atoms in the core, with eight {111} faces truncated by six smaller {100} faces (Figure 9a).[57,471−473] There is a higher percentage of regions where the surface construction changes from one type to another (gold atoms on the corners and edges of the truncated octahedron) on nanocrystals than on the planar substrates commonly used for SAM formation. For example, on a 1−2 nm Au cluster ~45% of all surface atoms are located on edges or corners (Figure 9a).[171] Thermal gravimetric analysis (TGA) has suggested that small nanoparticles (<4.4 nm) have a higher density of alkanethiols per gold atom (>60%) than an ideal, perfectly flat, single-crystal 2-D Au(111) surface (33%).[166] This high coverage has been attributed to the occupancy of alternative binding sites (edges and corners) and can be modeled with both a simple geometric model[166,168,170,171] and a computational model.[473] Such models need, however, to be considered with some caution as the mixture of reaction products from nanocluster preparations, especially the distributions of mass, has not been characterized as fully as is required to make direct structural assignments of this sort.

Another distinguishing characteristic of SAMs formed on the surfaces of nanoparticles is the high radius of curvature of the substrate. An important consequence of this curvature is a decrease in the chain density moving away from the surface of the core.[166] For *n*-alkanethiols the decreasing density translates into enhanced mobility of the terminal methyl groups. A cone can be drawn that encompasses the area available to each chain on a nanoparticle with a given diameter; the alkyl chain completely fills the volume of the cone at the surface of the nanoparticle but is unable to fill the larger end of the cone (Figure 9b and c).[474,475]

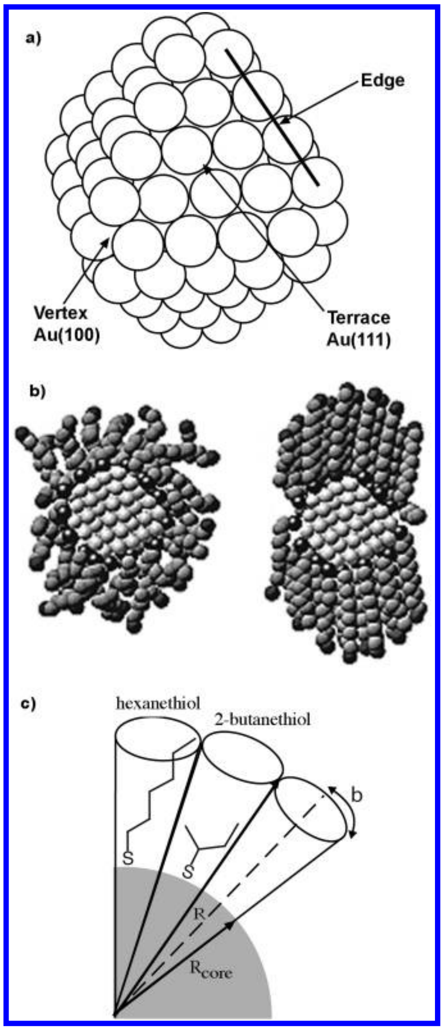


Figure 9. (a) Model of Au_{140} nanocluster with a truncated octahedral geometry. (b) Equilibrium configurations of dodecanethiol-passivated Au_{140} clusters obtained through a molecular dynamics simulation: (left) 350 and (right) 200 K. (Reprinted with permission from ref 473. Copyright 1998 American Chemical Society.) (c) Schematic diagram of a gold cluster (radius = R_{core}) protected with a branched and unbranched alkanethiolate. R is the radial distance, and b is the half-angle of the conical packing constraint. (Adapted from ref 168.)

Measurements of the hydrodynamic radii of monolayer-protected gold nanoparticles support the hypothesis that the outer part of the thiol layer is loosely packed.[175] A nanoparticle coated with a well-packed SAM (similar to those formed on thin films) is expected to have a hydrodynamic radius equal to the sum of the radius of the gold core and the fully extended alkanethiolate. This expectation does not, however, match experimental results: all measured hydrodynamic radii of monolayer-protected gold nanoparticles are smaller than the prediction, suggesting that the monolayer is not well packed along the outer edge.

6.3.1. Spectroscopic Evidence for SAM Structure on Nanoparticles

Spectroscopy (IR and NMR) provides information about the conformation and packing of the alkyl chains on the nanoparticles.[166,168,170,171,467,476,477] A solid-state IR study of the structure of SAMs of n-alkanethiolates on 1−2 nm gold clusters showed that the major difference between planar SAMs and SAMs on nanoparticles is that the SAMs on nanoparticles exhibit a higher number (10−25%) of chain end-gauche defects (for all chain lengths) than SAMs on planar substrates.[171] The same study found that SAMs on nanoparticles have a number of near-surface and internal kink defects similar to that of planar SAMs formed from alkanethiols of similar lengths. IR spectra of the same nanoparticles in carbon tetrachloride show a degree of disorder comparable to that of liquid n-alkanes.[470] One interpretation of the difference in IR spectra between solution and the solid phase is that the packing of the nanoparticles in the solid state induces some degree of order on the alkanethiolates. Alternatively, the solvation of the alkyl chains by carbon tetrachloride could account for the observed disorder.

As the size of the particle increases, the properties of the SAM become more similar to a SAM on a planar surface: particles with a core diameter greater than 4.4 nm, coated with a SAM of dodecanethiolates, have spectroscopic and physical properties approximating that of a planar SAM.[166] For 4.4 nm particles the majority of the surface comprises flat {111} terraces rather than edges and corners; this geometry leads to “bundles” of ordered alkanethiolates with gaps (areas with a disordered organic layer) at the corners and vertexes (Figure 9b).[170,472,473] These “bundles” have been hypothesized to play an important role in the solid-state packing of nanoparticles into lattices (see section 6.4).

6.3.2. Evidence for the Structure of SAMs on Nanoparticles based on Chemical Reactivity

The chemical reactivities, both of the metal core and the alkanethiolate ligands, have been used to evaluate the structure of SAMs on nanoparticles. For example, Murray and co-workers studied the kinetics and thermodynamics of the displacement of one alkanethiolate for another on the surfaces of gold nanoparticles (2 nm diameter) as a function of chain length.[446,459,478] They find that the alkanethiolates bound to the vertexes and edges have a higher rate of exchange than those in the dense, well-packed planar faces. The rate of exchange decreases as the chain length and/or steric bulk of the initial SAM increases.

The susceptibility of differently protected gold cores to a cyanide etchant gives an indication of the density of packing of the alkanethiolates in the SAM (section 8.1).[470,476,479] For nanoparticles, the rate of dissolution (etching) decreases with increasing chain length; the rate remains constant when the chain length is greater than 10 carbons, however.[470] This result complements the spectroscopic evidence, which indicates an ordered inner core with increased fluidity of the carbon chains in the outer shell.[170]

Monolayers on nanoparticles composed of branched alkane chains offer a higher degree of protection to chemical etching (sodium cyanide) than do straight chain alkanes.[470,476] Murray and co-workers found that SAMs formed from 2-butanethiol decreased the rate of etching by NaCN to the same degree that hexanethiol did.[470] In a related study, Rotello and co-workers formed SAMs from alkanethiols functionalized with a variety of amides and esters with branched end groups and evaluated the stability of the monolayer-protected clusters using cyanide etching and IR spectroscopy.[476] They hypothesized that “cone-shaped”, branched molecules would more effectively occupy the volume available at the outer edge of the monolayer than simple n-alkanethiolates, which have a linear geometry when extended in an all-trans conformation (Figure 9).

The chemical reactivities of terminal functional groups displayed on SAMs formed on the surfaces of nanoparticles are different than those on SAMs on planar surfaces. For example, Murray and co-workers demonstrated that S_N2 reactions occur more readily on the surfaces of nanoparticles than on planar surfaces.[470] The headgroups of ω-bromoalkanethiolates are less densely packed on curved surfaces than they are on planar surfaces; this lower density allows backside attack of the incoming nucleophile (amine) to occur. The rate is a function of the steric bulk of the incoming amine as well as of the relative chain lengths of the bromoalkanethiolates and the surrounding alkanethiolates. The measured rates are similar to solution-phase rates for S_N2 substitutions, in agreement with the spectroscopic data (section 6.3.1) regarding the fluidity of the SAMs on nanoparticles.

6.4. SAMs and the Packing of Nanocrystals into Superlattices

The same surfactants that are used to control the size and shape of nanocrystals also influence the organization of the particles into superlattices and colloidal crystals.[480−483] In colloidal crystals the nanoparticles are sometimes referred to as “molecules” and the van der Waals contact of surfactant layers on neighboring particles as intermolecular “bonds”.[54] When spherical nanocrystals, protected by a layer of alkanethiolates, are allowed to self-assemble on a TEM grid via slow evaporation of solvent, they form hexagonal close-packed 2-D arrays (Figure 10).[483−486] Preparations with shorter alkyl chains (hexanethiol) assemble in solution to form ordered 3-D, colloidal crystals.[486] The separation of the close-packed spheres is linearly dependent on the length of the alkyl chains (Figure 10b).[486,487] The increase in particle spacing per additional carbon (~1.2 Å) is about one-half of the expected value; this observation suggests that the alkyl chains might interdigitate with the chains on neighboring particles.[81,482,486,488] There are also examples of hydrogen-bonding control over interparticle spacing for gold nanoparticles with carboxylic-acid-terminated SAMs.[447,489]

Nanocrystals with other morphologies assemble, promoted by the hydrophobic tails of the capping

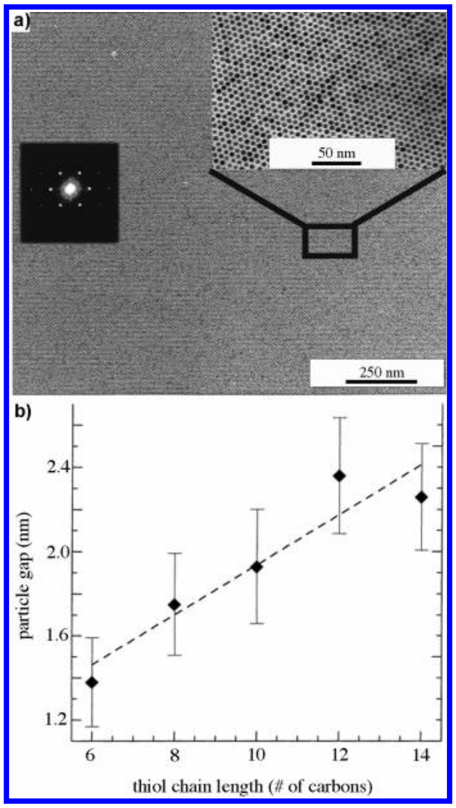


Figure 10. (a) TEM image of a long-range-ordered array of dodecanethiolate-protected gold nanoparticles (5.5 nm diameter) deposited from toluene onto a silicon nitride membrane. (Upper right inset) Enlarged view of the individual particles. (Left inset) Diffraction pattern of the array obtained by Fourier transformation of a portion of the image. (Reprinted with permission from ref 484. Copyright 2001 American Chemical Society.) (b) Dependence of the particle spacing in lattices of gold nanoparticles on thiol chain length. The slope of the line gives an increase of 1.2 Å per additional carbon atom. (Reprinted with permission from ref 486. Copyright 2000 American Chemical Society.)

agents, with close-packed geometries when allowed to assemble on a TEM grid. Several examples of superlattices formed by nanocrystals with different morphologies are shown in Figure 11. As discussed in section 6.3, there is an uneven distribution of thiols on the surfaces of angular polyhedra.[472,473] For example, the superlattices formed by silver tetrahedra and truncated octahedra have been analyzed using energy-filtered TEM to locate areas of high organic density.[450,488,490] The authors assume that the alkane chains on each face of a tetrahedron "bundle" and leave areas of lower organic density at the corners.[472] For both particle morphologies the packing of the nanoparticles that they observe is consistent with this model (Figure 11a and b).[480]

The uneven distribution of thiolates on the surface of nanoparticles can also lead to 1-D assembly (Figure 11c).[81,491] For example, the assembly of hexagonal platelets of ruthenium can be altered by changing the ratio of thiol to particle.[81] At high concentrations of thiol (where the nanoparticles are assumed to be completely coated with a monolayer), the particles arrange themselves in hexagonal lattices. At lower thiol concentrations, however, the platelets pack anisotropically into 1-D columns; this observation suggests that the thiols preferentially bind to the edges and leave the flat faces bare and prone to aggregation (Figure 11c). Similar behavior has been observed for silver rods that fuse into wires when assembled on TEM grids.[491]

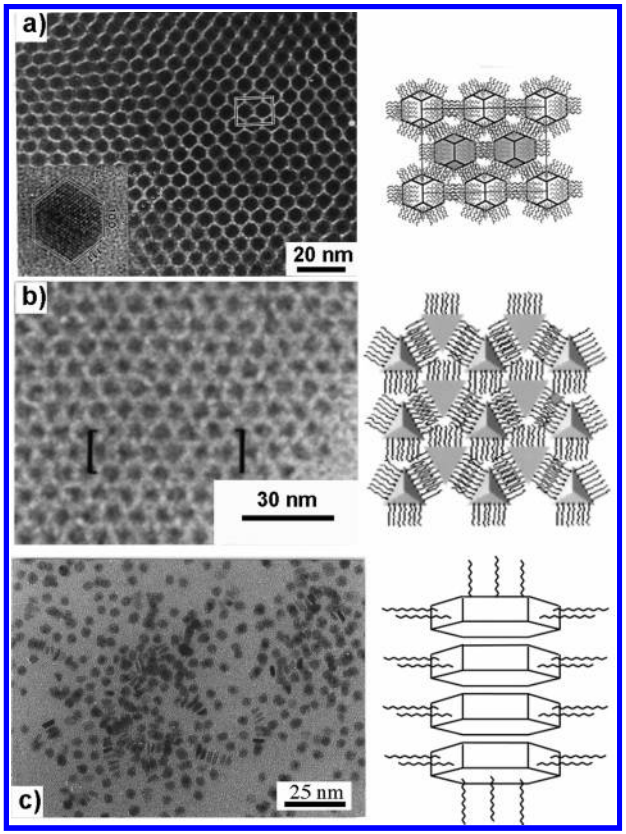


Figure 11. (a) (Left) TEM image of a face-centered, cubic-packed, array of silver nanoparticles, passivated with a dodecanethiolate monolayer, with a truncated octahedral morphology (see inset). (Right) Representation of the proposed packing of the particles via interdigitation of the bundled alkyl chains on each face. (Reprinted with permission from refs 450 and 490. Copyright 2000 and 1998 American Chemical Society.) (b) (Left) TEM image of a monolayer of self-assembled silver tetrahedra passivated with dodecanethiolates. The bracketed area most closely matches the proposed model. (Reprinted with permission from ref 450. Copyright 2000 American Chemical Society.) (Right) Possible model of the short-range orientational order of the assemblies of tetrahedra. (Reprinted with permission from ref 488. Copyright 1998 Wiley-VCH.) (c) (Left) TEM image of stacks of ruthenium hexagonal platelets protected with a monolayer of dodecanethiolates. (Right) Proposed model for the anisotropic packing of the platelets with low concentrations of thiols. (Reprinted with permission from ref 81. Copyright 2003 American Chemical Society.)

7. Patterning SAMs In Plane

Physical tools capable of selectively positioning or damaging organic molecules enable the fabrication of surfaces with well-defined patterns of SAMs in the plane of the surface with lateral features ranging from 10 nm to 10 cm. The techniques developed to generate patterns of SAMs on surfaces belong to a general class of techniques—termed "soft lithography"[130,492]—that can replicate patterns of organic (or organometallic) molecules and other materials on substrates with planar or nonplanar topographies. One strategy employed for patterning SAMs on surfaces is physical transfer of the molecular components of a SAM to the substrate in an imposed pattern. Microcontact printing (μCP, section 7.1) and scanning probe lithography are examples of methods that use this principle. (There are many variations of scanning probe lithographies for patterning SAMs that deposit molecules from the tip to the substrate or that scratch patterns into preformed SAMs.[493] A number of recent reviews address these topics explicitly, and the topic is not covered in this review.[132,133,362]) A key difference between μCP and scanning probe methods is that μCP can generate many features simultaneously on the surface in a single step, whereas scanning probes are serial techniques that only write one feature at a time. A disadvantage of the probe methods, therefore, is that they require long times (minutes to hours per cm^2) to write patterns; new technologies for arrays of independent scanning probes may improve the practicality of these methods for prototyping structures.[494]

Another strategy for generating in-plane patterns of SAMs relies on damage to a preformed SAM; an energetic beam of photons, electrons, or atoms, or mechanical scratching[213] can cause either chemical or physical damage to the SAM. Yet another strategy uses the composition or topography of the substrate itself to determine the defect sites in the SAM. Both of these strategies may be combined with methods for exchanging SAMs to replace the damaged regions with a SAM presenting different functional groups.

7.1. Microcontact Printing

Microcontact printing is a method for patterning SAMs on surfaces that is operationally analogous to printing ink with a rubber stamp on paper: SAMs form in the regions of contact between a topographically patterned elastomeric stamp, wetted with (or containing dissolved) reactive chemical ‘ink’ consisting of n-alkanethiols (or other molecules that form SAMs), and the bare surface of a metal, metal oxide, or semiconductor (Figure 12).[130] When forming patterned SAMs of n-alkanethiolates on gold, the stamp usually is left in contact with the surface for a few seconds (5−10 s) before it is removed. The lateral dimensions of the SAMs formed depend on the dimensions of relief features on the stamp used for printing; the size of the stamp determines the total area over which the pattern is formed. Typical patterns generated by μCP cover areas of 0.1−100 cm^2 with critical in-plane dimensions of ~50 nm to 1000 μm. If required, another SAM can be generated in the bare regions of the surface that remain after removing the stamp by immersion of the substrate in a solution containing another thiol for a few minutes (~1−10 min) or application of a second stamp wetted with another thiol.

7.1.1. Composition of Topographically Patterned Stamps

The most common material used for the stamp in μCP is poly(dimethylsiloxane) (PDMS). PDMS is a nontoxic, commercially available silicone rubber. It is well-suited for forming stamps because it is elastomeric (Young’s modulus ≈ 1.8 MPa) and has a low surface energy (γ = 21.6 dyn/cm^2).[495,496] The low

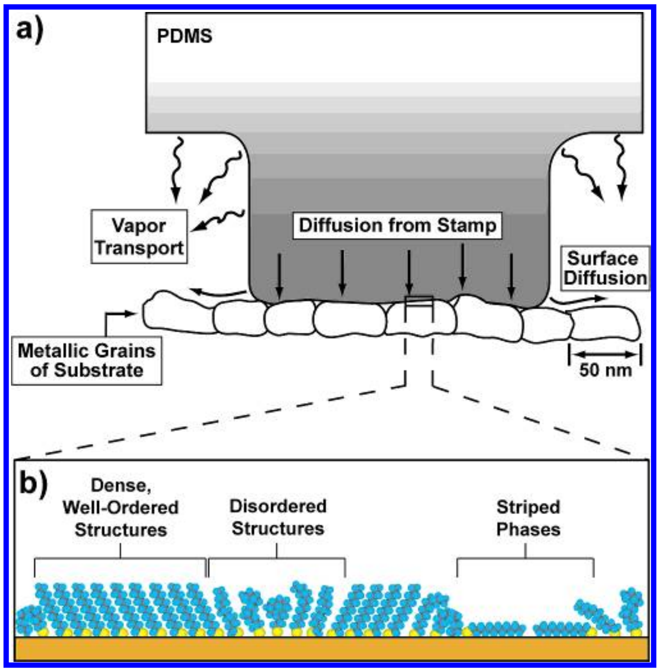


Figure 12. (a) Schematic illustration depicting the application of a PDMS stamp containing thiols to a polycrystalline metal film. The primary mechanisms of mass transport from the stamp to the surface are shown. The grayscale gradient approximates the concentration of thiols adsorbed in the stamp itself. (b) Magnified schematic view that illustrates the variety of structural arrangements found in SAMs prepared by μCP when the stamp is wetted with a 1−10 mM solution and applied to the substrate for 1−10 s.

surface energy makes it easy to remove the stamp from most surfaces and makes the surface relatively resistant to contamination by adsorption of organic vapors and dust particles. The flexibility of the stamp also allows conformal, that is, molecular level or van der Waals, contact between the stamp and substrate; it is thus critical to molecular-scale printing. This flexibility also makes it possible to print on curved (nonplanar) substrates. Another advantage of PDMS is that it is compatible with a wide variety of organic and organometallic molecules because it is unreactive toward most chemicals; it is, however, swollen by a number of nonpolar organic solvents.[497]

The stamps are formed by casting a PDMS prepolymer (a viscous liquid) against a rigid substrate patterned in relief—the ‘master’. Fabrication methods typically used to produce masters include photolithography, micromachining, or anisotropic chemical etching.[498] Commercially available micro- and nanostructured elements, such as diffraction gratings, also are practical structures to use as masters. Because the pattern transfer element is formed by molding, the size of the molecular precursors for the cross-linked polymer determines, in principle, the limitations on the minimum dimensions of the features replicated in the stamp. The smallest features that have been replicated to date by molding are approximately 1.5 nm; these features are defined in the direction normal to the surface of the stamp.[499]

Sylgard 184 is the most common formulation of PDMS used for forming stamps because it is commercially available, inexpensive, and easy to use.[500]

It can replicate features on the order of 0.3 μm without significant distortions of the features and without mechanical instabilities.[131,501] Sylgard 184 is a convenient material for replicating masters with features >1 μm that are separated by distances ~1−10 times the feature sizes. Large separations of features (~10 times the size of the features) lead to collapse of the stamp in regions between features, and small distances between features (ratios of feature sizes to separation distances less than ~0.5) lead to lateral collapse of the features.[131,502,503] The surface tension of the PDMS elastomer also distorts small (~20−100 nm), replicated features.[504] These mechanical instabilities make it difficult to reproduce reliably and accurately features that have lateral dimensions−and distances separating them from other features−smaller than ~500 nm and aspect ratios >1 (vertical dimensions greater than the lateral dimensions).

An alternative formulation of PDMS developed by Schmid and Michel[505] is more rigid than Sylgard. This 'hard PDMS' (h-PDMS) has a Young's modulus of 9.7 MPa and can replicate features as small as ~20 nm with high fidelity.[503] The material is, however, too brittle to use as a stamp: it cracks or breaks in handling. Composite stamps comprising a thin (~30−40 μm) layer of h-PDMS and a thick (~1 mm) layer of 184 PDMS combine the advantages of both materials and yield a stamp that can accurately mold small features and easily peel away from surfaces.[503] Attaching the composite stamp to a thin, rigid glass support allows large-area (>10 cm^2) printing of features that are less distorted than those produced when the stamp is applied manually to a surface.[505] A photocurable formulation of PDMS with physical properties between those of h-PDMS and 184 PDMS also has been reported.[495]

Another material used for stamps in μCP is block copolymer thermoplastic elastomers.[506] These stamps are less susceptible than 184 PDMS to sagging or collapse during printing, even under applied loads. The stamps are formed by compression molding at temperatures above 100 °C and with loads of ~200 g. These conditions may be appropriate for mechanically strong masters, e.g., micromachined silicon, but are not directly compatible with masters generated by photolithography, which consist of a patterned layer of organic photoresist on silicon wafers.

7.1.2. Methods for Wetting Stamps with Thiols

Common methods for applying thiols to the surface of a stamp include rubbing a cotton swab or foam applicator wet with a solution of thiols (0.1−10 mM), placing a drop of thiol-containing solution onto the surface of the stamp, or immersing the stamp in a solution of thiol [220,507−510] The excess solvent (usually ethanol) evaporates from the surface under a stream of nitrogen; the surface appears visibly dry afterward. Ethanol is only slightly soluble in PDMS,[497] but the effect of residual ethanol dissolved in the stamp on the process of forming SAMs by μCP is not known.

The common methods for applying inks do not distinguish between flat and raised regions of the stamp, that is, thiols are applied in both recessed and raised regions of the stamp. Another technique (called 'contact inking') uses a flat slab of PDMS soaked in a solution of thiols or a glass slide coated with a thin layer of thiols as an 'ink pad'. A stamp placed against the surface of the pad adsorbs thiols only in the regions of contact.[509,511,512]

Nonpolar thiols, especially *n*-alkanethiols, diffuse into the bulk of the hydrophobic stamp upon application. The favorable partition coefficient raises the effective concentration of the thiols in the stamp relative to that in the applied solution (~1−10 mM). Polar molecules, however, do not partition into the stamp and remain entirely on the surface of the stamp.[497] Plasma oxidation of the PDMS stamp improves the wettability of the surface of the stamp for polar molecules and, therefore, the uniformity of the patterns generated by printing with these types of molecules.[513]

7.1.3. Mechanism for Forming SAMs by Printing

The basic process for forming SAMs of alkanethiolates on gold is conceptually simple: the stamp impregnated with thiols is placed in contact with a bare gold surface, and the thiols diffuse from the stamp onto the surface where they assemble into ordered structures. Studies of the details of the process suggest, however, the process is complex and depends on a number of parameters, including choice of the SAM-forming molecules, concentration of molecules in the solution applied to the stamp, duration of contact, and pressure applied to the stamp.[501,506,514]

The mechanisms for mass transport of thiols during μCP include, at least, the following: (1) diffusion from the bulk of the stamp to the interface between the stamp and the surface of the gold contacted by the stamp; (2) diffusion away from the edges of the stamp and across the surface of the gold; or (3) vapor transport through the gas phase (Figure 12). The first mechanism is important for the formation of SAMs in the regions where the stamp is intended to be in contact with the surface but little information is available regarding relevant parameters such as the rates of diffusion of thiols (or other nonpolar molecules) in PDMS. The second and third mechanisms are important for understanding (and controlling) the lateral diffusion of SAMs into regions that are not contacted by the stamp; these processes lead to distortions of the lateral dimensions of the printed features and gradients of mass coverage at the edges of structures (determined by wet chemical etching). The relative contributions of each of these mechanisms in the formation of the SAMs in the regions contacted by the stamp and in nonprinted regions, however, are not completely understood.[514]

The degree to which thiols spread across the surface in a liquid phase during μCP is not clear. SAMs of alkanethiolates are autophobic, that is, the low-energy surface generated by the formation of the SAM is not wetted by liquid thiols. This characteristic limits the spreading of thiols past the edge of the SAM once formed. This effect can be observed macroscopically: the surface of a SAM on gold is dry when it removed from a solution of thiols.[515] Spreading is, however, a process that does occur in microcontact printing and is one factor that limits the performance of this method of replication.

Vapor transport is a primary mechanism for the spreading of SAMs in regions not contacted by the stamp, but it is not clear what role, if any, it plays in forming SAMs where the stamp contacts the surface. On a polycrystalline film with variations in roughness of ~3−10 nm it is possible that the stamp does not make van der Waals contacts with the entire exposed surface, especially in the crevices between the grains of the thin film. Whether surface-mediated diffusion or vapor transport through the air leads to the formation of SAMs in the crevices is not understood. Experiments using wet-chemical etchants to transfer patterns of SAMs into underlying metal films suggest that the boundaries between the grains of the thin film are susceptible to corrosion[220,516,517] and may indicate that SAMs have a higher degree of disorder when formed in the crevices than on the tops of the grains.

7.1.4. Structure of SAMs Formed by μCP

The composition, mass coverage, and organization of SAMs formed by μCP have been studied by contact angle goniometry,[511,518] STM,[508,518] AFM,[507,509,519] XPS,[511,520] RAIRS,[30,511] ellipsometry,[514] electrochemistry,[508] time-of-flight secondary-ion mass spectrometry (TOF−SIMS),[520] GIXD,[519] NEXAFS,[507] and sum-frequency generation (SFG) spectroscopy.[511,521] Direct comparisons between studies of the organization of SAMs formed by μCP are complicated by a lack of standards for conducting the printing experiments (methods for applying thiols to the stamps, duration of printing times, etc.). Taken together, however, the data from these studies indicate that the SAMs formed by μCP are usually a complex mixture of phases but can reach a state of organization that is spectroscopically indistinguishable from SAMs formed by adsorption from solution.

STM studies show that the SAMs formed by μCP for 3−5 s with 1−10 mM solutions of dodecanethiol on Au(111) exhibit a mixture of structures.[518] The structures observed include disordered, liquidlike regions, striped phases with $p \times \sqrt{3}$ packing arrangements ($p = 3.5, 4, 8, 5$), and dense $(\sqrt{3} \times \sqrt{3})$R30° structures with a c4 × 2 superlattice. The SAMs formed in these experiments consisted of islands of dense $(\sqrt{3} \times \sqrt{3})$R30° structures (~50−200 nm diameter) surrounded with striped phases and disordered regions; the crystalline islands were separated by distances of ~100 nm and occupied only 20−40% of the surface. SAMs formed by μCP with 100 mM solutions of thiol were nearly identical to those formed from solution (1 mM for 18 h): they contained only $(\sqrt{3} \times \sqrt{3})$R30° structures and c4 × 2 superlattices of the $(\sqrt{3} \times \sqrt{3})$R30° structures. The experiments suggested that the percentage of each type of structure and the domain sizes of the structures depend on the concentration of thiol used for printing and not small variations in contact time (0.3−30 s).

RAIR spectra and contact angle measurements suggest that the elimination of conformational defects (and probably low mass coverage phases as well) requires printing times from 1 min to 1 h; this time is less than that required in solution (12−18 h).[30,507,511] RAIR spectra also suggest that concentrated solutions of thiols (~100 mM) generate SAMs with a higher degree of chain organization than low concentrations (1−10 mM) when the stamps are applied to the surface for the same amount of time (60 s).[30] Studies using SFG microscopy have shown that the edges of 10 μm features printed on metal surfaces are not sharp and lead to regions of mixed SAMs when the bare regions of the substrate are filled with a second SAM.[521]

Overall, the data indicate that the SAMs formed by μCP on polycrystalline films of metal and used in most applications are not equivalent to those formed in solution when formed by printing for 1−10 s with stamps inked with 1−10 mM solutions of thiol. The thiols present near the surface of the stamp are responsible for the nonequilibrium state generated when printing for only a few seconds; it requires additional time for thiols to diffuse from the bulk of the stamp to the surface to increase the mass coverage.

The transition in the structure of a SAM from the printed to nonprinted regions has, to the best of our knowledge, not been observed directly, but the dependence of the surface structure on the concentration of thiols loaded into the stamp also implies that the structure of SAMs near the edges of printed features is different than that in the centers. On the basis of STM data for different concentrations of thiols applied by printing,[518] one possible structural transition could include an increase in the size of the $(\sqrt{3} \times \sqrt{3})$R30° domains close to the edges of printed features and a high percentage of low-density striped phases (>60%). As the distance away from the edges of the printed regions increases, the mass coverage must decrease; the low mass coverage would imply a more disordered or liquidlike state. Such variations in structure have been observed for SAMs patterned by dip-pen lithography.[522]

7.1.5. Transfer of PDMS to the Surface during Printing

Some studies report that trace contaminants of PDMS are left on the surface after printing.[511,520,523] The effect of these contaminants on the structure and properties of the SAMs is not clear. The composition of the prepolymer, the time over which the cross-linked PDMS is cured, the exact ratio of components in the prepolymer, and the procedures used to extract low molecular weight siloxanes probably determine the degree of contamination.[497]

7.1.6. Fabrication of Nanostructures by μCP

It is possible to form nanostructures by μCP with lateral dimensions as small as 50 nm, but the fabrication of such structures by μCP remains a more significant challenge than producing micrometer-scale patterns by μCP.[31,131,220,524−527] Two key factors that determine the limits of resolution are lateral diffusion of the molecules and distortions of the stamp. Lateral broadening of the printed features results from diffusion of the molecular ink through the gas phase or through a surface-mediated process.

Delamarche and co-workers have shown the extent of broadening of features depends on the vapor pressure of the molecular components of the SAM.[514] Long-chain n-alkanethiols ($n > 16$) exhibit less spreading than short ones: eicosanethiol ($CH_3(CH_2)_{19}$-SH) is a good choice among inks for printing submicrometer-scale features that subsequently are transferred into the substrate by etching. Alkanethiols with more than 20 carbons are less soluble in ethanol and in the PDMS stamp than shorter ones with 16−20 carbons and therefore are less suitable choices for printing. Macromolecules with molecular weights much greater than eicosanethiol (MW > 1000 Da) exhibit much less diffusion than alkanethiols and can produce patterns of organic materials on surfaces with critical dimensions less than 50 nm.[525] The concentration of ink adsorbed in the stamp and the time of contact for printing provide two parameters useful in controlling the extent of broadening in printed features, but in practice, there is still a large degree (10−50%) of variability in the size of small (<1 μm) features when the stamp is applied by hand.

The second source of variation in the size and shape of planar nanostructures generated by μCP is distortions of the soft stamp itself. Small features spaced apart by distances comparable to their size (~50−300 nm) tend to collapse into one another upon manipulation of the stamp. Composite stamps using h-PDMS exhibit less distortion of replicated features than the commercial 184 mixture and can be used to print features as small as ~50 nm.[131]

Distortions of the stamp also result from nonuniform pressures applied during printing. The pressure applied during printing is usually determined by the weight of the stamp itself and by the size of the features supporting the stamp. Additional pressure applied by hand or by a mechanical press tends to produce broadening of the features in the pattern or distortions of the pattern in-plane.[131,506]

7.2. Photolithography or Particle Beam Lithography

The technologies for generating patterns in two dimensions on planar substrates that are most highly developed (and commercially available) are photolithography[528] and beam lithography (electron-beam (e-beam) lithography,[529] X-ray lithography[530]). These tools are capable of generating features with dimensions as small as ~10 nm, and sub-100 nm structures are now common in commercial microelectronic devices.[531] The development of photosensitive resists capable of replicating patterns written by photons or electrons with resolution below 10 nm remains a challenge for chemistry and materials science. Typically, resists are thin films (10−30 nm minimum thickness) of polymers that become susceptible to chemical degradation when exposed to UV light or electrons.[532] The size of the individual polymers (~5−10 nm radius considered as random coils) and the extent of damage resulting from scattered electrons in the film determine the minimum resolution that can be achieved using these resists. Two characteristics make SAMs potentially useful as resists for lithography: (1) they consist of individual molecules that occupy areas smaller than ~0.25 nm^2 and (2) they are very thin (<3 nm).

The primary advantage of lithographic techniques over μCP for generating patterns in SAMs in-plane is that the resolution is determined by the size of the beam applied to the SAM and not by other factors related to the molecules forming the SAM such as diffusion by vapor transport or by surface-mediated processes. A significant disadvantage of these methods, however, is the cost of the equipment and infrastructure required, especially for high-resolution (<100 nm) instruments.

7.2.1. Photolithography

Irradiation of a SAM of alkanethiolates with UV light through a pattern of apertures in a chromium film on glass leads to photooxidation of the SAM in the exposed regions.[138,527,533] The oxidized species can be removed from the substrate by rinsing the substrate in a polar solvent, e.g., water or ethanol. The optical elements of the system determine the minimum resolution of the features produced. For a projection microscope using a mercury arc lamp as a source of UV light, the limit of resolution is ~0.3 μm.[138,534] Exposure times of 15−20 min are required, however, for power densities of ~5 W/cm^2 at the surface of the sample.[138] The use of an excimer laser ($\lambda = 193$ nm) makes it possible to generate arrays of lines as small as 100 nm in ~1 min using interference patterns generated with a phasemask.[535]

Another method uses a laser beam to write patterns directly into the SAM.[135] The laser ($\lambda = 488$ nm) does not cause oxidation of the SAM but induces thermal desorption of the SAM by local heating. The exposure times were ~0.1 s, but the minimum feature sizes demonstrated were ~20 μm.

7.2.2. E-Beam and X-ray Lithography

Beams of electrons also can generate patterns in SAMs.[536] Low-energy beams of electrons (10−100 eV) induce a number of chemical changes in SAMs of thiolates. Some of the processes that can occur include cleavage of bonds (C−S and C−H), formation of C═C bonds, cross-linking of adjacent molecules, fragmentation of molecules, and conformational disorder.[537] SAMs comprising alkanethiolates become disordered and more susceptible to desorption upon exposure to low-energy electrons.[538] The gold film underlying these damaged regions of these SAMs is susceptible to corrosion because the SAM does not block the diffusion of wet chemical etchants to the surface (see section 8.1). In contrast, SAMs formed from biphenyl thiol undergo cross-linking reactions with neighboring molecules after cleavage of the C−H bonds on the aromatic rings.[538,539] These damaged regions provide *better* resistance against etchants than the undamaged regions. Grunze and co-workers fabricated gold structures with lateral dimensions as small as ~10 nm using SAMs damaged by e-beams as etch resists (Figure 13).

X-rays provide an alternative source of high-energy radiation for patterning SAMs.[136] The nature of the chemical damage caused by X-rays is, however, nearly identical to that caused by e-beams because

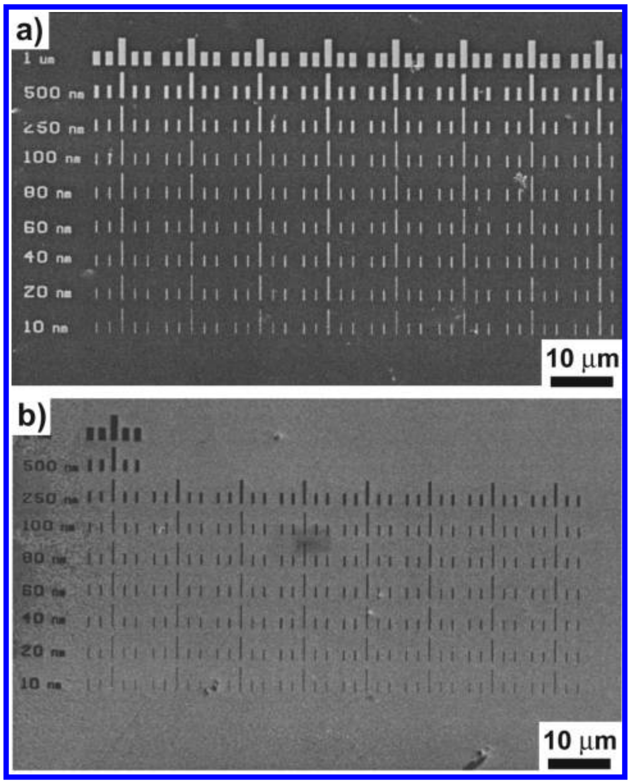


Figure 13. Scanning electron micrographs (SEMs) of patterned gold films generated by writing on SAMs of (a) biphenylthiolates and (b) hexadecanethiolates with an electron beam followed by chemical etching. The SAM of biphenylthiolates acts as a negative resist, that is, the SAM protects the underlying film from etchants wherever the beam of electrons patterns. The SAM of hexadecanethiolates acts as a positive resist: the electron beam damages the SAM and allows the etchant to attack the underlying gold more easily than in the undamaged regions. (Reprinted with permission from ref 538. Copyright 2000, AVS The Science & Technology Society.)

the photoelectrons and secondary electrons generated upon irradiation with X-rays also degrade the SAM (and, to some extent, the resolution of the pattern).[540] Grunze reviewed the chemistry of SAMs exposed to e-beams and X-rays in detail.[537]

7.2.3. Atomic Beam Lithography

Neutral atoms of rare gases excited into metastable states (~8−20 eV above the ground state) also can damage SAMs of alkanethiolates.[140,541] This system, in principle, provides the basis for a form of 1:1 projection lithography that effectively is unlimited by the effects of diffraction (which is unimportant for atomic systems).[542] The energy released when the metastable atom collides with the SAM and returns to its ground state seems to ionize the organic material in the SAM[543] and induce conformational disorder in the alkane chains;[141] it is also possible that the collision generates secondary electrons, which contribute to the damage.[544]

Dosages of >10 metastable atoms per thiolate are necessary to generate useful contrast between damaged and undamaged regions of SAMs (as determined by wet chemical etching); these levels of flux are difficult to achieve in periods of time less than 1 h.[544] Low dosages of metastable atoms (<1 per thiolate), however, cause enough structural disorder in the SAMs that it is possible to exchange a second thiol into the damaged regions selectively.[141] The disorder results from either a decrease in mass coverage or an increase in conformational freedom of the alkane chains after cleavage of the chains. The exposure times required are less than 15 min, and the difference in the rates of exchange for the second thiol into damaged and undamaged regions is sufficient to resolve features as small as 50 nm.

7.3. Other Methods for Patterning SAMs

7.3.1. Formation of Gradients

Continuously varying gradients of the functional groups presented in the plane of a surface are useful for studying materials properties such as wetting and adhesion[545] and for fundamental research in cell biology relating to cell adhesion,[546] chemotaxis,[547] and neuron growth.[548] Methods for producing uniform lateral gradients of SAMs composed of one or two molecular components include (1) controlled immersion into a solution of one thiol followed by immersion in a second thiol (Figure 14),[549] (2) diffusion of two thiols from opposite ends of a gold substrate supporting a polysaccharide matrix,[550] (3) electrochemical desorption of thiols from static or dynamic potential gradients,[551] and (4) gray-scale photolithography on photosensitive SAMs.[552] Microscopic gradients in lateral composition also appear to form at the edges of microcontact printed features.[521]

7.3.2. Ink-Jet Printing

Ink-jet printers are commercial devices for depositing nanoliter volumes of solutions containing organic dyes onto paper and plastic transparencies. This technology can be adapted to deposit solutions of alkanethiols on metal surfaces to generate patterns of SAMs with features ~100 μm in size.[553,554] The SAMs formed by this procedure may have more disorder and less mass coverage than the limiting case of SAMs formed from solution.[554] For some applications, however, the ability to generate micropatterns of SAMs easily over large areas (>1 m^2) may supersede requirements for high-quality SAMs.

7.3.3. Topographically Directed Assembly

SAMs formed on metal substrates patterned with topographical features−steps, edges−have different degrees of order depending on the topography. SAMs of alkanethiolates formed in the planar regions of the substrate adopt the organization and structure described in section 3, but the regions where the topography changes drastically−edges of topographical features−induce a higher degree of disorder in the SAMs formed there than on the planar surfaces.[212,214] The width of the disordered regions are somewhat dependent on the cross-sectional profile of the topographic features; sharp changes in topography (~90°) produce regions of disorder as small as 50 nm. The thiolates in the disordered regions are susceptible to exchange with other thiols, and thus, a SAM containing a second functional group can be formed by displacement.

7.3.4. Orthogonal Self-Assembly

Patterns of SAMs on surfaces are typically formed by positioning the molecules in a spatial-defined arrangement at the time of deposition using stamps, scribes, probes, or photolithography. An alternative approach is to generate substrates composed of two or more materials and then form SAMs that have affinities for specific materials. Combinations of materials and molecules that can form SAMs "orthogonally" are (1) carboxylic acids on aluminum (or nickel) and thiols on gold,[555] (2) isonitriles on platinum and thiols on gold,[123] and (3) silanes on silicon oxide and thiols on gold.[556]

8. Applications of SAMs on Thin Metal Films

SAMs on thin metal films are important for nanoscience and technology in two ways: (1) they are a nanostructured material that is easy to prepare and useful for studying interfacial phenomena that are strongly influenced by nanometer-scale topographies and composition and (2) they are suitable materials for fabricating micro- and nanostructures (when combined with tools for patterning SAMs). Some examples of interfacial phenomena studied with SAMs on thin films include wetting,[154,299b,340] corrosion,[343] adhesion, [342,557] tribology,[341,558] charge transfer through molecules,[559,560] nucleation and growth of crystals on surfaces,[561] and model surfaces for biochemistry and cell biology.[562,563] These studies depend primarily on the ability to synthesize interfacial films with specific compositions both in the plane of the surface and out of plane, but some, for example, electron-transfer processes, are extremely sensitive to the nanometer-scale thickness of the SAM. Other applications (resistance to etchants and protein adsorption, modified electrodes for electrochemistry) rely on the ability of SAMs to prevent diffusion of other molecules to the surface of the underlying substrate.

8.1. SAMs as Etch Resists

Hydrophobic SAMs formed from long-chain alkanethiols ($n > 16$) can protect metal films from corrosion by aqueous wet-chemical etchants.[564] Combining this ability with techniques for generating in-plane patterns of thiols (e.g., μCP) makes it possible to fabricate micro- and nanostructures composed of gold, silver, copper, palladium, platinum, and gold−palladium alloys. Some of the parameters that determine the minimum critical dimensions and quality (as measured by the density of pinhole defects on etching and on the edge roughness) of the structures are the composition of the SAM, the density of defects in the SAM, the selectivity of the wet chemical etchant, and the morphology of the thin film.

A number of etchants selectively dissolve regions that are not derivatized with a SAM (Table 4); their compositions were developed empirically. The addition of amphiphiles, such as octanol, or use of polymeric complexing agents, such as polyethyleneimine, decreases the number of pits and pinholes produced in the surfaces of etched structures, controls the vertical profile of the edges of etched features, and enables the use of SAMs as resists to pattern thick (>1 μm) electrodeposited films (Figure 15).[565]

Table 4. Selective Etchants for Patterning Thin Films of Metals Using SAMs of Alkanethiolates as Resists

metal	chemical components of etchant	ref
Au	$K_3Fe(CN)_6/K_4Fe(CN)_6/Na_2S_2O_3/KOH$	516
	$Fe(NO_3)_3$/thiourea	524
Ag	$K_3Fe(CN)_6/K_4Fe(CN)_6/Na_2S_2O_3$	516
	$Fe(NO_3)_3$/thiourea	524
Cu	$FeCl_3/HCl$ or NH_4Cl	568
	H_2O_2/HCl	569
	KCN/NaOH/KCl	565
	3-nitrobenzene sulfonic acid/ poly(ethylene imine)	565
Pd	$FeCl_3$	31,220
	$Fe(NO_3)_3$/thiourea	524
Pt	HCl/Cl_2	570
$Au_{60}Pd_{40}$	KI/I_2	567

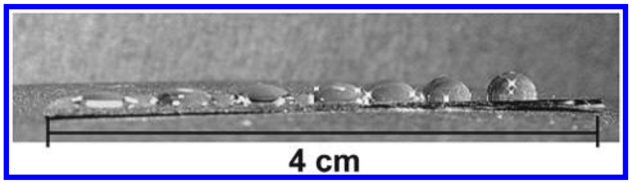


Figure 14. Optical photograph demonstrating a gradient in hydrophilicity, as measured by the spreading of drops of water on a SAM supported by a thin film of gold on a silicon wafer. (Reprinted with permission from ref 549. Copyright 2003 American Chemical Society.)

The density of critical defects (pinholes) that penetrate the entire thickness of a thin film and the roughness of the edges of etched features have limited the use of μCP and selective wet etching for fabricating structures with lateral dimensions <500 nm in gold.[517,566] Alternative substrates, such as palladium or gold−palladium alloys ($Au_{60}Pd_{40}$),[567] make it possible to generate etched structures that have smaller edge roughness and fewer pinholes than comparable structures in gold when SAMs are used as etch resists (Figure 16). An interphase of PdS formed between the bulk metal and the hydrophobic SAM enhances the contrast between the patterned and unpatterned regions.[30] An additional advantage of palladium and gold−palladium alloys as substrates is that they have small grain sizes (~15−30 nm); this morphology is better suited than that of gold (grain sizes ~35−75 nm) for fabricating metal lines with widths as small as 50 nm.[31,131,220] Unlike gold, palladium is compatible with complementary metal−oxide semiconductor (CMOS) manufacturing processes.[221]

8.2. SAMs as Barriers to Electron Transport

Processes that transfer electrons from one location to another over nanometer-scale distances (1−100 nm) are fundamental to important redox processes in biology (photosynthesis, respiration)[571] and to the operation of a wide range of devices, including photovoltaics,[572] transistors,[573] and catalysts.[574] The mechanisms of electron transfer in bulk materials (such as metals and semiconductors) and in homogeneous solutions of coupled redox species are reasonably well-understood.[559,575] Charge-transfer pro-

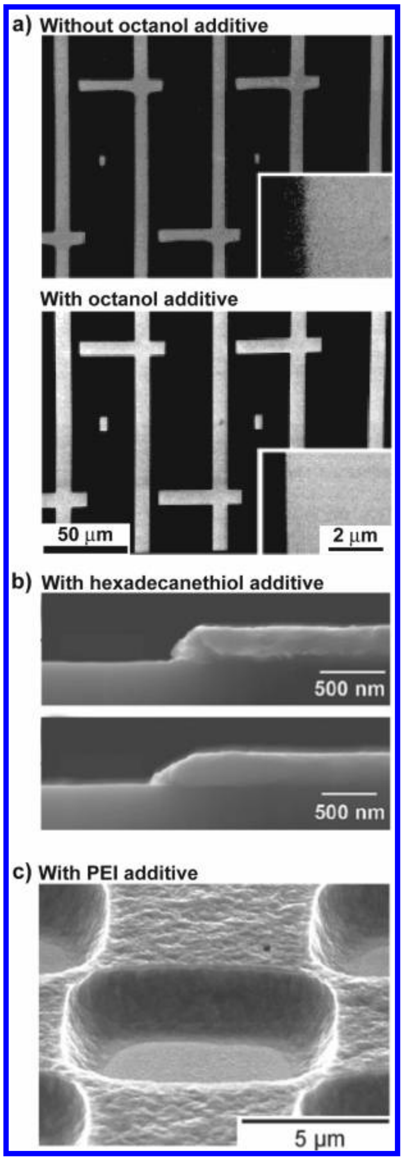


Figure 15. SEMs of copper microstructures formed by microcontact printing and etching. (a) Addition of octanol to a solution of KCN and KOH improved the quality of the copper structures generated by etching; the structures etched in the presence of octanol contained fewer etch pits and less edge roughness than those prepared without the amphiphile. (b) Addition of hexadecanethiol to a KCN/KOH etch solution altered the profile of the edges of etched structures. The SEMs show cross-sections of the structures etched in a solution containing hexadecanethiol with concentrations of 8 and 10 μM. (c) A solution containing 3-nitrobenzenesulfonic acid and poly(ethylene imine) was used to etch structures into 2.2-μm-thick electrodeposits of copper. (Reprinted with permission from ref 565. Copyright 2002 American Chemical Society.)

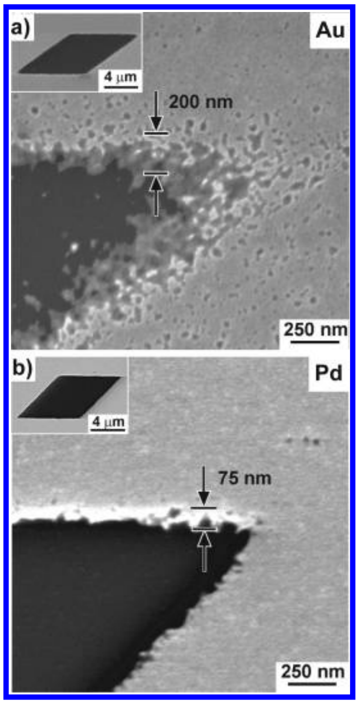


Figure 16. SEMs of the corner of a trapezoid etched into thin films of (a) gold and (b) palladium. The insets show the entire trapezoid. The trapezoid was generated by stamping a periodic array of lines twice with an offset angle of ~30°. The edge roughness and the number of etch pits is significantly greater for the gold structure than the palladium one.

cesses in biological systems are, however, often mediated by organic molecules, and future electronic systems may also involve electron transport through organic matter. The relationships between molecular and solid-state structure and the mechanisms for charge transfer in these types of systems are not well-established.[560,576]

For electron-transfer processes some of the interesting questions related to transport through molecules are as follows: What are the fundamental mechanisms (tunneling, hopping, thermionic conduction)? What are the potential barriers? What are the rates of electronic transport? How does chemical structure and composition affect the transfer process? How does the mechanism of electron transfer change as a function of distance? SAMs are useful systems for answering these questions because (1) they are essentially dielectric layers with relatively few defects and structures that can be controlled through molecular synthesis, (2) they are easy to form reproducibly, (3) they form highly ordered and dense structures, (4) they do not desorb readily in solution or in a vacuum. Their disadvantages are that they are not particularly stable (oxidatively, thermally), especially relative to silicon dioxide, and show a number of defects (pinholes, metal filaments, etc.).

8.2.1. SAMs for Electrochemistry

Chemical modification of an electrode for electrochemistry makes it possible to generate barrier layers that prevent free diffusion of electroactive species to the surface of the electrode and that immobilize electroactive species on the electrode itself.[577] SAMs are more convenient (and more effective) choices for modifying electrodes in electrochemistry than LB films or nonspecific physisorbed films because they form spontaneously, are easy to handle mechanically, and are relatively stable in solutions of electrolytes, that is, they do not desorb readily.

There are two experimental configurations used commonly in electrochemistry for studying electron-transfer processes with SAM-modified electrodes. One strategy uses a thick (1−2 nm), hydrophobic SAM to block a redox species (dissolved in the surrounding electrolyte solution) from diffusing to the surface of the electrode itself.[21] A second approach uses a mixed SAM where one molecular component terminates with an electroactive group (for example, ferrocene or ruthenium pentaamine); the immobilization of the redox species on the SAM minimizes effects of diffusion in the measured current responses.[233,322,578] An excellent review by Finklea covers the early experiments and theoretical developments for using SAM-modified electrodes to study the kinetics of electron transfer across thin organic films.[197] Other reviews describe recent advances in the field and applications of SAM-modified electrodes for electrochemical sensors.[559,579]

Some of the charge-transfer phenomena studied with these SAM-modified electrodes include (1) the parameters (distance from the surface, electrolyte, temperature, metal) affecting electron transfer through alkane chains[152,580] and through unsaturated chains (e.g., polyphenylene vinylene, polyphenylene ethynylene),[581] (2) coupled electron−proton-transfer reactions,[582] (3) the effect of solvation of electroactive species in hydrophobic environments on redox reactions,[583] (4) the effect of counterion motion on the rates of electron transfer,[584] (5) the dynamics of molecules in hybrid lipid bilayers,[585] and (6) the effect of orientation and conformation of electroactive proteins (cytochrome *c*, glucose oxidase) on the rates of electron transfer across SAMs−a factor important for making electrochemical sensors to detect enzymatic activity and studying electron-transfer processes.[586,587]

Gold is used most often as a substrate for SAMs in electrochemistry because it resists oxidation and supports SAMs that (generally) have fewer defects than those on silver or copper. The defects in the SAMs on gold, however, are significant in determining the current response in experiments where the SAM acts as a blocking layer.[588] The surface of mercury has three advantages over the surface of gold for supporting SAMs used in electrochemistry: [69,71] (1) it is atomically flat−no terraces, edges, pits, (2) it supports well-packed SAMs with no (or very few) pinholes, and (3) it is easy to generate a clean mercury surface by extruding drops from a syringe.

8.2.2. SAMs in Organic/Molecular Electronics

An area of research in nanoscience that has received considerable attention in both scientific and popular literature over the past 10 years is the development of electronic devices where the active components are molecules (rather than traditional semiconductors such as silicon or gallium arsenide).[560,589,590] Theoretical studies suggest that it might be possible to make molecules that mimic the function of common circuit elements found in microelectronics−conductors, rectifiers, transistors, logic gates.[591] Identifying such molecules requires electrical measurements and then interpretation of the relations between the molecular structure, the measured $I-V$ response, and the mechanisms of electron transport.

The state of molecular electronics is evolving rapidly both experimentally and theoretically, and it is marked with a number of concerns regarding the reproducibility and interpretation of the interesting results.[592] A complete evaluation of the various approaches and the proposed theories for electron transport in these systems is outside of the scope of this review. Several recent reviews and perspectives have attempted to summarize the state of the field and encourage new standards for comparing results between the various types of junctions.[560,593−595] Here, we describe how SAMs are used to generate molecular-scale electrical junctions and outline some of the difficult challenges that this area of research presently is facing.

Metal−Molecule(s)−Metal Junctions. Forming electrical contacts to individual, or even a few, molecules is a difficult task, but advances in nanofabrication and scanning probe methods have made it possible to generate a number of different types of two-terminal metal−molecule(s)−metal junctions. The basic configuration involves a single molecule, a few molecules, or many molecules sandwiched between two metal contacts. The number of interfaces (metal−molecule, molecule−vacuum, molecule−solvent) varies, however, depending on the junction.

SAMs are integral components in the two dominant approaches for constructing junctions because they assemble as well-ordered structures both on a single electrode (on which the second electrode is fabricated or positioned) and across a molecular-scale gap (1−2 nm) between two electrodes. The first set of structurally related junctions uses a metal film supporting a SAM as one contact and a second contact generated on top of the organic surface by (1) depositing a metal film by thermal evaporation or electrodeposition, [4,596] (2) transferring a metal film by flotation or nanocontact printing,[597] (3) positioning a conducting probe (STM,[598] conducting AFM,[576,599] crossing wire[600]), or (4) making a contact with a liquid metal contact (mercury).[590,594,601,602] A second configuration consists of two nanoelectrodes mounted on a planar surface with a SAM positioned across the gap between the electrodes; the gap is fabricated by breaking a single wire mechanically or electrochemically,[603] by narrowing a gap by electrodeposition of metal,[596,604] or by conventional methods for nanofabrication (e-beam or focused ion beam lithography).[605] A third type of junction that is essentially a variant of the first two classes described is one where a SAM-bearing nanoparticle is positioned between two metal electrodes or a metal surface and a conducting probe.[606] This arrangement produces two molecular barriers for electron transport and can take advantage of the quantized energy states of the nanoparticle itself (Section 9.5). Each type of junction has certain advantages and limitations; a review of the major classes of metal−molecule(s)−metal junctions by Mantooth and Weiss describes the relative merits of each and summarizes the experimental results from each.[607]

Some of the molecules studied in specific junctions have produced interesting $I-V$ characteristics, but interpretation of the results is difficult because the current responses are not reproducible in other types of junctions or even in the same type of junction in some cases. The most consistent set of data are those for electron transport through *n*-alkanethiolates: a number of different junctions confirm that the current through devices containing SAMs of these molecules depends exponentially on the thickness of the SAM. These results suggest the primary mechanism of conductance through these molecules is electron tunneling.[4,560,595,608−610]

Challenges for Molecular Electronics. Studying the rates of electron transfer and mechanisms for charge transport in molecules confined in solid-state junctions presents several challenges that are different from those familiar from studies of electron-transfer processes in solution or at electrode−solution interfaces. Some challenges relate to the ambiguity of the structure, orientation, and identity of the species present in the junction after assembly or fabrication; others relate to uncertainties concerning the interfaces between the molecules and the electrical contacts.[611] Still others are connected to the relatively harsh processing conditions used in fabricating or testing the devices (thermal evaporation, intense electric fields) and potential for structural rearrangements of these interfaces (for example, formation of metal filaments bridging two electrodes[612]); the latter is especially important for junctions involving gold. The development of unambiguous and predictive models that correlate the structure of individual molecules to their electronic properties will require research that addresses the factors described below.

Structure of "Complex" SAMs. The majority of the types of molecules that are predicted to have interesting electronic characteristics (insulating, conducting, rectifying) are not simple alkanethiols; they contain various organic functional groups, interlocking rings, branching structures, and organometallic redox sites.[613] The orientation and arrangement of molecules formed from thiols on gold, silver, palladium, and platinum are only known (to varying degrees) for *n*-alkanethiols, some aromatic compounds (biphenyls, phenylene ethynylenes),[614] and related compounds with minor structural variations (different end groups) (Table 2). SAMs of other types of molecules simply are not characterized.

Nature of the Interfaces between SAMs and Their Electrical Contacts. How the number and type of interfaces (van der Waals, chemical bonding, vacuum, solvent) affect the conductance observed for molecules in the junctions is unclear. At least one interface usually involves a metal−thiolate bond (when a SAM is used as the organic component). The influence of this interface on the electrical behavior of the system is, however, poorly understood,[576] especially for different types of metals with substantially different surface chemistries, e.g., palladium and silver (section 3.1).

In most junctions there is even less knowledge regarding the nature of the electrical contact between the SAM and the second electrode attached to the SAM and its influence on electron transport. It is evident that evaporation of a metal electrode onto the SAM can have a number of detrimental outcomes including formation of metallic filaments and extensive chemical reactions with the SAM.[612,615] Other contacts, such as scanning probes and mercury drops, may be less damaging than evaporated contacts, but these junctions introduce additional interfaces (SAM/vacuum/electrode or SAM/solvent/electrode) that also increase the complexity of the system. Rogers and co-workers reported a procedure for forming soft-laminate contacts that might serve to eliminate *some* of the most serious problems encountered with metal contacts evaporated on top of organic thin films.[616]

Mechanisms of Electron Transport in Metal−Molecule(s)−Metal Junctions. The basic mechanism for electron transport in these types of systems is generally thought to involve electron tunneling−a process where the molecule mediates the electron transfer but the electron does not reside on the molecule for any significant period of time−or, perhaps in some cases, resonant tunneling.[559,617] The subtle details of the electron tunneling process remain controversial, however, especially in molecules that are more complicated than linear alkane chains. Also, the degree to which other conduction mechanisms, such as thermionic emission (transport above the potential barrier of the junction) or electron hopping (transport where the electron does localize to specific sites in the molecule during transport), contribute to the total current remains an open question. Temperature-dependent current measurements are a common method for analyzing solid-state semiconductor devices but rarely are used to analyze molecule-based devices; these measurements may provide some mechanistic details of how the electrons are moving through the molecule in the junction.[4,608,618]

Perturbations to the Electronic and Vibrational States of Molecules. The effect of the intense electric fields applied in these measurements on the energy levels within the molecules is not known. Inelastic tunneling spectroscopy (IETS) is one method to determine the vibrational states excited in the molecule during tunneling events and can confirm the presence of the molecule in the junction after it is formed.[609,619] Unlike IR and Raman spectroscopy, the selection rules for excitation of different modes are not well understood.

Interpretation of $I-V$ Curves for Two-Terminal Devices. Experimentally observed $I-V$ data are difficult, if not impossible, to interpret correctly from two-terminal junctions because small variations in the electrostatic environment near the junction and in the electronic and physical couplings between the molecules and the electrical contacts affect the measured response. The addition of a third electrode (a gate) to metal−molecule(s)−metal junctions provides a means to vary the electrostatic environment of the molecule in a controlled manner and eliminates some of the variability common in two-terminal junctions.[605,620]

Defects in Junctions. The role of defects (both intrinsic and extrinsic) on the measured electrical responses has been recognized as a problem (Figure 17). There are, however, no real tools for characterizing their role in the electron-transfer processes and no good techniques for reproducing the defects in experimental systems. Some defects, such as filaments formed by evaporation, can be eliminated by

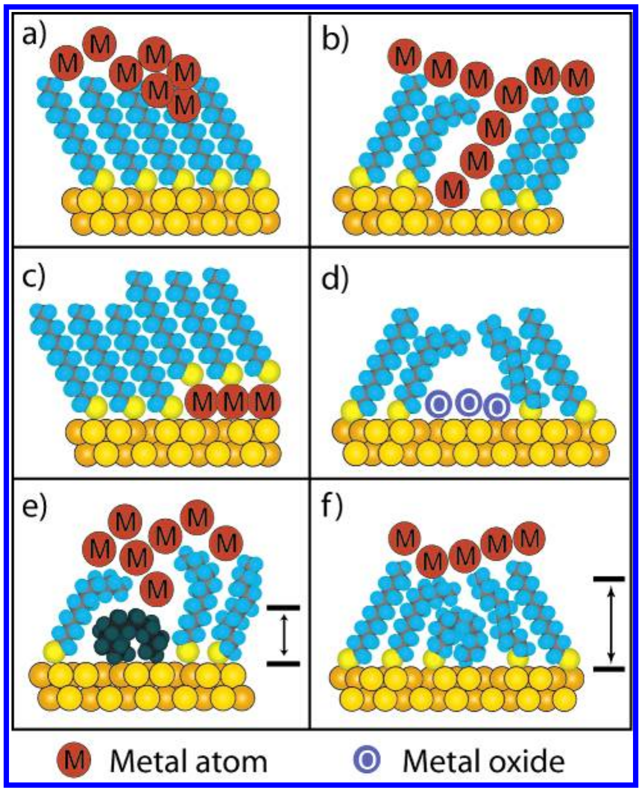


Figure 17. Schematic illustration of the types of defects in SAMs that can influence the rate of electron transfer in two-terminal (or three-terminal) devices. (a) Chemical reaction with the organic component of SAMs during evaporation of metal films. (b) Formation of metallic filaments during evaporation or operation of the device. (c) Deposition of adlayers of metal on the surface of the substrate supporting the SAM. (d) Formation of oxide impurities on the surface. (e) Organic (or organometallic) impurities in the SAM. (f) Thin regions in the SAM resulting from conformational and structural defects. In e and f the dimension normal to the surface that is denoted by the black arrows indicates the approximate shortest distance between the two metal surfaces; note that these distances are less than the nominal thickness of the ordered SAM.

developing other strategies for fabrication, but those formed during the operation of the device (thin spots, filaments) cannot be controlled presently.

Assessing the Future for Molecule-based Electronics. The question of how electrons move through molecules in solid-state systems is an intensely interesting area for research, even if it does not lead to practical analogues of (or substitutes for) semiconductor devices. SAMs will continue to contribute to this field because they are easy to form spontaneously in regions where direct placement is difficult (for example, nanometer-scale gaps) and because they are easy to modify (composition, structure, substrate). One primary experimental need is new types of junctions that are stable, reproducible, well-characterized, compatible with a wide range of organic and organometallic materials and physical conditions (temperature), and easy to assemble and use. Such junctions would make it possible to screen a range of molecules for interesting electrical behavior and identify large effects (at room temperature). We believe that junctions where one contact is formed by a liquid drop of mercury[217,590,594,601] represent a starting example for such systems, but these systems are not yet ideal (the temperature range over which they can be used is small, and they are two-terminal systems). The combination of easy-to-fabricate junctions for rapidly testing classes of different molecules and spectroscopic tools for studying the behavior of individual (or few) molecules should provide sufficient experimental data to establish some general relationships between molecular composition and rates of electron transport in these types of systems.

8.3. SAMs as Substrates for Crystallization

Long-range ordering of atoms and molecules is an essential step in the nucleation of crystals and organization of liquid phases. Nucleation events must involve at least two atoms or molecules, and thus, the nucleation site must be at least 1 nm in size. SAMs on metal substrates provide one system with which to test the parameters that influence the nucleation of crystalline solid and liquid phases. Some of the tunable parameters include composition of the functional groups exposed at the surface, orientation of these functional groups, topography of the substrate, and the dimensions of the area covered by the SAM (when tools to pattern the SAM are used). This section discusses the use of SAMs to control the orientation of ionic crystals nucleated on surfaces and the influences of the structure of SAMs and surface topography on the alignment of liquid crystals.

8.3.1. Oriented Nucleation of Crystals

Researchers interested in biomineralization and oriented crystal growth have taken advantage of the ordered projection of functional groups at the surfaces of SAMs to study the nucleation of crystals. Biological crystal growth is thought to occur within functionalized matrixes that control the polymorph, morphology, and orientation of the crystals.[621,622] Often these matrixes are poorly characterized and it is difficult to differentiate between the organic molecules that control the nucleation of the crystals (polymorph selectivity and orientation of the crystal) and those that control the growth of the crystals (morphology).

SAMs have been used to study the influence of well-defined, functionalized surfaces on nucleation of crystals because they are well-characterized, (relatively) uniform surfaces whose properties can be varied systematically. Crystals of many different materials have been grown on SAMs including proteins,[623] enantiomerically pure amino acids,[624] semiconductors,[625] iron minerals,[626] calcium phosphate,[627] and carbonate minerals.[561,628-636]

One of the best studied systems is the crystallization of calcium carbonate, an important biomineral, on SAMs of different ω-functionalized alkanethiols.[632,633] The primary results from these studies are that the ω-functionality (carboxylic acid, amino, sulfate, phosphate, hydroxyl, methyl) of the alkanethiols, the spacing of the headgroups (based on the lattice), and the spatial orientation of the headgroups determine both the polymorph (e.g., calcite, aragonite, vaterite or amorphous calcium carbonate)[628,636] and the nucleating face of the new crystals (Figures 18 and 19). The diversity of observed nucle-

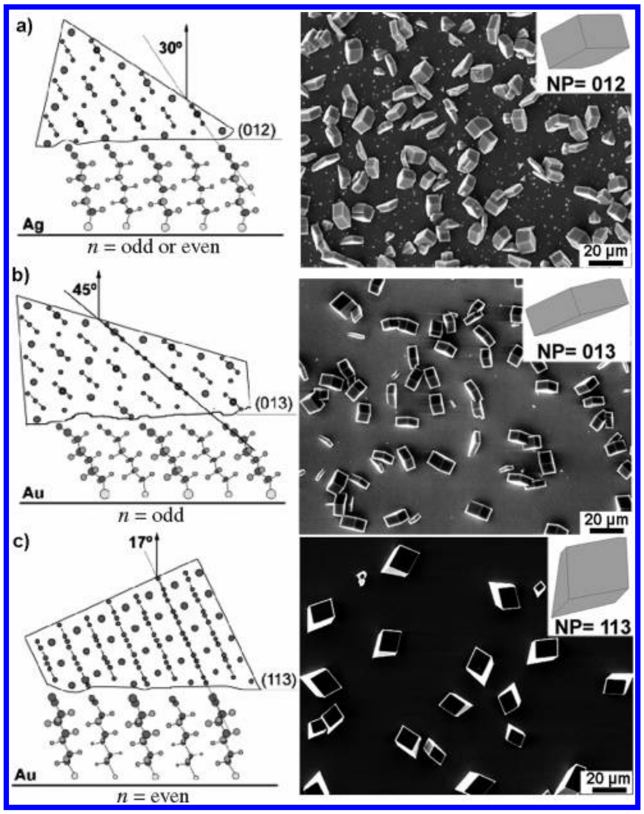


Figure 18. Schematic representations of the alignment of the carboxylic acid groups displayed by the SAM with the carbonate groups in calcite (left column) and the corresponding SEM micrographs of calcite crystals grown on the specified SAM (right column) for (a) odd (and even) chain length SAMs on silver, (b) odd chain length SAMs on gold, and (c) even chain length SAMs on gold. (Insets) Computer simulations (SHAPE V6.0 software) of similarly oriented calcite rhombohedra with the nucleating planes (NP) indicated. (Reprinted with permission from ref 629. Copyright 2003 Wiley-VCH.)

ation faces is not adequately explained by a simple epitaxial matching of distances of the functional groups in the monolayer with a given crystal face of calcite. To account for the observed results, in the case of carboxylic-acid-terminated alkanethiols the angle of the terminal acid group needs to match that of the carbonate in the crystal structure (Figure 18).[632] Han and Aizenberg confirmed this hypothesis by altering the angle of the carboxylic acid while keeping the spacing constant; these experiments used a series of SAMs of alkanethiols with odd and even numbers of carbons on gold and silver (Figure 18).[629]

The crystallographic orientation of the underlying SAM and the Au(111) lattice can be reflected in the lateral alignment of the calcite crystals.[630,634] Travaille et al. used thermally annealed SAMs of mercaptohexadecanoic acid, formed on highly oriented Au(111) films deposited on mica, to grow calcite crystals.[634] The resulting crystals are nucleated on their {012} faces and are laterally aligned with each other with preferred angles of 60° and 120°. The authors hypothesize that the alignment of the calcite crystals reflects the directions of the 3-fold symmetry of the Au(111) structure.

Microcontact printing combined with topographically defined patterns of different metals enables the formation of surfaces patterned with calcite crystals

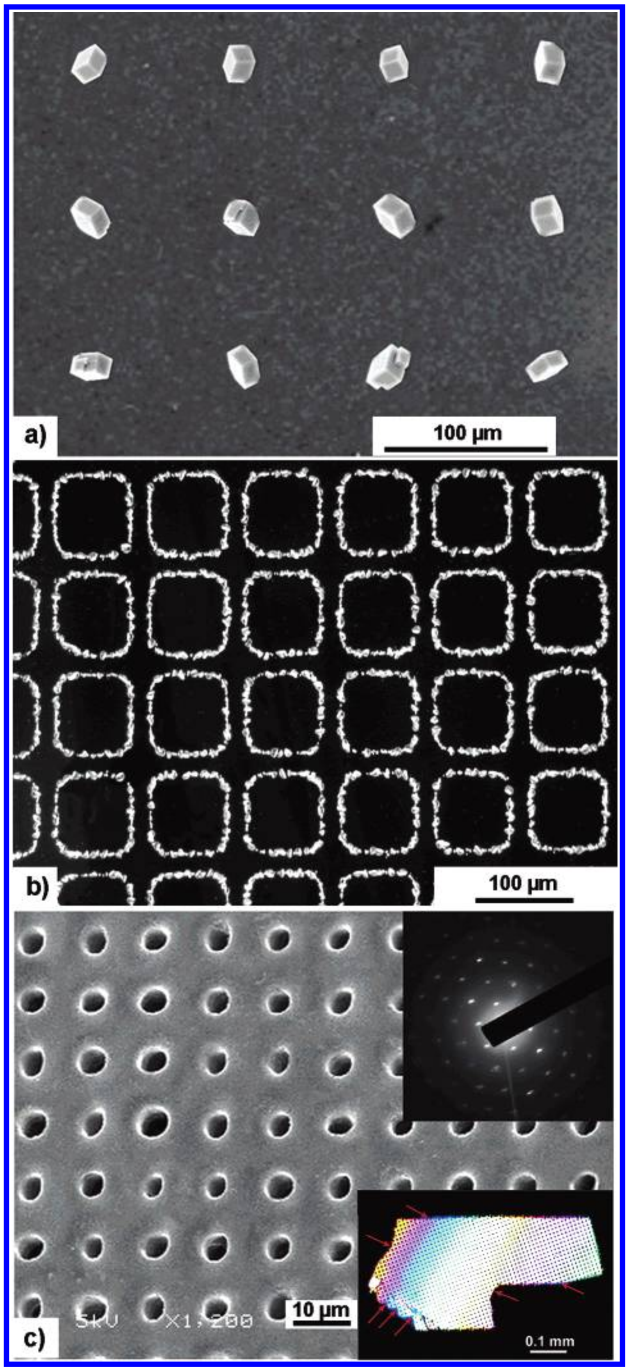


Figure 19. (a) Array of calcite crystals nucleated selectively from the (012) plane on a micropatterned SAM of 15 μm diameter circles of $HS(CH_2)_{15}COOH$ separated by 100 μm supported on Ag(111). The remaining surface is filled with a SAM of hexadecanethiol. A 10 mM calcium chloride solution was used to obtain one crystal per nucleation site. (Reprinted with permission from *Nature* (www.nature.com), ref 633. Copyright 1999 Nature Publishing Group.) (b) Selective calcite precipitation at regions of disordered SAMs of $HS(CH_2)_{15}COOH$ on a micropatterned surface of gold and silver. The concentration of the solution was below saturation for nucleation on the ordered SAMs resulting in crystallization only at the boundaries between the two metal surfaces. (Image courtesy of J. Aizenberg.) (c) SEM of a micropatterned calcite crystal prepared as described in the text. (Upper inset) Large-area (~50 μm^2) TEM diffraction showing that the section is a single crystal oriented along the *c* axis. (Lower inset) Polarizing light micrograph of the single-crystal, micropatterned calcite. (Reprinted with permission from ref 628. Copyright 2003 AAAS.)

with different orientations and spatial distributions (Figure 19a and b).[561,631–633] The disordering of SAMs that exists where two metals (e.g., gold and silver) meet (section 7.3.3) can be used to direct the nucleation of crystals (Figure 19b).[561] Two factors control the number of crystals per site: (1) the density and size of the printed features with the nucleating SAM and (2) the concentration of the crystallizing solution (Figure 19a).[561,632] Once a nucleus of some critical size forms, mass transport depletes the calcium and carbonate ions in the surrounding solution.

In biology there are many examples of textured, single crystals with controlled crystallographic orientations.[621,637] Using current technologies for crystal growth, it is difficult to fabricate the same types of intricate structures that Nature does from the "bottom-up". Aizenberg et al. demonstrated the use of micropatterned surfaces, functionalized with SAMs, to fabricate large (~1 mm), textured, single crystals of calcite with defined orientations (Figure 19c).[628] On a gold surface patterned with a square array of cylindrical posts (<10 μm with an aspect ratio >1), they formed a mixed SAM with terminal end groups (phosphate, methyl, and hydroxyl) known to suppress the nucleation of calcite and promote the formation of amorphous calcium carbonate.[638] Using an AFM tip a spot (1–2 nm) of a SAM terminated with a functional group capable of nucleating crystals (carboxylic acid, sulfate, or hydroxyl) was formed. When this surface was exposed to a crystallizing solution, initially, a layer of amorphous calcium carbonate formed across the whole surface. Within 30 min oriented nucleation began at the nucleating spot defined with the AFM tip, and the crystallization spread across the entire surface. This process resulted in large (~1 mm), textured single crystals of calcite with defined orientations (Figure 19c).

8.3.2. Alignment of Liquid Crystals

Liquid crystals respond to the nanoscale topology of the surface on which they are deposited.[639] Obliquely deposited films of gold (40°–60° angle of incidence) have distinct ripples (periodic variations in the topography of 1–2 nm that are spaced 5–50 nm apart).[301] When liquid crystals are formed on such a surface they align perpendicularly to the ripples; in contrast, no azimuthal (in the plane of the surface) or polar (away from the surface) orientation of the liquid crystal is observed on a polycrystalline gold surface.[640,641] If the liquid crystals are deposited on a rippled gold surface supporting a SAM of alkanethiolates, the azimuthal orientation of the liquid crystal depends on the number of carbon atoms (odd or even chain length) of the alkyl chain—that is, the liquid crystal is sensitive to the relative orientation of the terminal methyl group on the surface (section 3.1). SAMs with an even number of carbons orient the liquid crystals parallel to the ripples, while SAMs with an odd number of carbons orient them perpendicular to the ripples.[300,301,640,642]

Because the orientation of the liquid crystals depends on the topography of the surface that supports them, SAM/liquid-crystal systems can be used to detect binding of proteins, such as antibodies, to ligands displayed by the SAM surfaces.[643–646] The binding of a large macromolecule to the surface of a SAM on obliquely deposited gold destroys the azimuthal orientation of the liquid crystals. Depending on the design of the system, this result is either a reflection of a change in the nanometer-scale topography as a result of binding[186] or a masking of the functionality displayed at the surface that was interacting with the liquid crystal.[645] These systems could be used as label-free detection methods for protein–ligands interations[646] or as viral diagnostics.[643]

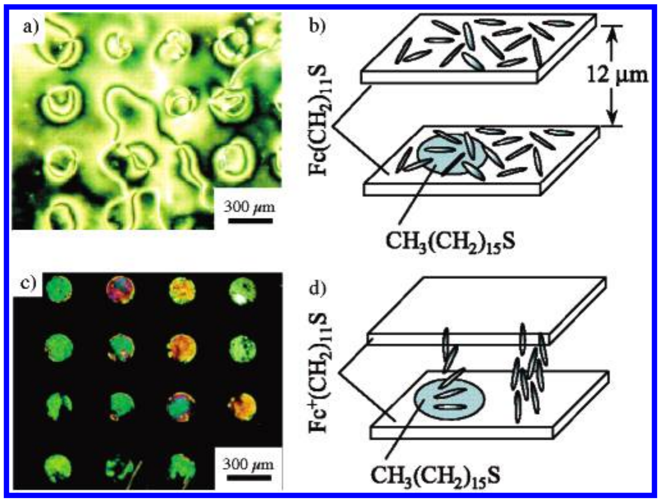


Figure 20. (a) Polarizing light micrograph of 4,4′-pentylcyanobiphenyl (5CB) in an optical cell prepared with one surface supporting an array of circles of hexadecanethiol SAMs fabricated using microcontact printing, surrounded by a SAM of $Fc(CH_2)_{11}SH$ (where Fc is ferrocene); the opposing surface has a SAM composed entirely of $Fc(CH_2)_{11}$-SH. (b) Schematic representation of the alignment of 5CB in a; 5CB is parallel to the planar surface with no preferred azimuthal orientation. (c) Polarizing light micrograph of 5CB containing benzyl peroxide (20 mM) in the same optical cell described in a. (d) Schematic representation of the alignment of 5CB in c; 5CB aligns perpendicular to regions presenting ferrocenium (Fc^+) but remains parallel to the circular regions presenting hexadecanethiol. (Reprinted with permission from ref 647. Copyright 2003 AAAS.)

SAMs can also control both the azimuthal and the polar orientation of liquid crystals on gold surfaces with minimal surface topography.[647] Applied electric fields can change the orientation of a bulk liquid crystal, but the strong surface interactions prevent the applied field from changing the orientation of the liquid crystal in the region near the surface.[639] Abbott and co-workers demonstrated that by using a SAM of a redox-active species (ferrocene), they can electrochemically drive the orientation (azimuthal and polar) of the liquid crystal from the surface (Figure 20).[647] Using microcontact printing, the surface-driven transitions in orientation can be patterned over a large area and may find use in electronic print or chemical sensors.

8.4. SAMs for Biochemistry and Biology

The biological membranes that define the boundaries of individual cells are naturally occurring examples of nanostructured organic materials with complex and dynamic behaviors.[14] They consist of supermolecular assemblies of proteins, glycoproteins, and large oligosaccharides anchored to or embedded in a fluid lipid bilayer or protein coat. The assemblies can have dimensions ranging from a few to hundreds of nanometers; for example, integrins are cylindrical transmembrane proteins (8−12 nm in diameter) that assemble into small clusters when cells attach to extracellular matrixes of protein.[648]

The broad range of membrane-bound assemblies present in biological membranes control many processes in living organisms (from bacteria to complex, multicellular organisms). The interactions between single ligand−receptor pairs (or often groups or clusters of molecules)[425] enable the cell to sense its environment, communicate with other cells, and regulate intracellular functions such as migration, adhesion, growth, division, differentiation, and apoptosis.

The compositional complexity and dynamic nature of biological surfaces make it difficult to study certain fundamental aspects of biological systems in detail. Model surfaces with well-defined compositions provide useful tools for studying the physical−organic chemistry of biomolecular recognition (for example, the thermodynamics and kinetics of the association/dissociation of proteins or other biomolecules with ligands) for determining the effect of individual recognition events on the functional behavior of cells and investigating the structural factors that enable surfaces to resist the adsorption of proteins. The development of biotechnological applications, such as cell culture, tissue engineering, and biosensors,[649] also can benefit from simplified systems that allow only one or a few types of interactions between species in solution (cells, biomolecules, analytes) and the surfaces of the engineered system. One primary challenge in developing model surfaces ex vivo is developing methods that allow precise control of the composition and structure of the surface while permitting natural biological interactions to occur in such a way that the results can be interpreted clearly and related to biology in vivo.

SAMs are useful as model surfaces for studying biological and biochemical processes. First, like the biological surfaces they mimic, they are nanostructured materials that form by self-assembly. Second, they can present a wide range of organic functionality rationally, including functionality that can resist the adsorption of proteins, at positions away from the plane of the substrate with nearly atomic-level precision. Third, it is easy to prepare SAMs functionalized with the large, delicate ligands needed for biological studies by either synthesizing molecules with the ligand attached to form the SAM or, more commonly, attaching the ligands to the surface of a preformed, reactive SAM (see section 5). Fourth, SAMs are directly compatible with a number of techniques (surface plasmon resonance (SPR) spectroscopy,[650,651] optical ellipsometry,[408,409] RAIRS,[409] QCM,[652] mass spectroscopy[653]) for analyzing the composition and mass coverage of surfaces as well as the thermodynamics and kinetics of binding events. Fifth, SAMs are less influenced by effects of mass transport than the thick gel layers sometimes used to immobilize ligands on surfaces for SPR.

One disadvantage of SAMs as model surfaces is that the structure of the SAM is essentially static. This characteristic differs from that of biological membranes, which are fluid and rearrange dynamically. Langmuir−Blodgett (LB) films[654] and reconstituted bilayers of lipids on solid supports[655] present two alternative technologies for creating dynamic models of biological surfaces. The utility of LB films in this area of study remains limited due to instrumental complexity and difficulties with reproducibility; LB films (at the air−water interface) do, however, generate systems in which in-plane diffusion and transmembrane experiments are possible. Advances in techniques for patterning regions of lipid bilayers on solid supports and defining their compositions also are beginning to emerge and could offer an important complementary tool for generating model biological systems.[656]

8.4.1. Designing SAMs To Be Model Biological Surfaces

To test a range of experimental conditions and facilitate the interpretation of the interactions observed, SAMs should have, at a minimum, three characteristics: (1) they should be able to prevent nonspecific adsorption of proteins or other biomolecules on the surface, that is, they should only allow interactions between the molecules and ligands of interest and thus permit meaningful analysis of observations made to determine the sensitivity or kinetics of these processes; (2) they should allow modifications to the composition and density of the immobilized ligands or biomolecules (proteins, sugars, antigens); and (3) they should present the ligands of interest in a structurally well-defined manner that minimizes the influences of the surface, e.g., limited mass transport, blocked binding sites, or induced conformational changes. It is also helpful if the model surfaces can be used easily with common analytical methods without modifying the existing instrumentation or without subjecting the samples to unnatural (for biology) conditions, e.g., in dehydrated form in UHV.

Protein-Resistant Surfaces. Surfaces that resist the nonspecific adsorption of other biomolecules and cells commonly are called “inert” surfaces. The best protein-resistant surfaces presently known are ones composed of oligo- or poly(ethylene glycol) (OEG or PEG).[657] Alkanethiols terminated with tri- or hexa(ethylene glycol) groups are a standard component of SAMs used to study biology and biochemistry.[658,659] On gold the alkane chains form a dense, ordered monolayer with the same molecular conformation found for *n*-alkanethiols, i.e., all-trans chains with a 30° tilt; the terminal ethylene glycol end-group adopts either a helical conformation aligned perpendicular to the surface or an amorphous conformation.[660,661] The helical structures yield a quasi-crystalline surface phase, but the amorphous chains produce a liquidlike phase. NEXAFS measurements indicate that both conformations exist on the surface simultaneously in a vacuum.[662] There is also evidence that these end groups can undergo order−order

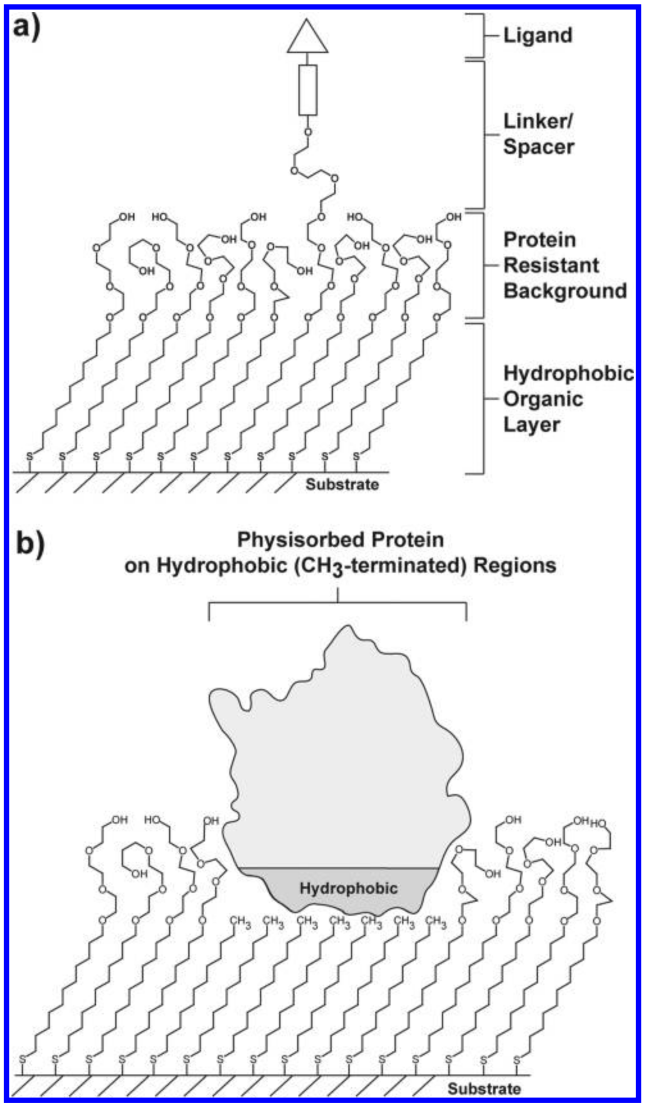


Figure 21. Schematic illustrations of (a) a mixed SAM and (b) a patterned SAM. Both types are used for applications in biology and biochemistry.

phase transitions to other structures, e.g., all-trans conformers, when heated above room temperature.[663]

Mixed SAMs as Model Surfaces for Biochemistry and Biology. Mixed SAMs containing two or more constituent molecules provide a practical experimental system with which to generate model systems to study fundamental aspects of the interactions of surfaces with bioorganic nanostructures, such as proteins, carbohydrates, and antibodies.[361,410,419,562,587,650,664−666] One widely used system comprises an alkanethiol terminated with ethylene glycol groups and an alkanethiol terminated with either a biological ligand or a reactive site for linking to a biological ligand.[664,667] These surfaces can present ligands of interest in a structurally well-defined manner against a background that resists the nonspecific adsorption of other biomolecules and cells (Figure 21a). The fraction of ligands on the surface is related to the mole fraction of the thiols in the solution used to form the surface. The surface density of ligands used in most studies of protein−surface or cell−surface interactions is less than 5%; this dilution of the ligand in the inert background reduces the extent of nonspecific adsorption of proteins, multivalent binding, and lateral steric effects, which can create erroneous or misleading measurements. Two underlying assumptions about these surfaces are that the ligands are, in fact, not aggregated at the low densities used and that phase separation of the components in the SAM is not significant; the organization of the constituents in the SAM can have a considerable influence on its functional behavior (see section 5.2.5 for a related discussion of this point).

Mixed SAMs presenting structurally well-defined hydrophobic groups (trityl moieties) have provided one approach to studying protein adsorption on surfaces by hydrophobic interactions.[666] SAMs presenting L-lysine-D-alanine-D-alanine groups mimic a part of the cell wall of Gram-positive bacteria recognized by the antibiotic vancomycin and have enabled the development of bifunctional polymers capable of binding bacterial surfaces and recruiting antibodies to the surface.[668] SAMs presenting ligands for binding specific proteins also provide a method for studying the effect of lateral interactions between proteins immobilized on a surface on the thermodynamics and kinetics of binding.[669]

SAMs as Components for Arrays of Biomolecules. Planar substrates, such as glass slides, that support microscale arrays of immobilized biomolecules are a developing technology for exploring the basic biology of ligand−receptor and enzymatic activities and for screening libraries of potential drugs. Some of the types of biomolecules commonly immobilized include DNA,[670,671] proteins,[672] carbohydrates,[673,674] and antibodies.[368,675,676] Because the surface chemistry of thiols on gold is reasonably well-understood, SAMs (especially mixed SAMs) are becoming important components of these systems. The combination of SAMs that resist nonspecific adsorption of proteins and methods for modifying the interfacial composition of SAMs (section 5) make it possible to generate surfaces with anchored biomolecules that remain biologically active and in their native conformations.[670,677] The planar format of the substrates makes it convenient to determine the biological activity by fluorescence[675] or electrochemistry.[678]

8.4.2. SAMs for Cell Biology

Most cells are not freely suspended in vivo but adhere to three-dimensional organic matrixes composed of proteins and other large biomolecules.[14] SAMs provide one method for generating model organic surfaces with specific ligands to which cells can attach or with which they can interact. The primary advantage of SAMs (especially mixed SAMs) over other methods of creating organic surfaces (polymer films, adsorbed proteins) is that the chemical composition of the surface can be modified in a deliberate manner. This characteristic is important for conducting mechanistic studies of cell attachment and investigating the intracellular signaling that occurs upon binding because it minimizes ambiguities concerning the nature of the substrate.

Mixed SAMs composed of a ligand-presenting molecule and a second SAM-forming molecule (usually one terminated with functional groups that can resist protein adsorption) make it possible to vary the type of ligand presented on the surface, its density, and, to some extent, its accessibility.[360,679,680] The density of active ligands on the surface is an important parameter for investigating processes that require multiple ligand−receptor interactions to initiate a biological response in the cell. To a reasonable approximation, the relative concentration of the ligand presented in the mixed SAM reflects its relative concentration in the solution used to form the SAM. Electrochemical analysis[678] and mass spectroscopic methods[653,674,681] can provide an accurate measure of the areal density and chemical composition of mixed SAMs presenting biologically active ligands.

The mechanism for immobilization of cells on surfaces is one example of a cell−surface interaction that has been studied using SAMs that present peptide sequences that bind to transmembrane receptors.[679,682] Another example of a surface-mediated process studied with SAMs presenting different functional groups is the adhesion of leukocytes.[683] This process is an indication of the immunological activation of these cells and is one parameter used to determine the biocompatibility of materials because it is one indication of an inflammatory response to the material.

Patterns of SAMs generated by μCP provide a second method for attaching cells on surfaces: hydrophobic SAMs are printed to define regions that allow cells to attach; subsequent immersion of the substrate into a solution containing a second thiol forms a SAM in the surrounding regions that resists the adsorption of proteins (and cells).[562,684] Extracellular matrix proteins, such as fibronectin, can adsorb onto the hydrophobic regions of the surface (Figure 21b); these adsorbed proteins facilitate the adherence of mammalian cells such as fibroblasts. The spatial pattern defined by the hydrophobic regions controls the size and shape of the adherent cells because the protein-resistant regions prevent the cells from spreading beyond the edges of the pattern. These patterned surfaces make it possible to study the biochemical response of cells to mechanical stimuli.[685] Electrochemical methods can remove or modify the SAMs to release the cells from the confinement originally imposed by the pattern of the SAM.[373,686] These procedures provide a basis for new types of assays using cell motility or other phenotypic responses.

8.4.3. Structure–Property Considerations for SAMs Used in Biology

The types of molecules used to form SAMs for applications in biology and biochemistry differ from *n*-alkanethiols in structure and composition. These molecules readily form SAMs, but the details of these systems may vary substantially in some cases from SAMs of alkanethiolates. Among others, three elements that are not accounted for in the structural model and general understanding developed for *n*-alkanethiols (with small terminal functional groups) on gold, silver, and palladium are (1) the size and shape of the immobilized ligands attached to the termini of molecules in the SAM, (2) the composition and dynamics of functional groups presented at the surface of the SAM that resist the adsorption of proteins, and (3) the interactions of the SAM with the aqueous medium (including dissolved proteins and other biomolecules) required for most biological experiments.

Influence of Biological Ligands on the Structure of SAMs. The ligands and biomolecules (DNA, proteins, carbohydrates) required for biological studies are large relative to the cross-sectional area of an alkane chain ($0.184\ \mathrm{nm}^2$). Molecules that consist of a large ligand ($\geq 0.25\ \mathrm{nm}^2$) attached to a single thiol moiety or a short alkanethiol (12 or fewer carbons) cannot form SAMs with the same organization found in SAMs of *n*-alkanethiolates: the steric bulk of the ligands hinders the formation of a densely packed monolayer and probably induces disorder in the system (Figure 22). In cases where ordered domains of adsorbates do form, the structural arrangement differs from that for SAMs of alkanethiolates and includes a large number of pinholes and defects.[687]

Other assumptions commonly made regarding mixed SAMs containing dilute ($\leq 1\%$) molecules with attached ligands are (1) the ligand does not interact with the surface of the substrate, especially near defects, (2) the ligand is well-solvated and presented some distance away from the surface when attached to a long (1−2 nm) linker, and (3) the ligands do not segregate into islands or bundles of molecules during or after formation of the SAM. While these assumptions probably are true for many cases, there is little experimental data and subsequent structural analysis available to support them. The majority of the data on these types of mixed SAMs is taken from analysis of the functional behaviors of these surfaces (cell attachment, protein binding) that result from varying the composition of the surfaces without rigorous attention to the details of structure.

Composition of Surfaces That Resist Adsorption of Proteins. The structural elements required for surfaces to resist the adsorption of proteins (especially mixtures of proteins) are poorly understood. Surfaces terminated with OEG (present in either a helical or an amorphous conformation when examined spectroscopically in dehydrated form in air or vacuum) resist the adsorption of proteins.[661] Experimental and theoretical studies of OEG- and PEG-terminated SAMs suggest a number of factors−the packing density of the chains, the hydrophilicity of the chains, the nature of the surrounding environment, and temperature−enable this class of SAMs to resist protein adsorption.[659,688] A number of SAMs terminated with other functional groups have been studied, and some (for example, oligosarcosines, and oligosulfoxides) are also usefully inert.[689] The ability to attach ligands easily to the surface of a SAM (using the “anhydride method”; see section 5.2.2) makes it practical to screen a large number of mixed SAMs presenting different functional groups as part of physical−organic studies that address this problem.[690,691] Some of the factors that seem to correlate with the ability of surfaces to resist the adsorption of proteins include polarity, overall electrostatic neutrality, absence of H-bond donors, and conforma-

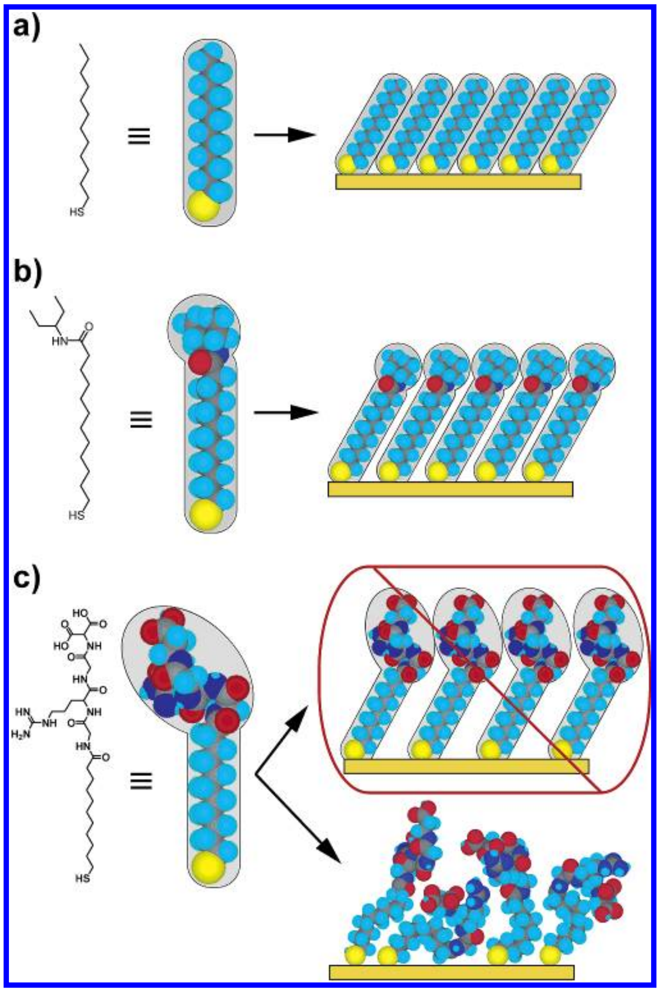


Figure 22. Schematic diagram illustrating the effects that large terminal groups have on the packing density and organization of SAMs. (a) Small terminal groups such as $-CH_3$, $-CN$, etc., do not distort the secondary organization of the organic layer and have no effect on the sulfur arrangement. (b) Slightly larger groups (like the branched amide shown here) begin to distort the organization of the organic layer, but the strongly favorable energetics of metal−sulfur binding drive a highly dense arrangement of adsorbates. (c) Large terminal groups (peptides, proteins, antibodies) sterically are unable to adopt a secondary organization similar to that for alkanethiols with small terminal groups. The resulting structures probably are more disordered and less dense than those formed with the types of molecules in a and b.

tional flexibility.[691,692] The structure of water present at the surface may ultimately play the key role in preventing proteins from adsorbing on surfaces.[392,693]

Behavior of SAMs under Physiological Conditions. Knowledge of the structure and properties of SAMs immersed in solvents is substantially less than that for SAMs of alkanethiolates in air or in a vacuum. The use of SAMs as substrates for studies in biology requires, however, extended contact between SAMs and an aqueous environment containing a high concentration of salts (∼200 mM) and biomolecules (enzymes, extracellular matrix proteins, plasma components, sugars). The structure and dynamics of the exposed surface of a SAM under these conditions have not been characterized completely but are critical for understanding the origin of certain properties (especially resistance to adsorption of proteins).

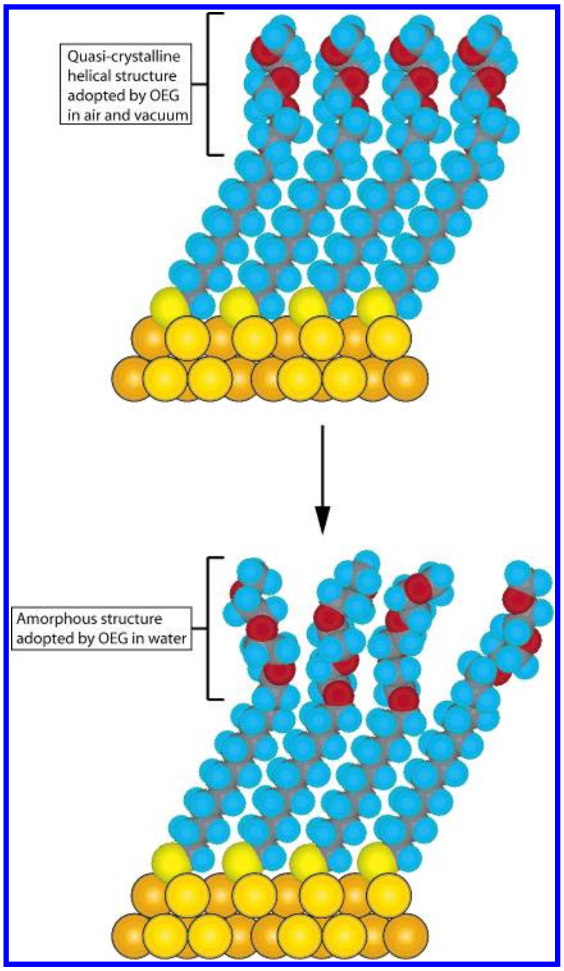


Figure 23. Schematic illustration of the order−disorder transition evidenced by SAMs of alkanethiolates terminated with triethylene glycol. The EG_3 group loses conformational ordering upon solvation in water.

Grunze and co-workers have shown the conformational changes at the exposed surface of SAMs terminated with PEG (45 EG subunits) upon exposure to water.[310] Each PEG at the surface adopts a helical structure in air to form a quasi-crystalline phase with the rods oriented nearly perpendicular to the surface. The structure of the SAM changes when immersed in water: the ends of the helical EG units transition to an amorphous state, and the amorphous interfacial region is solvated in a manner equivalent to dissolved PEG chains. For SAMs terminated with short oligomers of ethylene glycol (3−6 units), measurements suggest the entire oligomer becomes amorphous in water (Figure 23).[309]

Another poorly understood parameter is the effect of physiological conditions on the long-term stability of SAMs of alkanethiolates. Langer and co-workers have shown that SAMs terminated with EG develop substantial defects after immersion in phosphate buffer solution or in calf serum for 4−5 weeks.[694] The presence of cells at the surfaces accelerates the process: the ability of EG-terminated SAMs to prevent the adhesion of cells is compromised in ∼7−14 days.[222] One probable mechanism for the loss of resistance in these systems is oxidation of bound thiolates and subsequent desorption (see section 4.3). Molecular interactions between neighboring chains, such as networks of hydrogen bonds, could provide one means for improving the stability of the monolayer.[283,695]

9. Applications of SAMs on Nanostructures

Templated synthesis of nanostructures is an approach to forming nanometer-scale, metallic objects with nonequilibrium (and often nonspherical) morphologies. Although the shapes themselves may exhibit new and interesting physical properties (optical, electronic, or magnetic), much of the interest in these types of structures focuses on their potential applications, such as sensors, selective filters, or probes for biology. These nanostructures are smaller than cells; this size makes them useful for probing subcellular features. For example, magnetic nanostructures can be used to create very high localized field gradients or apply torque at subcellular levels.[696] Metallic nanostructures with uniformly functionalized surfaces could be used to target cells and bind to specific receptors. Without functionalization the native metal surfaces are prone to nonspecific protein adsorption and degradation (oxidation, decomposition).[42] For structures made from gold and other metals on which SAMs can form (Table 1), alkanethiols are used to impart new properties and functions. This section discusses some examples of templated nanostructures and applications of such structures that use SAMs to tailor the composition of their surfaces.

9.1. Electrodeposited Metal Rods

Electrodeposition of metals within mesoporous polycarbonate or alumina membranes—a technique pioneered by Martin[697]—can generate segmented nanowires with sections composed of different metals with controlled lengths (Figure 24a and b). There are reviews of the many applications of these rods including their use as circuit components,[698] their applications in biology,[699] and their use as bar-coded tags.[700] Rods containing nickel segments are particularly useful because of their magnetic properties.[701,702]

Many applications of these rods rely on the orthogonal functionalization of different metallic sections with different SAMs (section 7.3.4). For example, gold—platinum rods can be patterned with thiols on the gold segments and isocyanides on the platinum segments.[124] Gold—nickel rods can also be orthogonally functionalized using thiols to decorate the gold segments and carboxylic acids, which have a preference for the native oxide on the nickel,[39] to decorate the nickel segments.[41,42,702] Poly-histidine and proteins with poly-His tags have also been shown to bind selectively to nickel segments of gold—nickel rods.[701]

In biological applications orthogonally functionalized rods make it possible to localize different proteins on individual segments. One application of rods functionalized in this way is the delivery of DNA plasmids to a cell. Transferrin (a cell-targeting protein used for receptor-mediated gene delivery via endocytosis)[703] was linked to the gold segments via thiols and a DNA plasmid was localized on the nickel segments via electrostatic interactions with the amino group of 3-[(2-aminoethyl)dithio]propionic acid.[41] Similar chemistry has been used to functionalize the gold tips of nickel/gold rods with biotin; the rods were then magnetically manipulated onto silver surfaces functionalized with avidin.[702] Another approach to localizing proteins to one segment of a rod is to treat the gold segments with EG_6—thiol and the nickel segments with palmitic acid. The EG-coated gold resists protein adsorption, while the hydrophobic nickel segments readily adsorb proteins.[42]

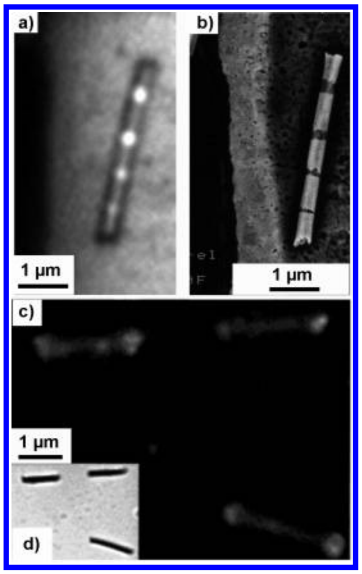


Figure 24. Optical (a) and FE-SEM (b) images of a segmented nanorod with ~550 nm gold segments and silver segments of 240, 170, 110, and 60 nm (from top to bottom). (Reprinted with permission from ref 704. Copyright 2001 AAAS.) (c) Fluorescence micrograph of gold nanowires functionalized with ssDNA only on the tips. After removal from the alumina membrane, the ssDNA was hybridized with a rhodamine-modified complementary strand of ssDNA. (d) Optical micrograph corresponding to the rods shown in c. (Reprinted with permission from ref 707. Copyright 2001 Wiley-VCH.)

SAMs on metallic "barcodes", rods patterned with sections of different metals, have been used to perform DNA hybridization assays and immunoassays.[704,705] The rods are first functionalized with mercaptoundecanoic acid and subsequently linked to the molecules or proteins of interest via peptide coupling reactions. The combination of the inherent reflectivities (Figure 24a) of the different metallic stripes—silver is more reflective than gold—and the fluorescence of a bound analyte is used as a readout for binding. Depending on the choice of metals and fluorescent labels, the barcode pattern can either be obscured by fluorescence or remain visible.

The tips of nanorods (rather than their length) can be functionalized with different SAMs by exposing the nanorods to a thiol solution before removing them from the membrane used for templating (Figure 24c).[706,707] This technique has been used to assemble rods in an end-to-end fashion using complementary single-stranded DNA.[707] It has also been used to form molecular "junctions" in the nanorods by exposing the growing rod to a solution of an ω-functionalized alkanethiol in the middle of the growth process and then depositing more metal on top of the organic layer.[706]

9.2. Gold Nanopores as Selective Channels

The same commercially available membranes used to make the nanorods also are used to synthesize gold nanotubes using electroless deposition methods.[204,708] Martin and co-workers extensively studied the use of these nanotubes as selective channels for the separation of molecules. As synthesized, these nanopores serve as channels for the passive transport of small organic molecules across membranes.[709] Forming SAMs of different ω-functionalized alkanethiols on the interior of these pores, however, makes it possible to control and modulate the types of molecules that can pass through them. For example, pores coated with hydrophobic, long-chain alkanethiols selectively pass toluene in preference to pyridine; this selectivity can be reversed by changing the lining of the pore to the more hydrophilic mercaptoethanol.[710] A two-molecule permeation experiment with a hexadecanethiolate-lined pore (2.0 nm diameter) showed that the flux of toluene was 165 times higher than that of pyridine.[711]

Besides the functional groups presented by the SAM, the length of the alkanethiol chain also affects the transport properties of the pore.[711] The primary effect is a variation in the partition coefficient of the molecule between the aqueous feed solution and the membrane. The pores coated with longer alkyl chain thiols, therefore, have higher fluxes of toluene than those with shorter chains.

Charged SAMs formed from cysteine (Cys) can be used to control the flux of ions through the nanopores.[712,713] Depending on the pH of the solution (and thus the protonation state of Cys), the membrane can become permeable to either cations or anions (Figure 25). At neutral pH, where the Cys is zwitterionic and thus (roughly) electrically neutral, the membrane becomes nonselective. A further level of selection is possible due to the size selectivity previously described.

Proteins can also be separated by size in gold nanopores coated with PEG−thiolates.[714] This technique has been improved by applying a potential difference across the membrane. This additional element of control allows proteins to be separated both by size and pI.[715]

One difficulty associated with this work is the characterization of the SAMs formed on the interior of the gold nanopores. While the experimental evidence argues strongly that there is some degree of coverage by the SAM and that the observed effects of the SAM in the pore are reproducible, it is unclear how completely the interior is functionalized by the alkanethiols and what is the structure of the SAM inside the pores. This uncertainty illustrates a general need for new analytical techniques for analyzing the structure of SAMs in confined, nanometer-scale spaces.

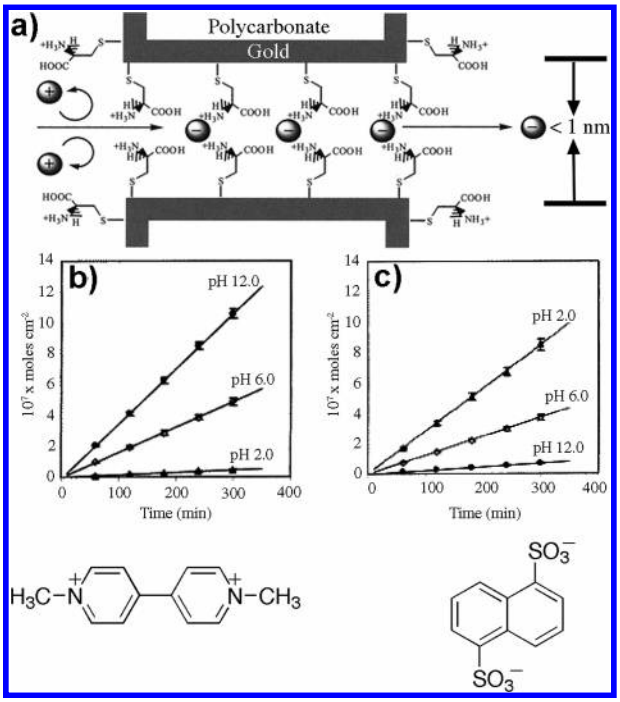


Figure 25. (a) Schematic representation of a gold-lined polycarbonate membrane functionalized with SAMs of cysteine. At low pH the positively charged channel is cation-rejecting/anion-transporting. (b) pH-dependent permeation data for the transportation of positively charged methyl viologen through a cysteine-lined nanotube. (c) pH-dependent permeation data for the transportation of negatively charged 1,5-naphthalene disulfonate through a cysteine-lined nanotube. (Reprinted with permission from ref 713. Copyright 2001 American Chemical Society.)

9.3. Arrays of Metallic Nanostructures

Several methods for forming ordered arrays of metallic nanostructures have been developed. Many of these methods rely on some form of self-assembly to control the position of nano- and submicrometer-scale objects in two dimensions.[716] Some potential applications for arrays of metallic nanostructures include cellular automata,[717] arrays of biomolecules, cell sorting, and information storage. In the following sections we describe how SAMs are used to add specific chemical functionality to such arrays and thereby widen their potential applications.

9.3.1. Arrays of Gold Dots

Block copolymer micelle nanolithography is a technique for forming ordered arrays of gold dots (~8 nm) in a close-packed hexagonal lattice; the specific spacing between the dots depends on the molecular weight and linear composition of the block copolymer.[718,719] In this procedure, a film consisting of a single layer of adsorbed micelles is prepared by removing a glass slide from a block copolymer micellar solution (polystyrene(x)-*block*-poly(2-vinylpyridine)(y)), which is also coordinated with Au(III) salt. The micelles arrange themselves in a hexagonal lattice on the surface of the slide. After treatment with a hydrogen plasma to remove the polymer, a hexagonal array of gold nanoparticles remains. This technique can be combined with focused e-beam writing to form more complex patterns of gold nanoparticles.[719]

Spatz and co-workers used arrays of gold dots, with varying lateral spacings, functionalized with SAMs of a cyclic derivative of the Arg-Gly-Asp (cRGD) peptide (linked to mercaptopropionic acid) to study cell adhesion.[720] The authors argue that the small size (∼8 nm) of the gold dots allows only one integrin (8−12 nm) to bind per site. By varying the spacing of the gold dots on which the cells are cultured, they estimate that between 58 and 73 nm is the farthest spacing between integrins that still allows them to cluster and activate the formation of focal adhesion complexes.

9.3.2. Silver Tetrahedrons for Localized Surface Plasmon Resonance (LSPR)

Nanosphere lithography uses a colloidal crystal (either single or double layer) of hexagonally close-packed silica or polystyrene spheres as a mask for material deposition.[721] Using this technique, arrays of silver nanoparticles with triangular shape and regular size and spacing can be generated on different surfaces (mica, fused silica, optical glass, and SF-10).[722] Van Duyne and co-workers demonstrated that the shape of the nanoparticles, the solvent in which the measurement is performed, the supporting surface, and the alkanethiols used to form the SAM on the surface all affect the frequency and line shape of the LSPR of these particles.[721,723,724] In addition, these particles can be used as substrates for surface-enhanced Raman scattering (SERS).[725]

Binding an alkanethiol to the surface of the silver nanoparticles alters the local refractive index and induces a shift in the surface plasmon frequency.[53] This shift is sensitive to the length of the alkyl chain (∼3 nm to the red for every additional carbon) and can be modeled with Mie theory. The sensitivity makes the system a good candidate for molecular sensors. As few as 60 000 1-hexadecanethiol molecules (∼100 zmol) binding to one silver nanoparticle results in a 40.7 nm shift to the red in the LSPR (Figure 26).[726] The adsorption can be monitored in real time using dark-field optical microscopy.

By forming SAMs of biologically relevant ligands the silver nanoparticles also can be used to detect the binding of proteins, such as antibodies, with high sensitivities, using relatively low-cost instrumentation.[724,727,728] By choosing the appropriate substrate for the silver nanoparticles these assays can be performed in real time in physiological buffer.[728] Haes et al. reported the construction of a sensor for anti-amyloid *β*-derived diffusible ligands antibodies (anti-ADDL) using arrays of silver nanoparticles functionalized with mixed SAMs of octanethiolates and ADDL linked to mercaptoundecanoic acid.[724] A sensor of this type might be developed into a diagnostic test for Alzheimer's disease.

9.4. Metallic Shells

9.4.1. Metallic Half-Shells

E-Beam deposition of thin layers of metal onto arrays of colloidal spheres forms metallic half-shells. If the colloidal spheres are dissolved, free-standing metallic half-shells several nanometers thick remain (Figure 27a). The half-shell shape is attractive since these particles cannot consolidate. When gold half-shells are functionalized with a hydrophobic SAM, the wetting properties of the aggregated particles are altered; this formation of a SAM converts a surface covered with half-shells into a superhydrophobic surface (Figure 27b and c).[729]

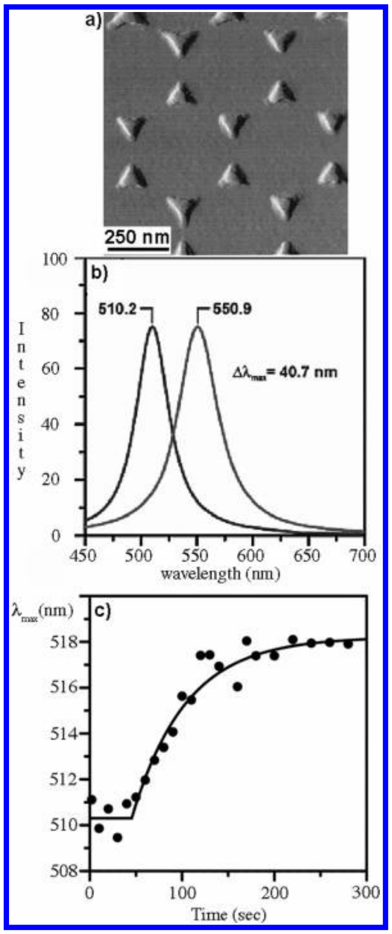


Figure 26. (a) Tapping mode AFM image of a silver nanoparticle array on a glass substrate. (Reprinted with permission from ref 53. Copyright 2001 American Chemical Society.) (b) UV−vis spectra of an individual silver nanoparticle before and after modification with 1-hexadecanethiol. (c) Real-time LSPR response of a single silver nanoparticle upon injection of 1.0 mM 1-octanethiol into the flow cell. The experimental data (circles) are fitted to a first-order response profile with k = 0.0167 s^{-1}. (Reprinted with permission from ref 726. Copyright 2003 American Chemical Society.)

Bao et al. left gold-coated colloidal particles intact and functionalized the asymmetric gold spheres with SAMs of thiolated single-stranded DNA.[730] The DNA was used to direct the assembly of these spheres, gold side down, onto patterned gold surfaces with the complementary DNA sequence. After assembly a second gold cap was deposited on the opposite side of the sphere. This technique can be used to form multiply functionalized spheres.

Particles with silver half-shells are also good substrates for surface-enhanced Raman scattering (SERS) because they generate high electromagnetic field gradients.[731] SAMs formed on the surface are used to concentrate the analyte of interest at the metal surface within the zone of electromagnetic field enhancement.[732,733] In a recent example a SAM of (1-mercaptoundeca-11-yl)tri(ethylene glycol) was used to selectively concentrate glucose from a solution containing serum proteins at the silver surface; this concentration improved the SERS signal and made

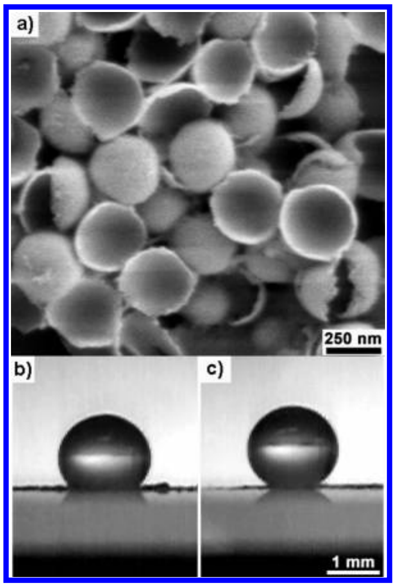


Figure 27. (a) SEM image of 10-nm-thick palladium half-shells (280 nm diameter). Optical micrographs of static water droplets (5 μL) on a thin film (50 μm) of unmodified (b) and hexadecanethiol-modified (c) gold half-shells. (Reprinted with permission from ref 729. Copyright 2002 American Chemical Society.)

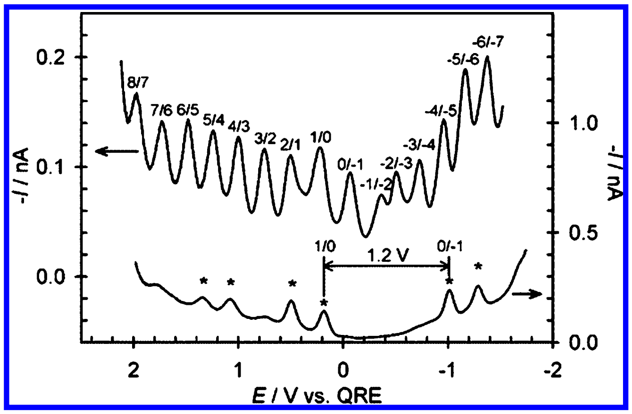


Figure 28. Differential pulse voltammetry (DPV) responses for a solution of monolayer-protected gold nanoparticles measured at a platinum microelectrode. Hexanethiol-protected Au_{147} clusters showing 15 high-resolution quantized double-layer charging (QDL) peaks (upper) and hexanethiol-protected Au_{38} clusters showing a HOMO−LUMO gap (lower). (Reprinted with permission from ref 743. Copyright 2003 American Chemical Society.)

the system feasible to consider as an in vivo glucose sensor.[733]

9.4.2. Gold–Silica Core–Shell Particles

Silica nanoparticles (diameter 55−110 nm) can be coated with a thin (10 nm) layer of gold using a seed-growth technique.[734] Briefly, small gold colloids (1−3 nm) are affixed to the silica surface via electrostatics, and then electroless growth conditions are used to enlarge the particles; this process eventually fuses the small nanoparticles together to yield a complete shell. Halas and co-workers used these core−shell particles to destroy tumors in mice: near-infrared (NIR) light causes local heating of the particles thus killing the cancerous cells.[735] To prevent the body from clearing the particles, the particles are coated with a protein-resistant SAM of PEG-SH.

9.5. Metal Nanoparticles and Quantized Double-Layer Charging

The use of various SAMs of alkanethiolates to stabilize and modify gold clusters has been an area of special interest, and many applications of them−in sensing, optics, bioanalytical assays, and chemical coding of information−have been reported (sections 6 and 9.6). The finite scale of these nanoclusters also brings with them unique properties which have no counterpart in planar SAMs. The most striking departures have been evidenced in the electrochemical studies of SAM-stabilized nanoscale colloids (notably those of gold).[57,736]

SAMs of alkanethiolates on planar gold surfaces generate classic behaviors in electrochemistry (section 8.2). The SAM forms a barrier to electron-transfer processes that can be described by Marcus theory.[737] The capacitances supported by a SAM upon application of an external potential reveals an essentially ideal dielectric response of the SAM and organization of electrolyte charge in the bounding double-layer. Nanoscale gold particles bearing a SAM, however, have remarkably small double-layer capacitances (typically much smaller than 1 aF). This difference leads to an electrochemical property that is unique to this class of material: quantized double-layer (QDL) charging.[176,738]

The physics of QDL has been described in considerable detail by Murray, Whetten, and others.[176,738−741] The model notes that the addition of charge to the cluster (whether via a potentiostatic oxidation or via reduction of the metal core) is sensitively influenced by the finite capacitance of the nanoparticle. Even single-electron additions to (or subtractions from) the core result in remarkable shifts (265 ± 14 mV)[742] in potential; this scaling follows approximately as

$$\Delta V \approx e/C_{\mathrm{np}} \tag{4}$$

where e is the electron charge and C_{np} is the capacitance of the SAM-coated gold cluster.[739,741] The capacitance depends on both the diameter of the metal core and the chain length of the alkanethiolates.[176,741] For monodispersed samples with gold core diameters of less than ~2 nm, the change of each quanta of charge leads to well-separated features in their electrochemical response.[739,742,743] Similar behavior is also observed for surface ensembles of gold nanoparticles on electrodes.[744]

The use of highly monodisperse gold nanoparticles that have specific diameters (0.5−5 nm)−formed in the presence of specific concentrations of thiols (section 6)−makes it possible to resolve single transfers of electrons per monolayer-protected nanoparticle.[742,743,745−747] The SAMs themselves also contribute to the finite dimensions of the particles and their electronic properties.[176,741,748] Figure 28 shows an especially intriguing example of results obtained using differential pulse voltammetry for a sample of Au_{147} (r = 0.81 nm) clusters stabilized with a hexanethiolate SAM.[743] These data show no fewer than 15 resolved (and reversible) electron transfers−

ones cycling the cluster through charge states ranging from −7 to +8.

As striking as these effects may seem, there are other remarkable insights that have come from these measurements. One notes that for the smallest particles (1−2 nm in diameter) the electronic structure of the cluster may be markedly different− more molecular in character−than that found in larger metallic clusters (Figure 28).[176,738,743,745−747] The ability to synthesize and purify samples of monodisperse gold nanoparticles of many discrete sizes allows the direct observation of the size-dependent transition from molecule-like to metal-like properties in the particles. The electrochemical data suggest evidence of incipient molecular behaviors in core clusters containing fewer than 140 gold atoms.[743,745,746,749] For Au_{38} clusters ($r = 0.55$ nm) a HOMO−LUMO gap of 1.2−1.3 V has been experimentally determined (Figure 28).[743,745] Such values pose intriguing questions regarding electronic structure in finite-scale systems−a topic that remains of great current interest in the field and the subject of continuing experiment and theory-based research.

9.6. Functional Surfaces on Nanoparticles

SAMs are useful for stabilizing nanoparticles during their formation (section 6), but the protective organic interface also can display a range of functional groups at the interface between the nanoparticles and their environment. These functional surfaces make nanoparticles useful as biological tools and platforms to study polyvalent interactions. The following sections present several such applications.

9.6.1. Biocompatible Surfaces on Quantum Dots

Semiconductor (II−VI) nanocrystals or “quantum dots” (e.g., cadmium sulfide, cadmium selenide, and zinc sulfide) have the potential to be useful biological probes because they fluoresce with high quantum efficiencies and do not fade upon repeated excitation and emission (as do organic dyes).[750,751] The nanocrystals alone, however, are toxic to cells, not easily transported into cells, and difficult to target to subcellular locations once inside of cells.[62,752] The use of SAMs to form biocompatible surfaces on quantum dots begins to address both of these obstacles; much work, however, remains to be done.[62]

Cadmium selenide nanoparticles coated with a less reactive and less toxic layer of zinc sulfide[751] can be functionalized with a SAM of thiolated DNA molecules or proteins either directly or via ligand exchange (see section 6.2).[753−755] To improve aqueous solubility and minimize nonspecific protein binding, Akerman et al. formed a mixed SAM with a PEG thiol and mercaptoacetic acid; the adsorbed mercaptoacetic acid was then further functionalized with different bioactive peptides.[755] Several groups have covalently linked a range of proteins and peptides to SAMs of mercaptoacetic acid, mercaptopropionic acid, cysteine, and thioglycolic acid using a variety of coupling reagents.[59,753,755,756] Some of these proteins, such as transferrin, are used to improve transport into cells.[753] Electrostatic interactions, with charged SAMs, have also been used to functionalize the surfaces of quantum dots with proteins and other polymers.[757]

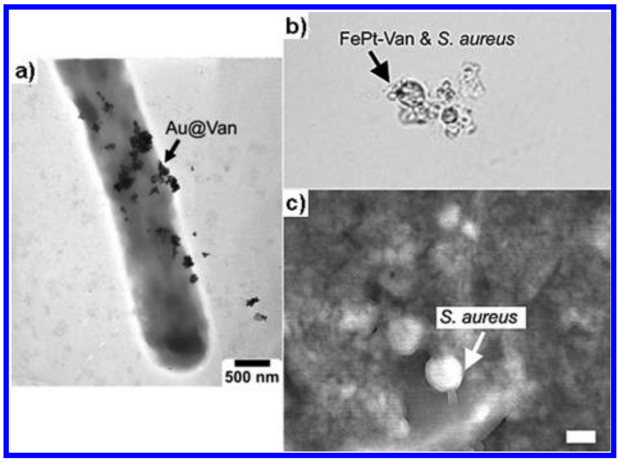


Figure 29. (a) Transmission electron micrograph of *E. coli* after being treated with gold nanoparticles functionalized with a SAM of vancomycin. (Reprinted with permission from ref 63. Copyright 2003 American Chemical Society.) Optical (b) and SEM (c) image of the magnetically captured aggregates of *S. aureus* and FePt nanoparticles functionalized with a SAM of vancomycin. (Reprinted with permission from ref 64. Copyright 2003 American Chemical Society.)

9.6.2. Functionalized Magnetic Nanoparticles

Magnetic nanoparticles can be used to enhance contrast for MRI, to apply localized (albeit small) forces on cells, and to capture and purify proteins or cells from a mixture.[429,758] For any of these applications the surface must be functionalized with ligands for binding to the desired target. Iron−platinum alloys are one of the few magnetic materials on which stable, thiol-based SAMs can form. Xu and coworkers have several recent reports using thiol chemistry to functionalize FePt nanoparticles; these particles are useful for separations.[64−66] In one example the FePt particles were decorated with a thiol derivative of vancomycin. These particles can capture Gram-negative[65] and Gram-positive[64] bacteria at concentrations $<10^2$ colony forming units per milliliter (cfu/ml); this value is below that detectable by traditional methods (Figure 29b and c). In another demonstration nitrilotriacetic-acid-modified FePt particles were used to extract His-tagged proteins from cell lysates.[66]

9.6.3. Nanoparticles for the Polyvalent Display of Ligands

Gold nanoparticles are easy to synthesize and functionalize (see section 6).[443] These properties make them a common platform for studies of polyvalent molecular recognition and bioinspired self-assembly of nanoparticles.[759] Because many of these examples have been extensively reviewed in recent years,[443,760] here we will only discuss several outstanding examples that take advantage of the ability to display multiple ligands on the surfaces of nanoparticles.

Nanoparticles with appropriately functionalized surfaces can specifically bind different proteins. For example, by forming mixed monolayers of EG_3−SH and a biotin−tiopronin conjugate on gold nanoparticles, Zheng and Huang demonstrated binding of streptavidin with negligible nonspecific binding of other proteins.[761] In related work Rotello and co-workers used nanoparticles (gold and CdSe) with charged monolayers to recognize and bind to chymotrypsin (ChT).[762-765] Depending on the composition of the monolayer on the particles, there are several different outcomes of binding. Upon binding to hydrophobic, negatively charged nanoparticles (85% mercaptoundecanoic acid and 15% octanethiol), ChT is inhibited and denatured.[763] Negatively charged nanoparticles with a more hydrophilic SAM, HS-$(CH_2)_{11}$−EG_4−COOH, inhibit ChT but do not denature it.[764,766] The density of negatively charged headgroups with both alkyl and EG linkers as well as the ionic strength influence the binding of the nanoparticles to ChT.[765] More recently, the same research group has demonstrated enhanced substrate selectivity for nanoparticle-bound ChT due to attraction of positively charged substrates to the negatively charged SAM on the nanoparticles.[764] These observations suggest that multivalent[425] interactions of the nanoparticle surface with the protein surface are, in part, responsible for the observed inhibition of protein function.

Rotello and co-workers also used gold nanoparticles with SAMs of positively charged alkanethiolates to inhibit the transcription of DNA.[767] The nanoparticles bind to the anionic phosphate backbone and sterically block the transcription enzyme, T7 RNA polymerase, preventing the production of RNA products. Similarly functionalized gold nanoparticles can also induce helicity in short peptides (17 residues) by binding to aspartic acid residues spaced i, $i + 4$, $i + 7$, $i + 11$ (defining one face of the helix).[768] The proposed mechanism for both of these processes relies on multiple binding sites being presented by the surface of the nanoparticle.

Gold nanoparticles capped with SAMs of a thiol derivative of vancomycin (see section 9.6.2) are more active than monomeric vancomycin against both vancomycin-sensitive and vancomycin-resistant bacterial strains.[63] TEM images of *E. coli* after treatment with the nanoparticles shows that they bind to the outer membrane of the bacteria (Figure 29a). Control nanoparticles protected with monolayers of Cys do not have significant activity against *E. coli,* and TEM images show no binding of the particles to the membrane.

Penadés and co-workers used gold nanoparticles to present multiple copies of carbohydrates involved in mammalian cell−surface recognition.[769-771] Using SPR and TEM, they studied the calcium-mediated, self-recognition of gold nanoparticles coated with SAMs of several oligosaccharides including a Lewis X (Le^x) trisaccharide and the disaccharide lactose.[770] Gold nanoparticles coated with SAMs displaying lactose can also reduce the progression of experimental lung metastasis in mice.[769] The roughly spherical presentation of a chemically well-defined surface of carbohydrates is hypothesized to be essential for the observed activity.

10. Challenges and Opportunities for SAMs

SAMs represent one of the best systems available for studying the contributions of molecular structure and composition to the macroscopic properties of materials. They provide organic surfaces whose composition, structure, and properties can be varied rationally. The extensive characterization of SAMs, especially those formed by n-alkanethiols adsorbed on planar, polycrystalline films of gold, has provided a broad understanding of several aspects of these systems including (1) thermodynamics and kinetics of their formation, (2) organization and conformation of the adsorbates, (3) intrinsic properties of the organic films (e.g., thickness, stability, durability), (4) influence of chemical composition on some macroscopic properties of the films (e.g., wettability, resistance to corrosion, or protein adsorption), and (5) practical considerations for working with these systems (e.g., how to prepare surfaces of mixed composition, how to exchange one SAM for another, how to desorb SAMs selectively, how to pattern SAMs in the plane of the substrate).

Nevertheless, SAMs have passed through their initial growth spurt and are now in a sturdy (but sometimes misunderstood) adolescence. Although SAMs are widely used in nanoscience and technology, many of the commonly accepted aspects of their structure and of processes they undergo remain more an artifact of collective belief than solid, scientific facts; examples include the mechanisms of adsorption of alkanethiols on metal surfaces in solution, the fate of the hydrogen from the thiol during this adsorption, the surface mobility of adsorbates, the nature of defects, and the fundamental issue of structure and order of most organic thiols when chemisorbed.

Many significant opportunities remain for fundamental studies of SAMs. One area of opportunity is the development of new models and additional tools for the characterization of the types of complex SAMs that are emerging as critical components for applications in both biology and nanoscience. It is not clear that the existing structural model developed for SAMs formed from alkanethiols with small terminal (ω) functional groups (on planar, metal (Au, Ag, Cu, Pd) substrates with dominant (111) textures) is sufficient to correlate the molecular composition of complex SAMs−ones formed from molecules that do not have linear (cylindrical) shapes or ones formed on substrates with nonplanar geometries, e.g., nanoparticles−to their properties. A second area of opportunity is simply the expansion of the classes of molecules that form SAMs and of the materials that support them. New adsorbate chemistries and alternative substrates might eliminate some of the types of defects common for SAMs of alkanethiolates on metals (though they also could introduce new types of defects) and might serve to enhance stability during demanding applications. A third opportunity is to expand the variety of functions exhibited by SAMs and the dynamic behaviors of SAMs. SAMs formed from alkanethiols are quasi-equilibrium structures that do not exhibit the range of complexities found in dynamic, out-of-equilibrium systems. There also remain important aspects of the structures of

SAMs that cannot be controlled effectively. Of these, methods to control defects and manipulate lateral gradients in composition at molecular length scales stand out as particularly important unsolved problems.

10.1. Rules for “Designing” Surfaces

For SAMs the convenient “rule” widely used to design new assemblies is a simple one, in fact, overly simple: “α,ω-functionalized alkanethiols will form ordered SAMs with the ω-terminus presented at the exposed surface”. The obvious problem with this rule is that it assumes that the organization and conformation of n-alkanethiols with small terminal (ω) functional groups ($-$OH, $-$CN, $-$COOH) and their structure$-$property correlations apply to *all* SAMs formed from ω-functionalized derivatives of these molecules. It does not account for a number of parameters that influence the resulting structure of the organic surface, including steric incompatibilities, differences in free volume of the molecules, lateral segregation in multicomponent assemblies, and interactions with neighboring molecules and the surface.

The influence of geometry, steric effects, electrostatic charge, and concentration of surfactants on the resulting structure of micelles and other self-assembled structures in solution are well-understood qualitatively for “simple” molecules (ones where the shape is roughly cylindrical or conical). These effects provide the basis for a clear set of rules, or guidelines, for designing new surfactants and rationalizing the relatively simple types of structures (spheres, cylinders, tubes) assembled from them.[474] The development of guidelines for designing SAMs that predict the organization and composition of the monolayer and incorporate all of these elements remains to be worked out.

10.2. New Methods for Characterizing SAMs

The initial studies made of SAMs required and benefited from the development of new protocols and methods for examining the organic interfaces formed by self-assembly. These advances, in turn, provided an opportunity for progress in research on interfacial phenomena; one example notably exploited in studies explored the connections between the molecular structure and composition of surfaces and the macroscopic property of wettability.[24,147,772] The combination of data from RAIRS, contact angle measurements, optical ellipsometry, XPS, electrochemistry, STM, and other techniques provided a reasonably clear understanding of the molecular-scale order in these systems—that is, we now know the *average* molecular organization and some details about the local environment of the alkane chains in the monolayer and the disposition of functional groups at the ambient interfaces of SAMs.[22] The structural dynamics of SAMs that are weakly ordered and the structural organization of SAMs formed by molecules that are geometrically different from n-alkanethiols or from mixtures of complex adsorbates, as a class, remain largely uncharacterized.

The nature of the defects present in SAMs is also a challenging issue. SAMs tend to minimize the populations of defects in their organization, but minority defects can never be fully excluded in a SAM. It is now understood, however, that these defects can be vitally important to many experiments conducted with them. For some applications such as organic and molecular electronics, the defects actually may determine many of the observed behaviors. Understanding the detailed nature of local defects in SAMs probably requires new protocols and analytical tools.

10.3. New Systems of SAMs

The most studied and most widely used system of SAMs is that of structurally simple thiols on metals, especially gold, and some semiconductors (gallium arsenide, II/VI materials such as cadmium selenide and zinc sulfide). Many combinations of ligands and surfaces other than RSH/metals have been studied but to varying degrees (Table 1). Each system presents its own set of problems, and the design of new systems tends to rely on a reasonably limited range of interactions (e.g., polar functional groups ($-$OH, $-$SH, $-NH_2$) for metal surfaces and polar charged groups ($-PO_3^{2-}$, $-SO_3^-$, $-COO^-$/COOH) for metal oxides). There remain many opportunities to apply the diversity and breadth of knowledge in organometallic chemistry to the design and characterization of new SAMs. Some of these opportunities include (1) new SAMs for technologically relevant semiconductors (Ge, InP, GaN), (2) SAMs that are orthogonal to one another, that is, SAMs that will form selectively on one metallic surface in the presence of another, (3) SAMs for compliant substrates and organic polymers, and (4) SAMs (and appropriate substrates) that are stable for longer durations and under harsher conditions, e.g., heat and abrasion, than those presently known.

10.4. SAMs with Different Physical Properties

SAMs offer, in principle, the opportunity to design ultrathin materials with a wide range of physical properties. Some of the physical properties of SAMs examined already include their wettability, electrical properties (resistivity, dielectric behavior), and ability to resist adsorption of proteins. Other physical properties remain relatively, or completely, unexplored: magnetic[773] and (electro)optical[647] responses, quantum effects,[774] and electrowetting.[317,775] Perhaps the most important characteristic of organic surfaces found in biology is their ability to adapt and respond dynamically to their environment and to internally generated signals. There are few examples of SAMs that can respond, albeit to a limited degree, to external factors (light,[776] electrical potential[317,775,777]) and none that display the same dynamic range and responsiveness common to even the simplest biological systems.

10.5. In-Plane Patterning

Heterogeneity in the composition, topography, and order of surfaces significantly impacts their physical properties and, consequently, all applications. Controlling nonuniformity at a molecular scale (~1−2 nm) in SAMs is important for, among other things, (1) improving the ability of SAMs to resist the adsorption of proteins, (2) studying chemical interactions that require cooperative binding events such as in multivalent systems, (3) understanding the nature of the solid/liquid or solid/gas interface, and (4) exploiting SAMs as active structural elements in complex functional devices, notably as the mediators of electron transport in metal/organic/metal junctions. The capability to position molecules, and perhaps more importantly specific *defects*, laterally within a SAM with molecular-level precision does not presently exist.

The ability to manipulate the organization of SAMs microscopically is, in fact, quite advanced. Currently, so-called "top-down" methods for patterning SAMs (soft lithography,[130,492] scanning probe lithography,[132−134,165] e-beam lithography[529]) can generate patterns of SAMs where the critical dimensions in the plane range from tens of nanometers to millimeters. Self-assembly, however, appears to be a better strategy in many applications for patterning SAMs at the molecular scale than "top-down" approaches. Mixed SAMs formed from asymmetric disulfides present one approach for placing molecules of different composition near each other on a surface, but reorganization of the surface during and after formation of the monolayer complicates the placement of the components in the film. STM studies on the organization of SAMs formed with hydrophilic and hydrophobic components suggest that these systems are often heterogeneous because the molecules rearrange or phase separate in the plane to form small (~15 nm^2) islands of uniform composition. Designs of asymmetric disulfides that contain cross-linked groups or asymmetric sulfides could minimize this effect.

11. Outlook and Conclusions

Self-assembled monolayers are a prototypical form of nanotechnology: the molecules that form the SAM carry the "instructions" required to generate an ordered, nanostructured material without external intervention. SAMs demonstrate that molecular-scale design, synthesis, and organization can generate macroscopic materials properties and functions. Although the details of the thermodynamics, kinetics, and mechanisms of assembly will differ significantly, SAMs establish a model for developing general strategies to fabricate nanostructured materials from individual nanometer-scale components (molecules, colloids, or other objects).

SAMs are important components of many other forms of nanotechnology. Because SAMs can assemble onto surfaces of *any* geometry or size, they provide a general and highly flexible method to tailor the interfaces between nanometer-scale structures and their environment with molecular (i.e., subnanometer scale) precision. SAMs can control the wettability and electrostatic nature of the interfaces of individual nanostructures and thus their ability to organize into large assemblies. SAMs add chemical functionality and thermodynamic stability to the surfaces of relatively simple inorganic nanostructures (quantum dots, superparamagnetic particles, nanowires) and make it possible to connect them to more complex systems, e.g., biological systems.

SAMs support a number of other forms of nanotechnology: because SAMs are the most highly developed method for modifying the interfacial properties of surfaces and nanostructures are predominantly "all surface", they are broadly useful in modifying the properties of nanostructures "by design". Whether or not nanoscience will produce a technology that revolutionizes the way we live and interact as a society is not clear, but many of the developments in nanotechnology will depend on improvements to interfacial chemistries.

For some applications—especially those in biology—the progress of interesting and useful nanotechnologies will depend on advancing the understanding of the structural aspects, thermodynamics, and kinetics of existing systems of SAMs and establishing new types of SAMs capable of dynamically responding to their environments. The basic understanding of SAMs and the factors that influence their structure and assembly have developed rapidly over the past 20 years, but the maturation of SAMs and its union with other forms of nanotechnology will probably take many years more.

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