

Chemisorbed Self-Assembled Monolayers

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1 INTRODUCTION

Since the second half of the twentieth century, the preparation and characterization of self-assembled molecular films on solid surfaces have attracted very great and widespread interest, both as a fundamental intellectual and technological challenge to chemists, physicists, and materials scientists. The very possibility of designing and creating surfaces from scratch marks a profound departure from traditional surface science. One major attraction of surface-confined molecular assemblies is its potential to combine and manipulate topological, chemical, and functional features that are essential for a wide variety of technological applications such as microanalysis, biotechnology, nanofabrication, or corrosion protection, just to name a few examples.

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As we move further into the new century, self-assembled thin films seem indeed to offer almost unlimited opportunities for fundamental and applied surface science. At present, self-assembled monolayers (SAMs) constituted of chemisorbed species represent fundamental building blocks for creating complex structures by the so-called “bottom-up approach.” The self-assembly of molecules into structurally organized thin films exploiting the flexibility of organic and supramolecular chemistry has led to the generation of synthetic surfaces with well-defined chemical and physical properties. Chemical synthesis offers the appeal of an unparalleled level of control over the selection of functional features while hydrophobic and van der Waals interactions lead to the spontaneous association of the predesigned building blocks into stable, well-defined surface structures.

In this work, we first sketch the fundamental aspects of chemisorbed SAMs as a tool for building complex molecular systems. Using thiol SAMs as model systems, we first briefly review the self-assembly, surface structure, and stability under different experimental conditions. We also point out the characteristics of SAMs that make them suitable especially for building active micro- and nanostructured molecular systems on surfaces, and stress their limitations resulting from defects, contaminants, and disorders. Finally, we present examples of interfacial architectures drawn from supramolecular and covalent systems to illustrate the potential of SAMs as robust platforms for functional 3D structures on solid substrates.

2 BASIC CONCEPTS ON SAMs

Self-assembly is the construction of systems without guidance from external sources other than those provided by the environment.¹ SAMs are examples of intermolecular self-assembly that takes place at different interfaces.²

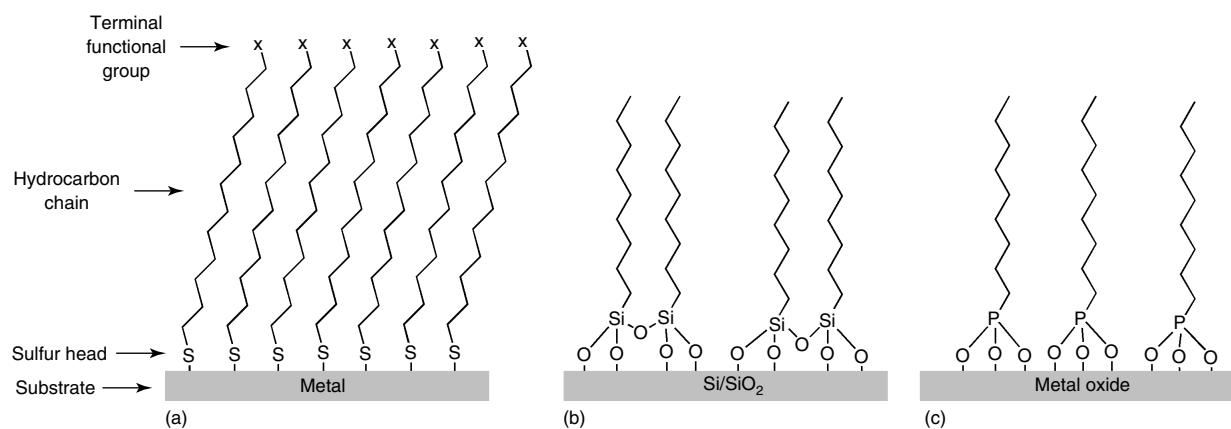


Figure 1 Chemisorbed SAMs. (a) Thiols, (b) silanes, and (c) phosphonates. Panel (a) describes the typical structure of chemisorbed alkanethiolate self-assembled monolayers on metal surfaces.

In particular, solid surfaces are often used as scaffolds for the construction of these supramolecular systems at gas–solid and gas–liquid interfaces. In fact, these two-dimensional structures, usually with a thickness between 1 and 3 nm, are spontaneously formed on a variety of solid surfaces such as metals, semiconductors, and oxides by different molecules or mixtures of different molecules from both gas and liquid phases.³ The thickness can be precisely tuned through the molecular dimension and its arrangement on the surface.

In a typical SAM, the molecules (building blocks) are bonded to the solid substrate by a reactive head that provides a strong molecule–substrate link to the system (Figure 1).³

Metals (Me) (such as gold, silver, and copper) easily react with thiol, alkylsulfide, or alkyldisulfide molecules forming a strong covalent S–Me (thiolate) bonds (typically ≈ 2 eV), in comparison the C–C bond is ≈ 3.5 eV (Figure 1a).^{3,4} On the other hand, hydroxyl groups present on Me, Si, and glasses can react with alkylchlorosilanes, alkylalkoxysilanes, and alkylaminosilanes yielding covalent Si–O–Me or Si–O–Si (siloxane) bonds (4.6 eV)^{2,5,6} (Figure 1b). Also oxidized surfaces react with alkylphosphonate molecules^{7–9} and alkylphosphates^{10,11} forming P–O–Me bonds (Figure 1c).

On the other hand, dispersive forces between molecules stabilize the supramolecular assembly introducing long- or short-range ordering depending on the molecule and the substrate.^{2–4} The terminal group of the molecule provides chemical functionality to the SAM (Figure 1). They can be used to tailor the physical chemistry of the solid surface changing completely their properties, such as complexation or molecular recognition centers for sensing devices, microarrays, catalysis, and biocatalysis, and also to provide reactive chemical groups for linking other molecules in templating-directed synthesis for building pre-organized three-dimensional molecular architectures.³

3 CHEMISORBED SAMs

Silanes, alkylphosphonates, and alkylphosphates form dense SAMs on oxidized surfaces through chemical reactions that involve the surface OH groups of the substrate. Alkylsiloxane SAMs can be formed on the surface of SiO₂/Si,^{5,12–15} Al₂O₃/Al,^{16,17} quartz,^{18,19} and mica.^{20,21} The two-dimensional system seems to exhibit chemical,²² mechanical,²³ and thermal stabilities.²⁴ The self-assembly process takes place by exposing the oxidized surface to a solution containing the silane molecules. However, the SAM quality strongly depends on the hydrocarbon chain length, solvent, and temperature. In many cases, siloxane films involve extensive cross-linking,²⁵ and they are usually thick, not surface conforming, and have disordered alkyl chains.²⁶

Alkylphosphonates and alkylphosphates self-assemble on common engineering metals such as steel, stainless steel, aluminum, copper, and brass,²⁷ among many other oxidized surfaces such as Al,²⁸ Ti,⁸ and Zr.²⁹ Phosphonate SAM formation involves the adsorption of the phosphonic acid followed by heating. Layer formation of self-assembling molecules of alkylphosphonic acid on mica from ethanol involves nucleation, growth, and coalescence of densely packed islands of phosphonates.³⁰ The structure of islands depends on the length of alkyl chains. Self-assembly of phosphonates has also been observed from aqueous solution using octylphosphonic acid. The height of these islands was practically equal to the length of molecule indicating the formation of a single molecular layer. Infrared reflection–absorption spectroscopy indicates that phosphonate SAMs on Zr(IV) have alkyl chains in a liquid-like environment.³¹ A higher degree of order and packing density within the monolayers was found for alkyl phosphates with alkyl chain lengths exceeding 15 carbon atoms self-assembled on Ti surfaces.³² The shift of the symmetric and antisymmetric C–H stretching modes in

the IR spectra to lower wave numbers observed is consistent with higher two-dimensional crystallinity. Experimental data also show that the molecules in the SAMs have an average alkyl chain tilt angle of 30° to the surface normal and intermolecular spacing of 0.5 nm similar to thiol SAMs on Au surfaces.

SAMs based on organophosphonates are more durable than siloxane films.^{32,33} Phosphonate SAMs are surface conforming and more ordered than siloxane layers. In fact, it was found that on native titanium oxide loading for the phosphonate was four times greater than that for the siloxanes, and also the hydrolytic stability of the siloxanes was poor.³³ The metal bisphosphonate SAMs are shown to be receptive to complexation by organic acids and acid-containing polymers such as fluoropolymers and ethylene-*co*-methacrylic acid, opening interesting technological applications.²⁷

Selenols (Se) on metals have been explored as an alternative to thiol SAMs. These monolayers are similar to thiol SAMs (Figure 1a) but with the replacement of S atom by Se. A comparative study of benzenethiol and benzeneselenol on Au(111) has shown that the selenol SAMs are more ordered than the thiol SAMs, but they are less strongly bound to the gold substrate than the thiol analog.³⁴ In contrast, it has been recently reported that the selenium-based SAMs are more stable than their sulfur analogs.³⁵ More experimental work on these systems is needed for a better understanding of selenol SAMs.

However, our knowledge of silane, phosphonate, and selenol SAMs at the molecular level is considerably smaller than that we have for thiolate SAMs on metals and semiconductors, in particular for thiols on Ag and Au surfaces. These SAMs exhibit well-ordered (crystalline) structures that can be characterized by surface science techniques at molecular or even at submolecular level.^{3,4} Therefore, in the next section, we concentrate on the thiol–Au(111) and Ag(111) SAMs, although information concerning thiol self-assembly on other surfaces such as metal and semiconductor surfaces are also included.

4 THIOL SAMs ON Au(111)

4.1 Sam Preparation and Structure

Preparation of thiol SAMs can be achieved from gas and liquid phase by using thiols (aliphatic, aromatic), alkyldisulfides, or dialkylsulfides,^{2–4} on clean single crystal, rough or nanocurved surfaces of metals,^{3,4} and semiconductors.^{36,37} The SAMs can be studied by using a large variety of surface characterization technique.³⁹

The gas phase self-assembly is performed in UHV (ultra-high vacuum) chamber by introducing small amounts of

the reactive molecules that adsorb onto the clean substrate surfaces. This method is applied to short molecules with high vapor pressures, and it results in SAMs of good quality that can be “*in situ*” characterized by all the usual surface science techniques.³⁸ STM (scanning tunneling microscopy) and LEED (low energy electron diffraction) results show that self-assembly initially involves, in the case of Au(111), the formation of lying down phases. By increasing the thiol pressure, the system undergoes a phase transition from the lying down to dense phases of standing up molecules.^{2–4} The stable phases detected at equilibrium are the $\sqrt{3} \times \sqrt{3}$ R 30° and its $c(4 \times 2)$ superlattice for Au(111) (Figure 2),^{2–4,40} $\sqrt{7} \times \sqrt{7}$ R 19.1° for Ag(111).^{2,3,41} On the other hand, for Cu(111) two structural phases are observed, a “honeycomb” phase and a pseudo-(100) reconstructed surface phase.⁴² The nearest neighbor distances in these cases is between 0.5 nm in Au(111)^{2–4} and 0.43–0.47 nm in Ag(111),^{2,3} close to the distances observed in solid alkanes by X-ray diffraction. Coverage consistent with these structures has also been observed for thiols on Ni(111).⁴³ Dense phases of standing up alkanethiols on GaAs³⁷ and InP⁴⁴ have also been reported. The tilt angle of the molecules in the standing up configuration is ≈ 10 – 19° for Ag(111) and Cu(111),^{2,45,46} 14 – 18° for Pd,⁴⁶ and 30 – 40° for Au(111).^{2,47,48}

In the case of self-assembly from liquid phase, a clean Au, Ag, or Cu substrate is immersed in thiol containing solutions of ethanol, hexane, toluene, benzene, or neat thiols depending on the substrate–molecule system, for times ranging from minutes to days depending on the thiol molecule.^{2,3} Well-organized SAMs with crystalline order usually requires times ranging from 12 to 24 h as chain organization is a slow process. The role of the solvent is crucial to obtain high-quality SAMs. It is well known that the molecular environment around a supramolecular system is also of prime importance to its operation and stability. In fact, some solvents are able to form hydrogen bonds, and exhibit electrostatic and charge-transfer properties. Therefore, they can interact strongly with the supramolecular assembly.

For instance, for reactive metals, such as Cu, hexane or toluene is preferred to ethanol to avoid oxide formation, although it has been recently claimed that better results are obtained by using self-assembly in alkaline solutions where the oxide is completely reduced by the thiol.⁴⁹ In the case of dense standing up phases of dithiol SAMs on Au, the self-assembly from hexane solutions is preferred as it has been observed that ethanol induces oxidation of the terminal SH group leading to disulfide formation.^{50,51}

In solution deposition (ethanol, hexane), the lying down phases reported on Au(111) substrates are not observed and the system evolves directly to the same standing up structures ($\sqrt{3} \times \sqrt{3}$ R 30° and $c(4 \times 2)$ superlattice)

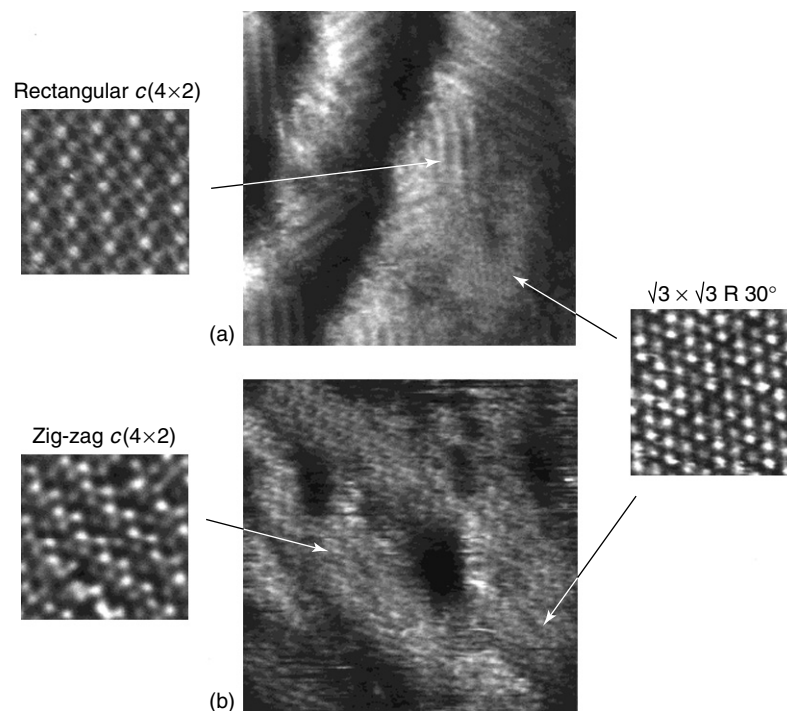


Figure 2 STM images showing well-ordered domains of alkanethiols on Au(111): (a) hexanethiol ($20 \times 20 \text{ nm}^2$) and (b) mercapto undecanoic acid ($18 \times 18 \text{ nm}^2$)-covered Au(111) surfaces. The rows and the dense regions correspond to $c(4 \times 2)$ and $\sqrt{3} \times \sqrt{3} \text{ R } 30^\circ$ domains, as shown in the high-resolution ($4 \times 4 \text{ nm}^2$) STM images. (Reproduced from Ref. 40. © American Chemical Society, 2001.)

observed in gas phase.⁴ For Ag surfaces and also for Cu substrates, the thin native oxides (silver oxide or copper oxides) are spontaneously reduced by the thiol molecules to metallic Ag or Cu while they are oxidized to sulfonates. Afterward the fresh metallic surfaces react with additional thiol molecules resulting in ordered SAMs.^{52,53} In the case of Pd, the reactive Pd surface initially breaks the S–C bond of the thiol molecules producing a diluted sulfide layer that practically “passivates” the Pd surface allowing further chemisorption of thiol molecules.^{54,55} Thus, in this case the surface is composed by a mixed sulfide–thiol adlayer. Some amount of S has also been observed for thiol self-assembly on Cu surfaces.⁵⁶ *In situ* STM in electrolyte solutions has also been shown that thiols form (2×2) and $\sqrt{3} \times \sqrt{3} \text{ R } 30^\circ$ on Pt(111) surfaces.⁵⁷ The formation of alkanethiols SAMs on Pt(111) have also been observed by XPS and complementary techniques.⁵⁸ Dense SAMs of long alkanethiols can be formed on polycrystalline Ni and Ni(111) surfaces in aqueous solution under potential control in order to eliminate the NiO layer from the surface.⁵⁹

Irrespective of the metal, thiol covered metal exhibits in XPS (X-ray photoelectron spectroscopy) data the characteristics of a “thiolate bond” (162 eV).⁴ This analysis also shows, in some cases, small amounts of adsorbed S (161 eV), with the exception of the above-mentioned Pd surfaces that have about 0.4 monolayer of S as sulfide, and

free thiols (163 eV). The latter can be removed by carefully rinsing with the solvent.

The self-assembly process of these molecules is accompanied by a reconstruction of the metallic surfaces. In fact, experimental and theoretical evidences seem to indicate that the Au(111),⁴ Ag(111),^{41,60} Cu,⁶¹ Ni(111),⁴³ and Pd(111)^{53,54} surfaces reconstruct resulting in the case of Au(111) in the formation of a metal adatom–thiolates complexes on the surface.⁴

From the above discussion, we can conclude that SAMs of thiols can be formed on different metal and semiconductor surfaces opening a wide range of possible applications in technology. In the next section, we discuss the presence of defects, contaminants, and the stability of these systems under different environmental conditions that could seriously limit their applications.

4.2 Defects, contaminants, and stability

The stability of the thiol SAMs is extremely important for their applications. Thermal stability is restricted up to $\approx 100^\circ \text{C}$.⁶² Increasing the temperature above this value results in thiol desorption mainly as disulfides and finally as thiol molecules. Recent results from thermal-programmed desorption have shown that disulfides are desorbed at around 400 K.⁶³ These disulfides arise from the thiol

molecules in standing up configuration present in dense, well-defined SAMs. On the other hand, desorption from the lying down molecules of diluted thiol phases has been observed around 500 K. Finally, desorption of an appreciable amount of gold-containing molecules is observed around 700 K, thus supporting the presence of thiolate–gold complexes. The stability range of thiols is smaller than that exhibited by self-assembled silane monolayers that remain stable up to 500° C.⁶⁴

Chemical stability is also an important factor. In ambient conditions and also in liquid media such as ethanol, the presence of light and O₂ leads to thiolate oxidation to disulfides and also to sulfonates.⁶⁵ Both species are easily desorbed from the surface so that continuous exposure results in SAMs degradation. It has been proposed that O₃ molecules react with the S heads forming oxidized S products. This is supported by the fact that photolithography performed with UV radiation is usually employed to patterning thiol SAMs covered metals.⁶⁶ Oxidation takes place at a fast rate for short hydrocarbon chains.⁶⁷ Recent results of methanethiol SAMs on Au formed from ethanolic solutions of dimethyldisulfide indicate a rapid decomposition to form adsorbed S.⁶⁸ Rapid degradation yielding S species has been also reported for 4-mercaptopyridine on Au(111) surfaces.⁶⁹ Degradation of the SAM terminal groups has also been reported. The exposed–SH groups of hexanedithiol on Au(111) can form disulfide species with adjacent chemisorbed species and/or nonchemisorbed dithiol molecules during self-assembly in ethanolic solutions.⁵⁰ This process is avoided by performing the self-assembly process in hexane, and in the absence of O₂ and light. Also light and O₂ cause the oxidation of amine-terminated SAMs.⁷⁰ Using time-of-flight secondary ion mass spectrometry (ToF-SIMS), the oxidation of the amino groups to nitroso groups was evident when exposed under ambient conditions.

Electrochemical stability is also important in device fabrication and SAM metallization.⁷¹ In many devices such as amperometric sensors and biosensors, thiol SAMs are important structural or functional units.⁷² Thiol exhibits reductive and oxidative desorption at threshold potentials (which depend on the chain length) below or above which they are reductively desorbed or oxidized, respectively. Therefore, the potential reached by the system must be within the stability range of the thiol SAMs. For reductive desorption the stability range of the SAM increases to ≈ 0.04 V/CH₂ in aqueous solutions and 0.025 V/CH₂ in 95% methanol + 5% water, revealing the important role of hydrophobic interactions in SAM stability.⁷³ In general, no changes have been reported for reductive desorption of thiol SAMs in the pH range 5–13, but the system becomes more unstable at lower pH values.⁷¹ At a constant pH and for a given thiol, the electrochemical stability

range increases as Au⁷¹ < Ag⁷¹ \approx Ni⁷⁴ < Pd⁷⁵ \approx Cu.⁷¹ Therefore, for electrochemical applications, one can select the metal considering the stability range. Thus, for SAMs metallization from electrodeposition Cu seems to be an excellent candidate.

SAMs exhibit structural and conformational defects. Structural defects consist of molecular vacancies, missing rows, and domain boundaries resulting from the nucleation and growth process while conformational defects involve chain disorder.^{2,4} Chain disorder for aliphatic short thiols is revealed by the asymmetric stretching of the methylene groups detected at wave numbers >2920 cm⁻¹.^{47,48} On the other hand, well-ordered chains, typical of long thiols (C > 12), exhibit the asymmetric stretching of the methylene groups at wave numbers <2920 cm⁻¹. Thus, the degree of chain ordering increases markedly as the hydrocarbon chain length is increased. In fact, for aliphatic thiols the chain to chain interactions increased about 1 kcal mol⁻¹/CH₂ unit. However, even for this crystalline SAMs, chain disorder appears at step edges and around Au vacancy islands, formed during thiol adsorption.⁴⁸ The control of the structural ordering of aromatic thiol SAMs has also become a crucial issue in tailoring various SAM properties. It has been demonstrated that the degree of order for aromatic thiol SAMs can be remarkably enhanced by increasing the number of benzene rings in the molecular backbone.⁷⁶ For anthracene-based thiols, the molecules form long-range-ordered monolayers stabilized by parallel-displaced π – π stacking interactions.⁷⁷

Small amounts of contaminants can also be found in thiol SAMs.³ As mentioned before, usual contaminants are S—which is present as traces in as-received thiol or results from S–C bond cleavage for reactive metals (Pd, Ni, and Cu)—free-thiol (unbound thiols), thiol molecules trapped by chain–chain or hydrophobic forces in the organic layers, small amounts of oxides for reactive metals such as Cu or Ni when prepared from the liquid phase, and so on.

Both types of defects have strong impact in the applications of SAMs⁴: they are preferred path to incorporate ions, water, and metal atoms during evaporation on SAMs, and molecules into the SAMs. Therefore, the barrier properties of the monolayer and their ability to precisely control the metal-immobilize species distance (within the subnanometer scale) are lost. From the positive point of view, conformational disorder allows to incorporate by weak forces different species into the SAMs that can be then released to the environment by applying some kind of stimulus.

Finally, it should be noted that stability, contaminants, defects, and the metal substrate used are the crucial points to be considered when some kind of molecular architecture or device is built using SAMs as structural functional elements. Temperature, solvent, pH, oxidizing conditions, side reaction products, exposure to the atmosphere and light,

impurities, the metal substrate and its topography, among many others, are factors that should be taken into account in order to use these fascinating two-dimensional molecular platforms.

4.3 Building molecular structures by bottom-up approaches using SAMs

The strategies used to build more complex molecular architectures starting from SAMs involve different types of interactions. One possible way to classify them is the following: (i) nonspecific adsorption, (ii) covalent bonding, and (iii) specific adsorption. Each of these strategies exhibits advantages and disadvantages. Before discussing this point, we want to emphasize that the difference between “specific” and “nonspecific interactions” is difficult to be distinguished.⁷⁸ Following Ref. 78 here, we consider that “nonspecific” contributions originate mostly from electrostatic and hydrophobic interactions.

5 BUILDING MOLECULAR STRUCTURES BY BOTTOM-UP APPROACH USING SAMs

5.1 Nonspecific Interactions

Nonspecific adsorption of molecules and biomolecules on thiol covered metallic surfaces involves electrostatic and hydrophobic interactions. This strategy has a variety of advantages: it is simple, fast, direct, reversible, immobilize lipophilic molecules, and it allows retention of the three-dimensional structure of biomolecules.⁷⁹ The disadvantages are easy desorption by change of ionic strength, pH, or detergents, and random orientation of the molecules or biomolecules.

Proteins, dyes, phospholipids have been nonspecifically adsorbed onto the thiol monolayer.³ In the case of positively charged lipophilic ions such as methylene blue, they can be incorporated into the SAMs at structural and conformational defects and delivered to the environment under appropriate concentration gradients. The amount of incorporated dye results from two opposite effects: the presence of defects required for incorporation, which decreases with the hydrocarbon chain length of the SAMs, and the stabilizing effect of these chains by hydrophobic forces, which decreases as the chain length is reduced.⁴⁸ Maximum incorporation was found for C10–C12 alkanethiols. This approach is interesting to charge bioactive molecules into hydrophobic pockets at thiol-capped gold nanoparticles that can be delivered to the cell by thermal stimulus or under light.⁸⁰

Proteins have been adsorbed onto thiol SAMs.³ It has been shown that they are adsorbed more efficiently onto

hydrophobic-terminated thiols than onto hydrophilic (OH terminated) ones. In fact, hydroxyl-functional SAMs are of interest in biological applications for use as neutral surfaces, which minimize both protein adsorption and nonspecific interactions. On the other hand, inhibition of protein adsorption onto hydrophobic SAMs was achieved by simple adsorption of trimethylamine oxide, a small amphiphilic molecule on the SAM surface.⁸¹ The principle of osmolyte exclusion from the protein backbone seems to be responsible for the protein-resistant property of the surface.

Azurine has been immobilized on the hydrophobic surfaces (methyl terminated) of alkanethiol SAMs on Au.⁸² Reversible charge transfer from the Cu redox centers to the Au surface becomes more difficult as the length of the hydrocarbon chains is increased. Laccase has also been immobilized on COOH-terminated thiol SAM on Au(111). The enzyme shows a good catalytic activity for oxygen electroreduction.

Hybrid phospholipid bilayers consisting of an outer phospholipid monolayer on a thiol SAMs (formed by liposome or vesicle fusion or by the Langmuir–Blodgett technique) have been prepared by this approach.³ These bilayers exhibit extremely low capacitance values, so that they can be used in sensor devices to test ions and lipophilic molecules. Thiolipids can also be used as an alternative to directly form the hybrid bilayer on the metal surface (Figure 3).⁸³

However, hybrid bilayers are not suitable for protein incorporation because water is needed at the inner part of the bilayer to avoid protein denaturalization.⁸⁴ In order to avoid this problem, Au surfaces were functionalized with a short hydroxylated dithiol (dithiothreitol, DTT) which adopts a lying down configuration with the OH groups exposed to the environment.⁸⁵ Vesicle fusion on these DTT surfaces allows phospholipid bilayer formation with a water layer between the DTT SAM and the inner phospholipid monolayer. The phospholipid bilayer exhibits good fluidity as has been shown by *in situ* AFM (atomic force microscopy) imaging. These bilayers have been formed on both planar and nanostructured [SERS (surface enhanced Raman spectroscopy) active] gold surfaces.⁸⁵

Different enzymes have been immobilized on gold surfaces by nonspecific interactions after self-assembly of 5-(octyldithio)-2-nitrobenzoic acid (ODTNB).⁸⁶ The ODTNB includes a long chain in a short-length thioacid, which provides a heterogeneous-like alkanethiol layer after adsorption onto gold electrodes. Membrane-bound enzymes such as D-fructose dehydrogenase, D-gluconate dehydrogenase, and L-lactic dehydrogenase were immobilized onto ODTNB-modified gold surface simply by adsorption. The ODTNB allows both thioacid–enzyme electrostatic interactions and alkanethiolate–enzyme hydrophobic interactions that are important for these lipophilic, membrane-bound enzymes.

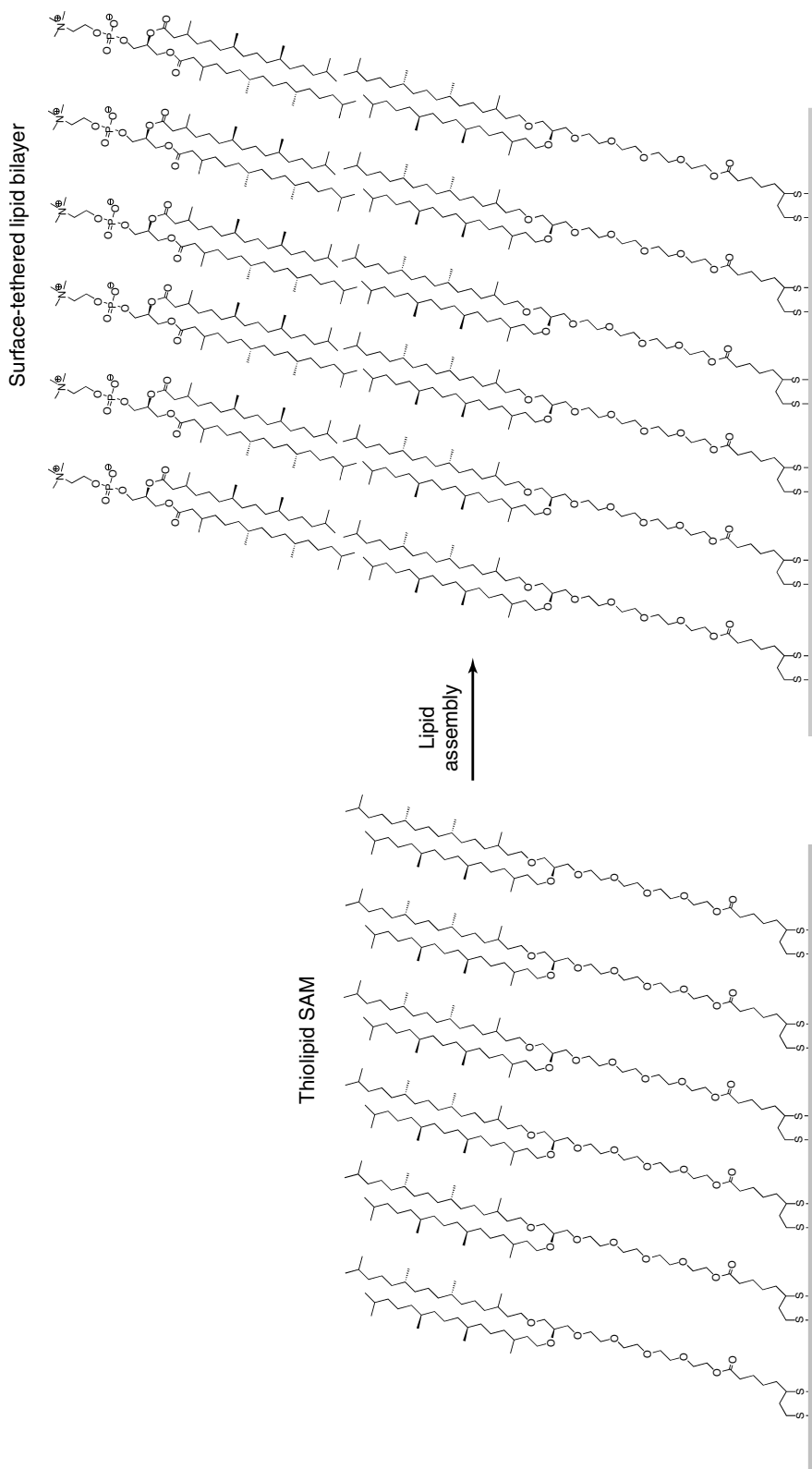


Figure 3 Molecular assembly of a thiolipid monolayer on a gold surface followed by the formation of a lipid bilayer.

Cationic redox polymers containing osmium–bipyridine complexes strongly interact with anionic enzymes, such as glucose oxidase and lactate oxidase.⁸⁷ In this approach, gold electrodes were first functionalized with SAMs of negatively charged thiols (mercaptopropionic, mercaptosulfonic, and mercaptoundecanoic acids) followed by alternate immersion in solutions of a positively charged redox polymer such as poly[(vinylpyridine)Os(bipyridyl)₂Cl^{2+/3+}], and a negatively charged enzyme such as glucose oxidase. Practically, a glucose biosensor and a lactate biosensor were fabricated via electrostatic layer by layer assembly.

5.2 Covalent Bonding

The covalent coupling route is more facile for the immobilization of molecules and biomolecules in terms of good stability and high binding strength. Gold substrates modified with thiols with suitable terminal groups can be functionalized with enzymes, catalysts, and redox species through standard organic reactions. Then, the modified surface can be used as a molecular recognition unit. Advantages of this method comprise good stability and high binding strength, while disadvantages involve random orientation, slow kinetics, and the irreversible character of the bond.

There are two different methods that can be used in this approach. The first one involves the synthesis of the species of interest with a pendant thiol group and then the self-assembly of these molecules and a diluent thiol on the metal substrates to form a mixed SAM. This is a simple approach but one needs to spend additional time in the synthesis of each thiolated species and also in the characterization of the resulting SAM. In particular, one must know the surface coverage, the surface structure, and the order of the SAMs formed by the thiolated species.⁸⁸ The second approach is to first assemble an SAM containing a terminal reactive group that can serve as a well-defined platform to bind the desired molecule by a chemical reaction. However, most chemical reactions exhibit low yields, low specificity, and difficulty in introducing the reactive functional groups.⁸⁹ Surface chemistry is much more difficult than solution chemistry because incomplete and side reactions lead to unreacted and by-product species that could be incorporated into the SAM covered surface.⁹⁰ In order to avoid these problems, the surface reaction should be quantitative, fast, resistant to side reactions, and easily monitored by routine surface characterization techniques. In the next section, we review some examples of surface chemistry modification of SAMs by covalent binding. It is important to note that most examples are given for Au surfaces, although, as shown in this chapter, modification could be adapted to large number of metal and semiconductor substrates that are able to be modified with different SAMs.

The Schiff-base reaction using glutaraldehyde as a cross-linker provides a covalent bridge between amine groups of biomolecules and amine-functionalized surfaces under moderate conditions. This reaction has been widely used for the construction of thiol-based biosensors. Thus, on a cleaned Au surface, cysteamine monolayer was formed and the terminal amino groups were exploited for cross-linking reactions using glutaraldehyde and 1,4-diamino anthraquinone used as mediator onto which the enzyme glucose oxidase was immobilized.⁹¹

Aldehyde-modified gold surfaces for amine-modified oligonucleotide attachment have also been reported.⁹² In this case, di(10-decanal) disulfide is added to the surface, forming an SAM with an aldehyde group sticking up from the surface. To this aldehyde group, amino-modified DNA can directly bind, replacing the oxygen. This forms a Schiff base, which is then reduced with sodium cyanoborohydride.

The flavin analogs, methylformylisoalloxazine, produced by replacing the carbohydrate tail of riboflavin with a methyl aldehyde group were covalently bound to an amino-terminated SAMs on gold surfaces.⁹³ This method results in an SAM of tethered, catalytically active flavin analogs.

Bioreactive surfaces on gold were prepared by self-assembly of hydroxyl-terminated dendron thiols self-assembled on gold and subsequent bridging reactions using generation-two amine-terminated dendrimers.⁹⁴ The hydroxylated SAM was activated by the homobifunctional cross-linker *N,N*-disuccinimidyl carbonate (DSC), and linked to amine-terminated dendrimers via bridging reactions.

Amino-terminated SAMs have demonstrated to be an outstanding platform for innovative developments in bioelectrochemistry. Willner and coworkers introduced a very elegant methodology based on the reconstitution of apo proteins on cofactor-modified electrodes as a general protocol to electrically contact redox enzymes with electrodes.⁹⁵ According to this approach, an electron relay unit is linked to the amino-modified electrode, and the cofactor unit is covalently tethered to the relay element. The native cofactor associated with the enzyme is eliminated from the protein to yield the respective apo-enzyme. The reconstitution of the apo-enzyme on the relay-cofactor monolayer introduces two key advantages in the molecular design of the bioelectrode: (i) the biomolecules are linked to the electrode in identical configuration, and (ii) the relay units are located between the cofactor and the electrode leading to a more efficiently mediated electron transfer.

This methodology was also extended to the molecular design of integrated enzyme electrodes consisting of diffusional cofactors and enzymes that reveal electron transfer communication with the electrodes. For example, “wiring” of glucose oxidase to gold electrodes was accomplished by bridging reconstituted enzyme with the electrode through

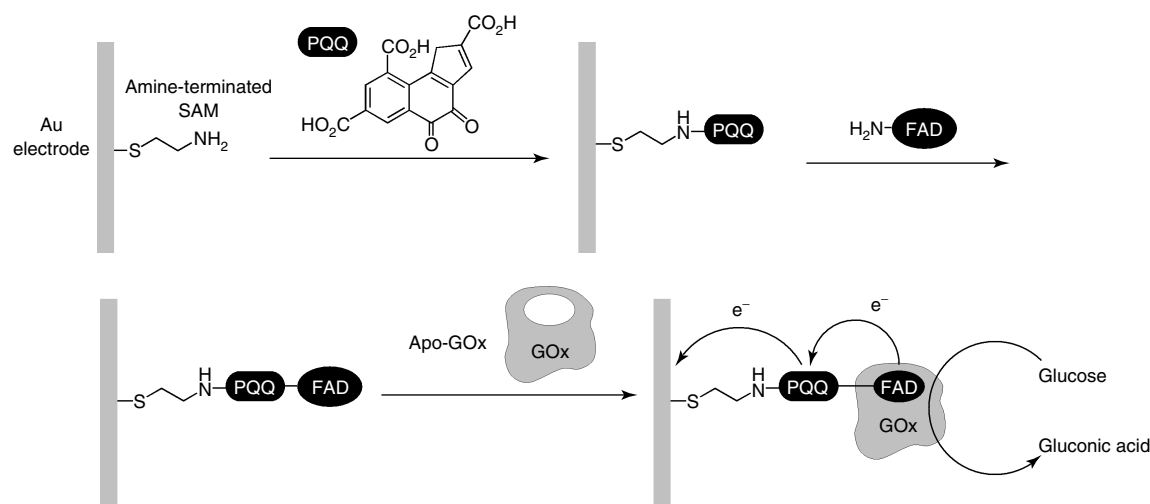


Figure 4 Surface reconstitution of apo-glucose oxidase on a PQQ/FAD interfacial architecture built up an amino-terminated self-assembled monolayer.

pyrroloquinoline quinone (PQQ) relay units (Figure 4). PQQ moieties were conjugated to an amino-terminated SAM-modified Au electrode, and subsequently *N*⁶-(2-aminoethyl)-flavin adenine dinucleotide (amino-FAD) was covalently linked to the PQQ sites. The reconstitution of apo-glucose oxidase onto SAMs derivatized with “bridged” FAD sites led to a structurally aligned enzyme monolayer connected to the gold electrode in which the PQQ electron relay units not only mediated the electron transfer between the FAD sites and the electrode but also activated the bioelectrocatalyzed oxidation of glucose. The electron transfer turnover rate was estimated to be 900 s^{-1} , a value which is similar to the exchange rate between the enzyme redox center and its native electron acceptor.

This modular approach based on the conjugation of NH_2 -terminated SAMs enables the incorporation of a wide

variety of building blocks in order to create new avenues for the assembly of the electrically contacted enzyme electrode. This was implemented with an aim of substituting the scarce amino-FAD cofactors with the natural FAD cofactor. The pyrroloquinoline quinone-monolayer-functionalized electrode was reacted with 3-aminophenylboronic acid and, subsequently, the native FAD cofactor was linked through the vicinal hydroxyl group to the boronic acid ligand. The reconstitution of apo-glucose oxidase on the FAD cofactor sites led to an electrically contacted enzyme electrode displaying a turnover rate of electrons between the redox center and the electrode of $\sim 700 \text{ s}^{-1}$.

Amino-terminated thiol SAMs on Au can also be modified with carbohydrates (Figure 5). An SAM of cysteamine is first formed on gold in ethanolic solutions. The

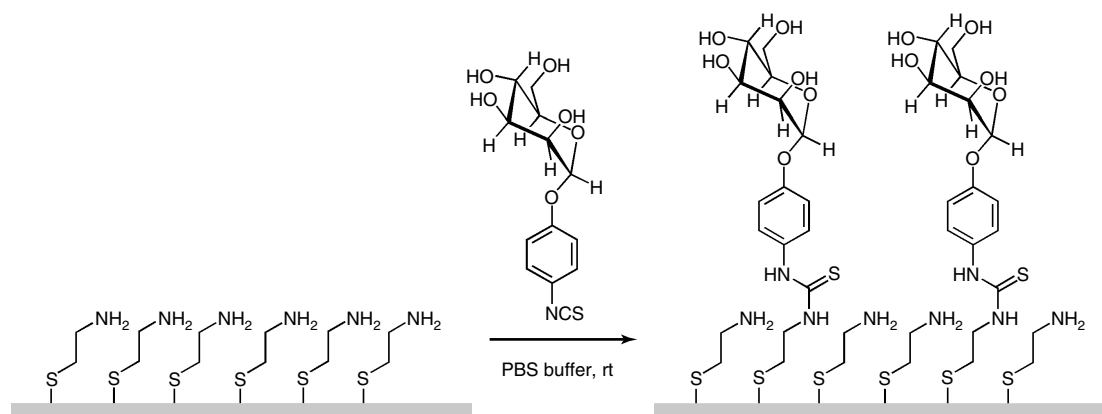


Figure 5 Construction of mannose-functionalized surfaces through conjugation of isothiocyanatophenyl α -D-mannopyranoside onto amino-terminated self-assembled monolayers.

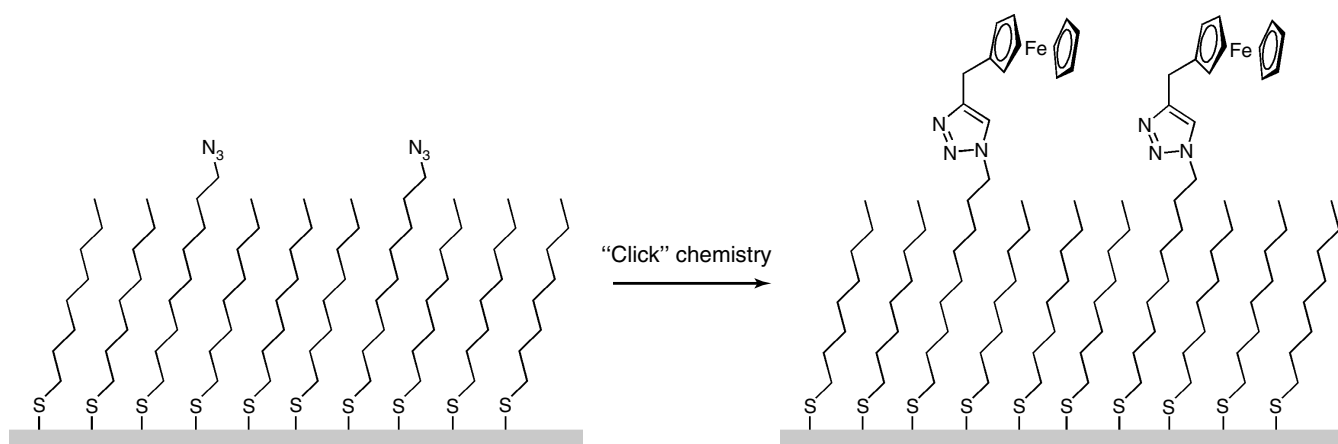


Figure 6 Covalent coupling of redox-active functional groups via a "click" chemistry approach.

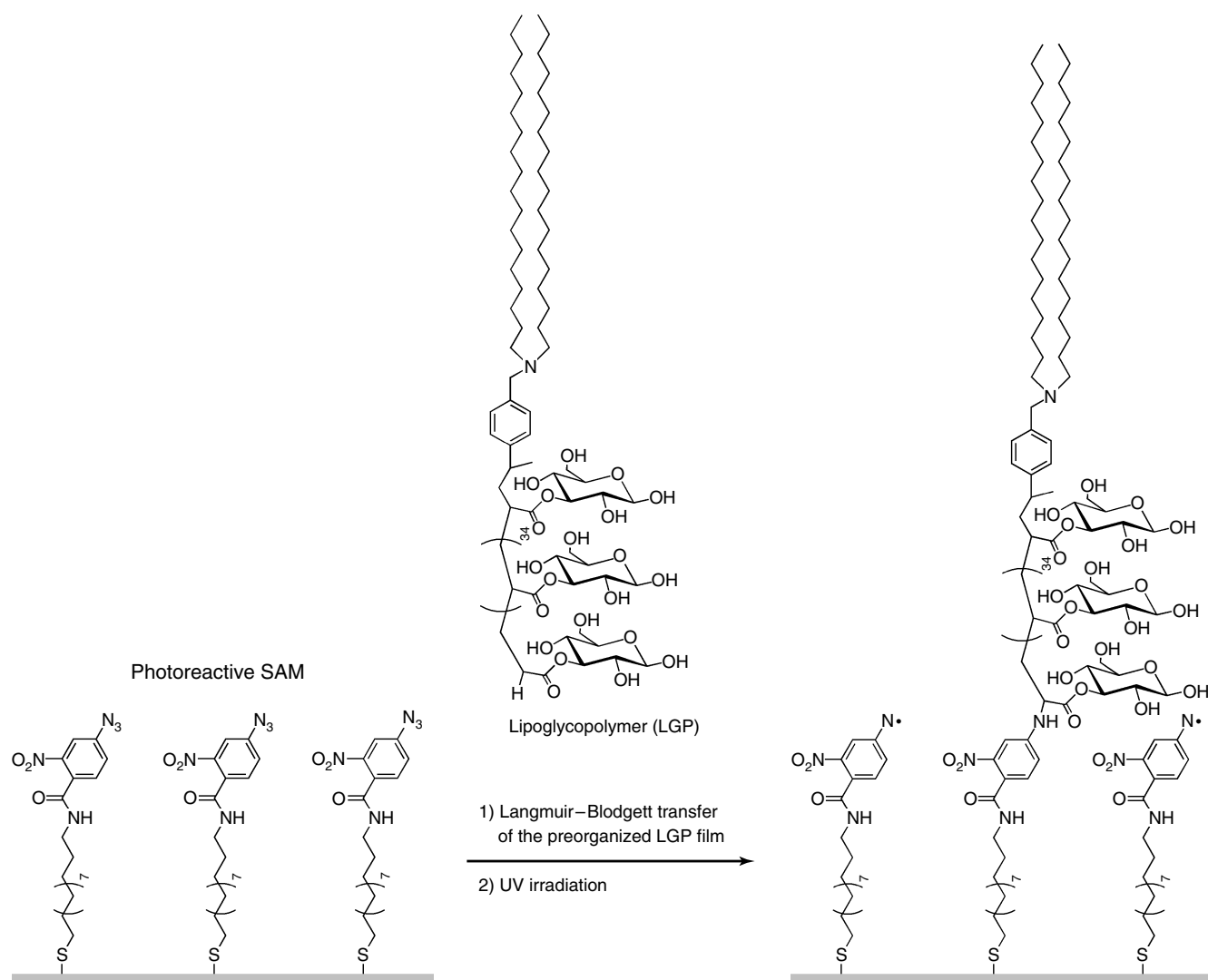


Figure 7 Photochemical attachment of lipoglycopolymers onto photoactive self-assembled monolayers.

resulting self-assembled cystamine monolayer-modified surfaces were then modified with isothiocyanatophenyl α -D-mannopyranoside in phosphate buffer (pH 7.4), to yield the thiourea-monosaccharide monolayer-modified electrodes of phenyl α -D-mannopyranoside.⁹⁶ This platform is used to build up stable assemblies of glucose oxidase (GOx) layers mediated by the recognition properties of concanavalin through carbohydrate–lectin interactions.⁹⁷

Mixed SAMs on gold electrodes from azido alkane thiols and various ω -functionalized alkanethiols were prepared. In the presence of copper(I) catalysts, these azide-modified surfaces are shown to react rapidly and quantitatively with terminal acetylenes forming 1,2,3-triazoles via “click” chemistry (Figure 6).^{98,99} In this way, thiol SAMs have been modified with complex functional molecules such as single-stranded DNA, porphyrin redox catalysts, and receptors for gold nanoparticles and other materials.

The use of photoactive SAMs has also been explored as a route to covalently anchoring supramolecular structures on solid surfaces. Recently, Knoll and coworkers introduced a new covalent immobilization procedure that utilizes photochemical surface attachment to assemble complex supramolecular architectures of defined orientation from aqueous solution (Figure 7).¹⁰⁰ First, the photoreactive surface is built up by making NH_2 -terminated SAMs to react with 5-azido-2-nitrobenzoic acid chloride (ANB) to introduce the photoreactive group. Then, a Langmuir–Blodgett trough was used to form an oriented molecular lipoglycopolymers (LGP) film at the air–water interface, and transfer it to the ANB-modified gold surface. Finally, efficient photoactivation of the LGP/ANB-terminated SAM interface under short-time UV irradiation results in the robust covalent anchoring of the LGP interfacial architecture.

On the other hand, the proximity of adjacent chains in SAMs makes it possible to perform chemical reactions between them, leading to “two-dimensional” extended covalently bound structures. This represents a different kind “covalent” modification of SAMs resulting in surfaces with different properties. For example, diacetylenes

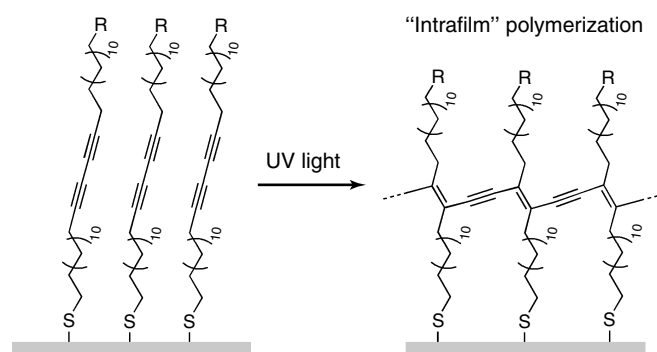


Figure 8 Light-induced “intrafilm” polymerization of diacetylene-containing thiolate self-assembled monolayers.

containing terminal mercapto groups form monolayers on metal surfaces.² Extensive experimental work demonstrated that irradiation of these monolayers with ultraviolet (UV) light causes polymerization of the molecular film (Figure 8).¹⁰¹ This is a remarkable observation, as polymerization of diacetylenes is only observed in well-ordered systems such as crystals or micelles. The fact that thiolate monolayers of diacetylenes can polymerize to give a so-called “blue form,” characterized by a prolonged conjugation length, indicates a high degree of structural order in these monolayers.

However, light is not the only stimulus enabling the formation of “intrafilm” covalent bonds; electrochemistry has also been exploited as a tool to manipulate the occurrence of “intra-chain” reactions. Recently, Roncali *et al.* described the electropolymerization of thiolate SAMs bearing a bithiophenic system leading to the formation of a stable electroactive extended conjugated system (Figure 9).¹⁰² The characterization of the electropolymerized monolayers by IR spectroscopy, ellipsometry, contact angle measurements, and XPS revealed the presence of compact monolayers. The analysis of the current–voltage characteristics of the monolayers by using AFM before and after electrooxidation showed that the enhancement of the effective conjugation resulting from electropolymerization leads to a significant increase in the transport properties.

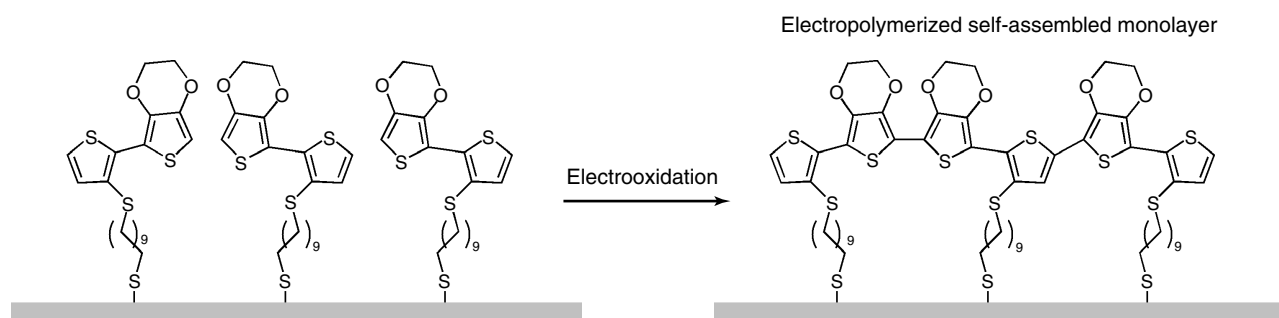


Figure 9 Electropolymerization of a 3,4-ethylenedioxythiophene-thiophene-terminated self-assembled monolayer.

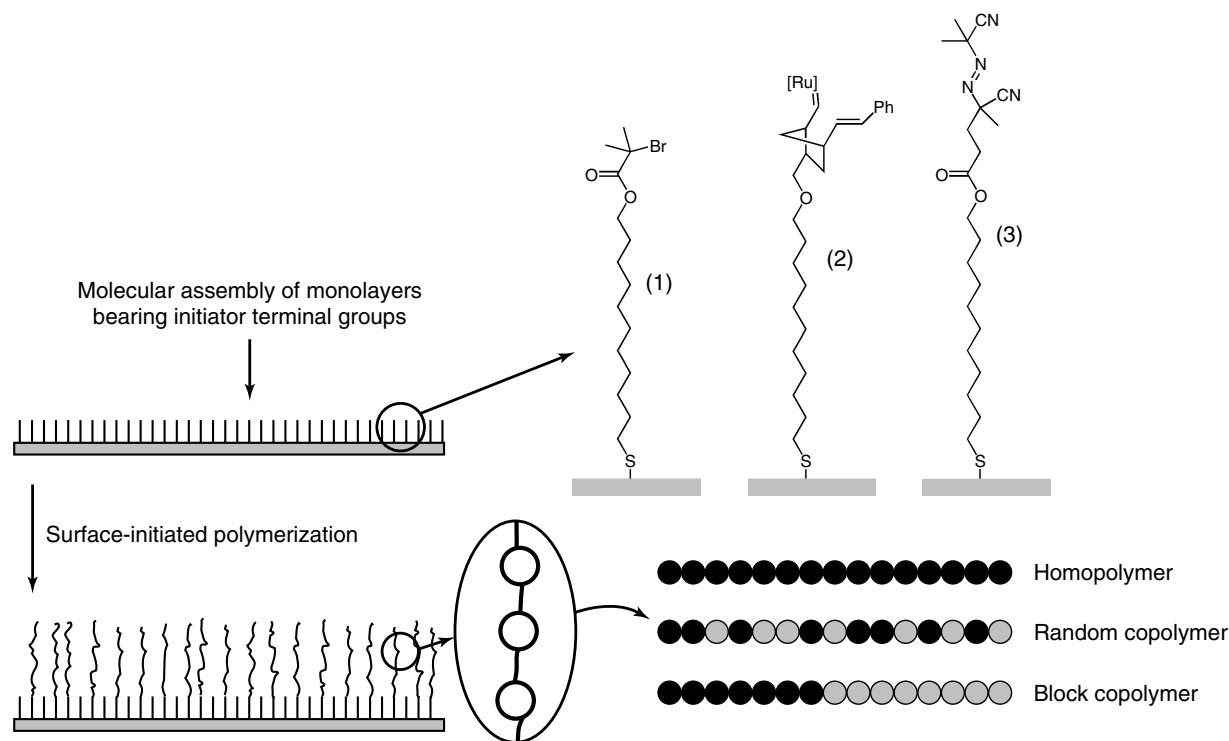


Figure 10 Schematic depiction of a surface-initiated polymerization process leading to a variety of homopolymer and copolymer architectures. In the figure are also described the chemical structures of typical initiator-terminated alkanethiolate SAMs for different polymerization techniques: (1) atom transfer radical polymerization, (2) ring-opening metathesis polymerization, and (3) thermal free radical polymerization.

With regard to covalent anchoring of complex interfacial architectures using self-assembled platforms, surface-initiated polymerizations are probably one of the most far-reaching applications of reactive SAMs. The use of SAMs bearing initiator terminal groups has contributed a simple protocol in which polymers can be grown in a controlled way from surfaces, that is, “polymer brushes,” by implementing “living” cationic, anionic, nitroxide-mediated, ring-opening, and atom transfer radical polymerization techniques (Figure 10). The blend of concepts from polymer chemistry, surface science, and nanotechnology has propelled the widespread use of “polymer brushes” as robust tools to design a wide variety of molecular films.^{103,104}

5.3 Specific Interactions

This strategy involves host–guest interactions. The word “specific” refers to an interaction that is unique to a couple of binding partners, that is, to the selectivity of the binding process. In molecular recognition, the receptor or host interacting with an analyte or guest to form a supramolecular unit is an essential step. The advantages of this strategy are improved orientation of the immobilized species, high

specificity and functionality, well-controlled, and reversible adsorption, while the disadvantages include the use of biocompatible linker molecules, which is expensive and slow.

Coordination chemistry can also be used to detect small amounts of metallic cations. Ligands that are able to specifically chelate metal ions can be used as the terminal groups of different alkanethiol SAMs. Thus, SAMs of 2-mercaptobenzimidazole on Au surface have been used to detect Hg(II) by stripping voltammetry at low and high pH with a detection limit of 0.05 ppm.¹⁰⁵ The complexation of Hg(II) ions with the organic molecules occurs at the nitrogen centers.

Electrochemical sensors for Cu(II) in environmental samples have been prepared by modifying gold electrodes with SAMs of L-cysteine. Square wave voltammetric determination of Cu(II) with a detection limit below 5 ppb has been demonstrated.¹⁰⁶ The application of 1,9-nonanedithiol (NDT) SAM on gold for the electrochemical determination of Cd²⁺ has also been reported.¹⁰⁷ Interestingly, it was found that the dithiol SAM strongly affects the stripping wave of Cd, resulting in a sharp peak that was used for electroanalytical determination of Cd²⁺ in aqueous solutions.

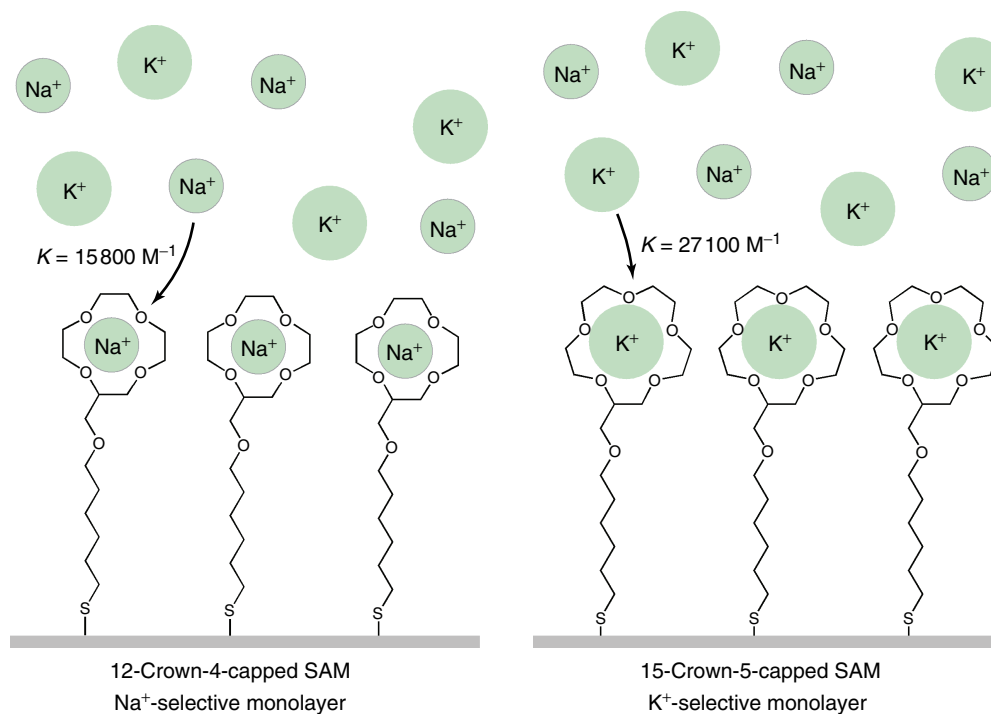


Figure 11 Molecular recognition of specific alkaline ions in the presence of different crown-ether-terminated self-assembled monolayers.

Other excellent example of metal ion trapping by SAMs has been proposed by Kolb *et al.* In this case, SAMs of N-containing thiols¹⁰⁸ were used to trap Pd(II) ions from solution. The Pd(II) ions are then reduced electrochemically to produce a monolayer of metallic Pd onto the organic monolayer. This approach was used as an alternative to metallize thiol SAMs from vapor phase, where the diffusion of metal atoms through SAM defects destroys the metal-thiol-metal device.

Selective recognition of specific ions on SAM-modified surfaces in the presence of different ionic species is feasible by incorporating recognition elements, for example, crown ethers, as the terminal group of the monolayer (Figure 11). These SAMs have been exploited as versatile sensing elements due to the dynamic and reversible character of the ion recognition.¹⁰⁹

However, it is worthwhile mentioning that the supramolecular processes taking place in the SAM can be affected by the intrinsic low-dimensional characteristics of the system. Echegoyen *et al.* reported the use of bis-podant thiol monolayers on gold as a platform to discriminate recognition of K⁺ in the presence of Na⁺, Cs⁺, Ba²⁺, and Ca²⁺ ions.¹¹⁰ However, K⁺ does not bind to preformed SAMs, but only to monolayers assembled in the presence of K⁺. Reflection-absorption infrared spectroscopy (RAIRS) also indicated a more compact and oriented monolayer when grown in the presence

of K⁺, providing indirect evidence of the templating process.¹¹¹

In this context, molecular printboards represent a benchmark example of supramolecular interactions at surfaces. Molecular printboards consist of SAMs of heptathioether-functionalized β -cyclodextrin (β CD) on gold.^{111,112} These form well-ordered and densely packed monolayers with a hexagonal lattice onto which a variety of univalent or multivalent guest molecules can be positioned by either adsorption from solution, microcontact printing, or dip-pen nanolithography with submicron resolution. Single supramolecular interactions are commonly relatively weak, but multivalent interactions, that is, the simultaneous binding of multiple binding sites on one molecule to a surface with multiple receptors, can overcome this problem. The formation of stable assemblies at surfaces, but still having control over the binding by external stimuli, is an essential requirement in diverse nanotechnological applications that molecular printboards can easily fulfill.

Another interesting application of specific interactions in SAMs is the use of ligand-derivatized thiols to build up complex biosupramolecular architectures via molecular recognition-driven processes. Typical examples include the use of biotin- and mannose-terminated SAMs to biorecognize and assemble streptavidin and concanavalin A protein layers, respectively, on metal surfaces with diverse purposes (Figure 12).^{113,114}

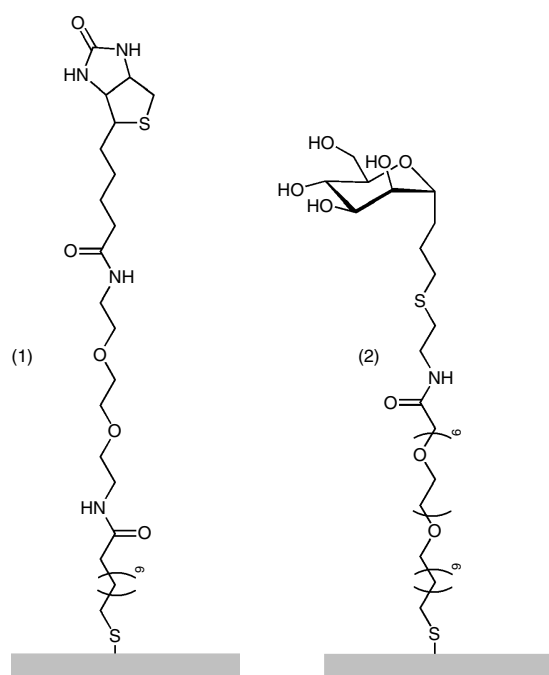


Figure 12 Chemical structures of (1) biotin- and (2) mannose-functionalized SAMs.

6 APPLICATIONS OF SELF-ASSEMBLED MONOLAYERS—A BRIEF SUMMARY

We have seen that spontaneous assembly of amphiphilic molecules represents a simple and highly reproducible chemical protocol that allows the creation of well-ordered

molecular assemblies, in which the choice of the functional groups of the adsorbates enables the exact tuning of the chemical properties of the substrates. In this context, chemisorption of SAMs has proved to be a very powerful tool for introducing new applications of organic thin films in surface science. For example, the ability to chemically pattern surfaces using soft-lithographic techniques is an attractive aspect of SAMs, provided that we can easily achieve spatial control over the chemical processes that might take place on a surface. In fact, the implementation of high-resolution techniques, such as STM or AFM, has significantly contributed to corroborate the formation of well-defined chemically patterned domains. In a similar vein, the use of SAMs in sensing devices seems promising because all receptor adsorbates are in direct contact with the analyte medium, which should result in very short response times. Hence, SAMs are excellent candidates for transducing molecular recognition events into detectable signals—the cornerstone of “supramolecular surface science.” The immobilization of photoswitchable and/or redox-active SAMs on conductive surfaces would allow the tuning of the response in applications from dye-based solar cells to sensors and molecular electronics. The use of reactive SAMs played a fundamental role in the development of polymer brushes via surface-initiated polymerization routes. As a result, it is now possible to grow polymer brushes on virtually every surface, to any thickness, of every composition, incorporating a multitude of functional groups, and containing series of blocks. Along with the development of new electroanalytical methods, SAMs can also provide new insights into (bio)molecular

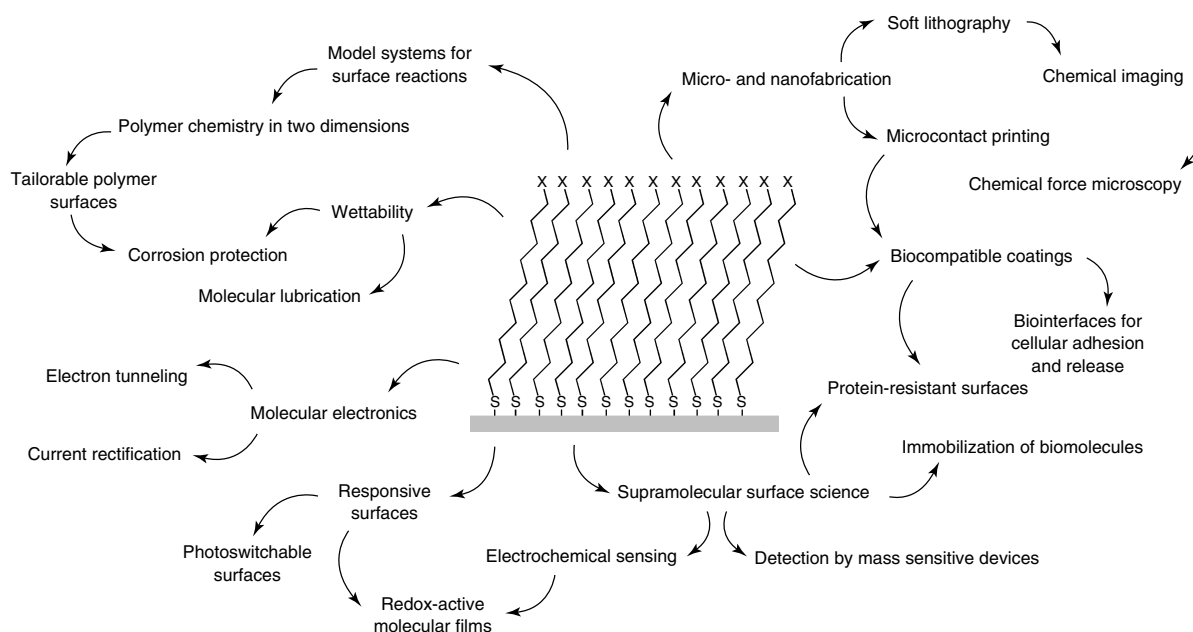


Figure 13 Simplified diagram of the multiple applications of self-assembled monolayers.

recognition events at electrochemical interfaces, which may foster new approaches in bioelectrochemistry. Regarding this latter, the application of SAMs in biointerfaces has received an increasing attention as a tool to manipulate the immobilization of biomolecules on surfaces, control cell attachment and motility, and reduce the nonspecific adsorption of proteins. In few words, the confinement of reactive functional groups within ordered arrays of molecules on surfaces has opened many promising prospects for the preparation of new functional interfaces. Such applications are briefly summarized in Figure 13; however, we believe that the creativity of chemists and materials scientists will soon provide a means for developing a wide variety of new applications, especially concerning the construction of complex interfacial architectures on functional surfaces. We are confident that this progress will stem from interdisciplinary work exploiting organic and supramolecular chemistry as key enablers to rationally design molecular building blocks entirely from scratch.

7 CONCLUSIONS AND OUTLOOK

We have presented a brief overview on the different SAMs that are currently used to modify the physical and chemical properties of solid surfaces, and also to build complex molecular structures with potential applications that range from molecular electronics to medicine. We have reviewed, by selecting few key examples, the different strategies employed for this purpose that include nonspecific and specific interactions, and covalent bonding. Although the review is mainly focused on thiol SAMs on metals, because they are the best-known systems, their capabilities and limitations can be extended to the other SAMs. In particular, we have stressed the presence of structural and conformational defects, thermal, their chemical, and electrochemical stabilities, and incorporation of contaminants in the organic films, all factors that could have a strong impact in the applications of SAMs. Despite these limitations, SAMs continue to play a key role in a multitude of applications in nanoscience and nanotechnology not only as model systems to study interfacial interactions but also as the main strategy to chemically graft active molecules.

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