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Applications of Self-Assembled Monolayers for Biomolecular Electronics

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Abstract

Preparation and characterization of ordered ultrathin organic films (a few nanometers to several hundred nanometers) has recently attracted considerable attention because of the possibility of controlling order and interactions at the molecular level and has triggered several innovative applications ranging from molecular electronics to tribology. Monomolecular films prepared by self-assembly are attractive for several exciting applications because of the unique possibility of making the selection of different types of terminal functional groups as well as length scales more flexible. The present article discusses various applications of self-assembled monolayers (SAMs) in molecular electronics ranging from biosensors to optoelectronic devices with specific examples. Similarly, SAMs and multilayers of bifunctional molecules on polycrystalline substrates can be effectively used to carry out specific reactions between pendent functionalities and solution or gaseous species to produce new hybrid materials for devices such as molecular diodes. The importance of SAMs in controlling nucleation and growth is also illustrated using biomimetic synthesis of ceramic thin films (biomineralization) of zirconia.

Index Entries: Self-assembled monolayers; biomolecular electronics; biosensors; nanocluster superlattices; biomineralization.

Introduction

The formation of a self-assembled monolayer (SAM) induced by strong chemisorption between the substrate and head group of selected organic molecules provides one of the most elegant approaches for making ultrathin organic films of controlled thickness *(1–3)*. The simple way of getting a well-defined and organized surface by the immersion of the substrate in a dilute (~1 m*M*) solution of the adsorbate at room temperature has been recently utilized for studying several fundamental phenomena such as distance-dependent electron transfer *(4)*, the mechanism of single electron transistors *(5)*, and the observation of molecular events such as Coulomb

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staircase *(6)*. The strong chain-chain interactions ensure tight packing and stability of the monolayer leading to several applications including chemical sensing *(7)*, control of surface properties such as wettability and friction *(8)*, corrosion protection *(9)*, patterning *(10)*, semiconductor surface passivation *(11)*, and optical second harmonic generation *(12)*.

Molecular electronics is an emerging interdisciplinary area, of which the objective is to design supramolecular systems capable of electronic operations such as switching, gating, rectification, and amplification *(13,14)*. The primary objective is to design and synthesize biologic compounds with novel and potentially useful electronic properties. Although both individual molecules and organized assemblies can show this kind of behavior, this has to be contrasted with conventional solid-state devices using semiconductors. Since the miniaturization of electronic components (VLSI and ultraLSI) could soon reach a physical limit (presently ~0.1-μm microchips may decrease to 0.01 μm, but quantum limitations will adversely affect the performance), the use of a single molecule designed to be equivalent to an electronic device in all aspects is considered an ultimate aim.

Let us first consider the advantages of single molecules acting as electronic devices. First, if single molecules can serve as switches and logic devices, their size will allow the utilization of about 10^{13} units/cm^2 compared with the presently used level of 10^8 units/cm^2. For memory applications, "one bit per molecule," if achieved, can give unprecedented storage density along with other attendant advantages of size reduction. The method of the SAM allows a simple way to organize 10^{13} molecules/cm^2 and hence is immensively suitable for achieving the objectives. Second, in addition to this 10^5 size reduction, there is an enhancement in the response time of these devices from the currently available nanosecond-to-femtosecond regime *(15)*. Recent examples include the design of molecular wires (a quasi-one-dimensional molecule that can transport charge carriers), single-electron transistors, and molecular switches, and it is believed that machines and computers will all be available in the near future based on similar molecules *(14–20)*. Similarly, several rotoxanes have been found to be useful for constructing nanoscale motors *(19,21)*, and several other molecular shuttles piloted by the intervention of the solvent have been found recently *(20)*. The design of these molecules using biologic components such as nucleotides, proteins, antibodies, and receptors allows several applications in biomedical fields. An important problem in rational drug design and in biomolecular structural recognition is the generation of binding modes between two molecules, also known as molecular docking. Geometric fitness is a necessary condition for molecular docking, which involves recognition of molecular surfaces *(22)*. In several cases, the use of biologically active or biomimetic molecules is essential (e.g., as in biosensors and biochips), and the broad field is referred to as biomolecular electronics *(15)*.

In the present work, we explain the utility of SAMs and multilayers in biomolecular electronics. We first compare the efficiency of both Langmuir-Blodgett and SAM methods in designing molecular assemblies with con-

Table 1
Comparison of SAM vs Langmuir-Blodgett Methodology

Self-assembly technique	Langmuir-Blodgett technique
The overlayers are formed in a simple and near equilibrium procedure and exhibit strong adsorbate-substrate bonding.	It is a potentially nonequilibrium procedure with weak monolayer-substrate bond (van der Waals or hydrogen bonding) and poor stability.
It provides precise control of molecular ordering at the solid-liquid interface.	It provides precise control of ordering at the liquid-air interface.
Only selected substrate surfaces such as Au, Cu, Ag, and Hg can be used for monolayers; multilayer formation is difficult.	Any substrate can be used to pick up the monolayers, and multilayer formation is easy by sequential transfer.
Specific functional groups such as thiols (SH) and disulfides (S-S) are required.	Any long chain amphiphilic molecule can be organized on the air-water interface.
The densely packed and oriented films are thermodynamically stable and robust (chemisorption).	Transfer to a solid surface may change the structure of the monolayer (physisorption).
SAM formation is restricted by the solubility of the molecules, and solvent plays an important role.	There is no solubility restriction; the molecules are preorganized at the liquid-air interface before transfer.

trolled architectures. This is followed by the application of monolayers to specific examples of biomolecular electronic devices as demonstrated during the last couple of years.

SAM vs Langmuir-Blodgett Methodology for Ultrathin Organic Films

The capability of designing ultrathin films with specific functionalities allows us to study many of the reactions occurring in biologic systems in order to understand their speed and specificity. This is very clear from the increasing efforts devoted to create artificial model systems of liposomes, vesicles, bilayers, and so forth that mimic cellular and membrane functions using organic mono/multilayers. These ultrathin organic films are generally formed by either a forced interfacial transfer of floating amphiphiles on an air-liquid interface (Langmuir-Blodgett) or by the spontaneous adsorption of molecules from solution (SAM). Compared to the former method, the near equilibrium procedure enables a more stable and mechanically robust film by SAM (see Table 1). The great advantage of SAM over other methods is that important parameters such as monolayer thickness (length scale), hydrophobic-hydrophilic balance, and terminal functional groups

can be controlled in a precise manner. In addition, the effect of conformation and geometric constraints can be studied systematically using different types of monolayers. The design of different types of monomolecular arrays with different functional groups can be positioned in geometric arrangements (molecular engineering), and several examples of these systems are known to have electrical communication capabilities.

One of the important aspects of self-assembly is to understand the chemical interactions between the underlying surface and head groups of the adsorbate molecules so that a defect-free monolayer can be prepared for applications. This necessitates the characterization of SAMs by various analytical tools such as XPS *(23)*, AFM *(24)*, STM *(25)*, ellipsometry *(26)*, SERS *(27)*, and QCM *(28)* despite different advantages and limitations. Electrochemical techniques such as cyclic voltammetry *(29,30)* and impedance technique *(31,32)* are especially significant for accessing the quality of SAMs in terms of degree of coverage and nature of defects.

Mono/Multilayer-Based Synthesis

The formation of SAM provides an elegant way to form well-defined organic assemblies with a wide range of surface functionalities as a first step for designing organo-inorganic materials for molecular electronics. The mere presence of a suitable monolayer can make metals and semiconductors compatible with biologic systems, thus suggesting the usefulness of monolayers in designing biomolecular systems. Among the broad spectrum of substrates and functional groups used for the formation of SAM, long chain alkane thiols and disulfides on gold are the most widely studied and well-characterized systems *(1)*. Although ω-terminated alkanethiol derivatives have been extensively investigated, the formation of monolayer is also possible with disulfides, diselenides *(28)*, and sulfur-containing even planar π systems. Complex biomolecules such as porphyrene systems can also be used with the appropriate functional group, and enzyme immobilization on noble metal surfaces can easily be conducted with the help of monolayers. For example, the self-organization of metal (Ag, Au) and semiconducting nanoclusters (CdS, CdSe) on SAMs with dithiol functionalities gives rise to interesting nanostructures. Similarly, the effective utilization of the functionalized interface of SAMs in two-dimensional reactions has been demonstrated recently by forming multilayers of zirconium phosphate and copper dithiol *(33,34)*. Furthermore, SAMs have been found to be valuable for preparing chiral-functionalized surfaces of oligopeptides for intended applications of molecular electronics *(35)*.

The organic interfaces prepared by the self-assembly of long chain alkanethiol on gold are suitable model systems for the study of protein adsorption at interfaces *(36,37)*. The structural and functional similarities between SAMs and biologic membranes allow the utilization of these mono/multilayers as surrogate membranes for holding biologic molecules.

For example, SAMs provide a medium that mimics the natural environment of membrane proteins and can therefore be used to create a model system for studying processes that occur at cell surfaces. The interfacial properties of these densely packed monolayer assemblies can be controlled by changing the tail groups. In different studies, ω-functionalized long chain alkanethiols on gold are used to study the interactions of protein. The amount of protein adsorption can be controlled by varying the monolayer composition, and the adsorption of several protein SAMs that contain different functionality (e.g., alkyl heterocyclic groups) correlates approximately with the hydrophobicity of the surfaces. This has been exemplified in a study involving SAMs of five well-characterized proteins to adsorb on these mixed SAMs. It was demonstrated that adsorption increased as the hydrophobicity increased. In a number of studies, SAM prepared with -COOH-terminated alkanethiol $HS(CH_2)_nCOOH$ has been used successfully to immobilize horse cytochrome-*c* in a stable electroactive state to understand the mechanism of electron transfer *(38,39)*.

Organization of Nanoclusters

The organization of quantum dots of metals and semiconductors recently has attracted significant interest because the tailoring of sizes and interparticle separation can, in principle, cause unique magnetic, optical, and electronic behavior *(40–44)*. For example, several nanocluster assemblies organized in different length scales have been found to be promising owing to their potential applications in many diverse areas such as optoelectronic devices, single electron transistors, and chemical sensors *(45–48)*. Nanoclusters of transition metals become semiconductors if small enough, and the main advantage is that particle size as well as interparticle coupling can be controlled *(49)*. Attaching nanoclusters to biomolecules such as DNA (DNA-crosslinked Au dimers and trimers) and proteins can allow electrical communication to such organized assemblies, and an unlimited field of applications in biomedical electronics can be foreseen *(50)*.

The formation of SAM offers a simple and flexible method for organizing nanoclusters on noble metal surfaces (Fig. 1), and there have been few attempts recently to obtain a systematic arrangement of metal and semiconductor nanoparticles in different dimensions *(47,51)*. For example, orientationally ordered self-assembled silver nanocluster superlattices were recently constructed in which the branching adsorbates between facets of Ag cores form the basis for the geometric assembling of truncated octahedral nanocrystals *(49)*. One of the important advantages of this approach is that since many metallic and semiconductors clusters (e.g., Au, Ag, CdS, CdSe) have high affinity for amine and thiol moieties, a chemical means of control of both size and interparticle separation will lead to a tailoring of band structure. While it generally has been proved that both Ag and Au nanoclusters can be organized on the SAM surface, the sequential extension of this organization to demonstrate optical and electrochemical prop-

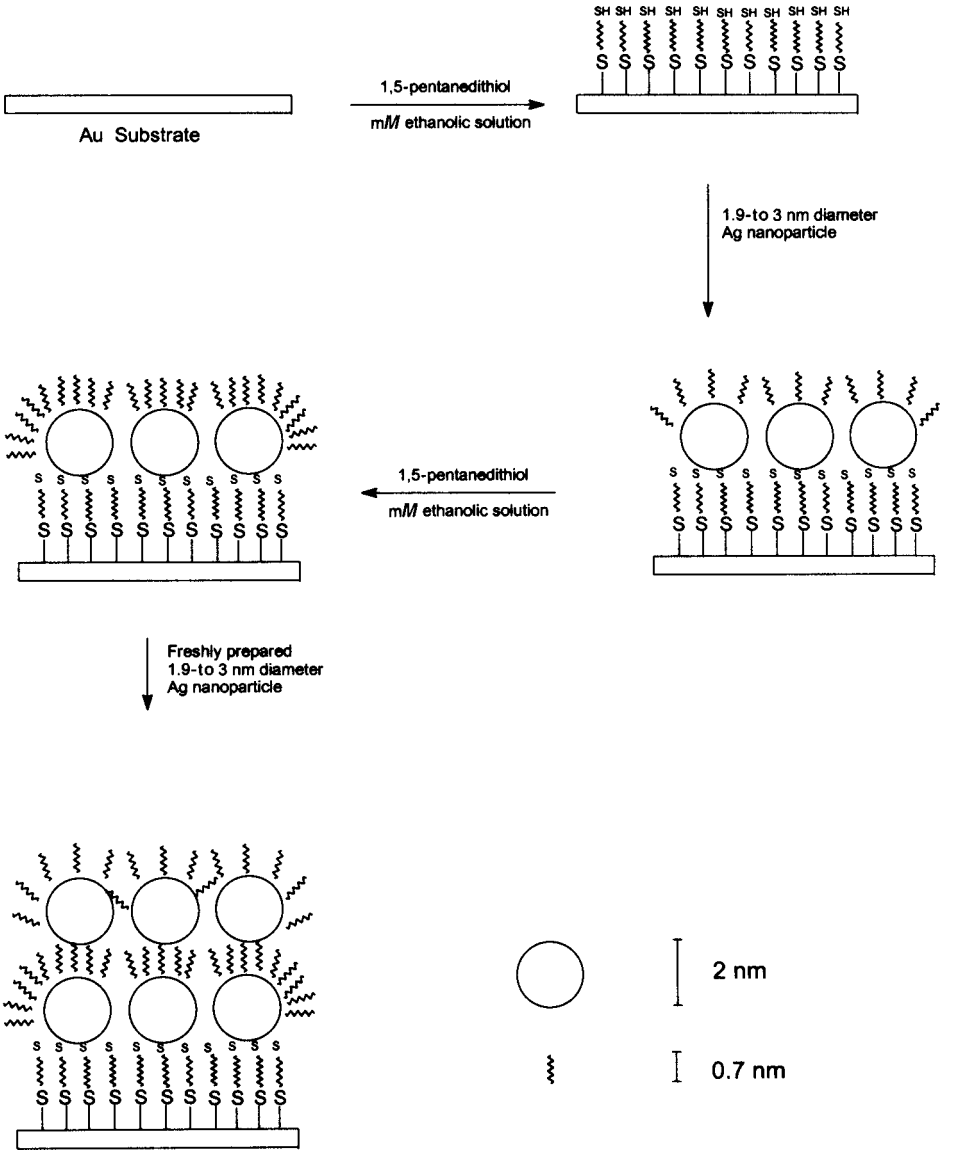

Fig. 1. Schematic drawing of a layer-by-layer organization of Ag clusters on Au surface modified with 1,5-pentanedithiol after dipping the substrates in m*M* ethanolic solution of the organic molecule for 24 h.

erties has been recently attempted (unpublished results). X-ray diffractogram of two and four layers of Ag nanostructures on SAM-functionalized gold substrate reveals two peaks at 0.31° and 3.45°, respectively, illustrating the sequential organization, while a sharp reversible peak in the cyclic voltammogram suggests that Ag clusters act as nanoelectrode arrays collectively enabling the passage of electrons through SAM. The optoelectronic properties also are interesting since the room temperature emission

spectra of three transitions could be explained using new broadened and delocalized quantized states called minibands *(52)*. More significantly, the presence of ligand on the cluster surface can lead to disorder in the superlattice formation, and it is important to know whether a sequential approach can be adopted to extend the organization to biomolecular systems. Two-dimensional organization of these clusters requires control of the interparticle coupling, and long-range electron transfer, relevant in most biological ET systems, could be investigated using SAMs of long chain molecules to connect between clusters.

The current-voltage characteristic of these clusters exhibits very interesting behavior. For example, instead of the expected linear behavior (Ohm's law) of bulk materials, the so-called Coulomb blockade is observed in both solid-state and solution forms, suggesting single electron transfer. To observe single electron transfer experimentally, the electrostatic energy (E_{elect}) must be large as compared to the available thermal energy (kT) as

$$E_{elect} = e^2/2C >> kT$$

and it is experimentally possible to verify that this temperature depends on quantum size effect as the capacitance C becomes small enough. More significantly, depending on the size of the clusters (eg., C = 10^{-19} F for Au_{55} clusters), this effect can be observed even at room temperature. For all these applications, the use of nanoclusters in future electronics is unambiguously limited to the availability of clusters organized in one, two, or three dimensions, and SAM offers a powerful route for the realization of nanocluster devices. The compatibility of SAMs with semiconductor device processing is also an added advantage, as illustrated by the recent discovery of a nanofield effect transistor with an organic SAM as the gate insulator *(53)*.

From Molecular Wires to Molecular Motors

The concept of molecular wire is based on an unsaturated chain of atoms acting as a conduit for electrons as illustrated by polyenes. All such one-dimensional systems are inherently unstable (Piereles distortion), making charge transport between chain ends dependent on the phonon processes. Self-assembly of fully conjugated oligomers on metal surfaces offers a simple way to form molecular wires, and along similar lines self-assembled systems of conjugated molecules on nanoclusters can be designed as a two-terminal molecular wire with a tunnel barrier that can serve as a resonant-tunneling diode. However, the way in which the contact is made at the end groups has a profound effect on electron transport, and improvements in the form of individually addressable contacts are still being developed.

One of the principal objectives of biomolecular electronics is to understand the mechanism of the molecular level of operation of biologic motors, such as muscle fibers, flagella, and cilia, that convert chemical energy into coordinated movement. Similarly, in brain, impulses within neurons are

transmitted by the diffusion of sodium and potassium ions across semipermeable membranes. The electrochemical action potential stimulates the release of neurotransmitters across synapses; however, the molecular basis of these operations is not completely clear. We can design an appropriate elementary form of these molecular motors based on the principle of performing mechanical movement using chemical, electrochemical, or photochemical stimuli as demonstrated by molecular antennas, switches, or shuttles. One such example is the gated biomolecular optoelectronic system *(54)* that transduces optical to electrical signals through photoisomerization of the monolayers. These devices are believed to play a major role in shaping the future of information processing on the molecular level. Self-assembly processes are quite useful for making the nanoscale construction of these motors. For example, ionic transport through channels in cell membranes can be investigated using artificial bilayer membranes prepared using these methodologies. Similarly, molecular recognition processes controlled by membrane proteins play a central role in the biochemistry of the immune processes, and suitable model systems can be designed using SAMs.

One recently illustrated example includes the design of molecular actuators, in which the molecule undergoes a change in shape in response to an external force and is hence capable of performing work. Two-level systems such as *cis-trans* isomers can be considered the simplest examples, whereas biomolecular devices based on the conversion of right-handed to left-handed DNA represent more complex and elegant examples. One of the major challenges to be solved is the limitation that these systems are incapable of providing continuous unimolecular motion, and attempts are being made to overcome this problem *(21)*.

Biomimetic Mineralization

Biomineralization is a complex process that involves controlled growth and nucleation of ceramics from aqueous solution based on the natural processes of the creation of intricate materials at ambient temperature and pressure. For example, seashell consists of complex arrangements of proteins and polysaccharides secreted by the animal in an inorganic matrix. Although this does not strictly come under biomolecular electronics, some of the substrates could be developed using this strategy based on SAMs. When a biologic organism generates a matrix for nucleation and growth, it not only can control the solution concentration but also the kinetics and direction of growth by using soluble proteins. By using functionalized surfaces with SAMs, biomineralization routes can be used to prepare high-quality, oriented, and patterned ceramic films at low temperatures. For example, different materials including iron oxides, apatite, CdS, and ZrO_2 have been prepared recently by this approach *(28)*. More significantly, by manipulating surface energies through surface

functionalizations and solution additives, it is possible to control the crystal phase, morphology, orientation, and chirality *(55)*.

The basic assumption of this type of biomimetic synthesis is that SAM surfaces are analogous to tailored surfaces of macromolecules in living organisms. Surface functional groups can mediate nucleation and growth, and SAM formation (bifunctional molecules) provides model surfaces on both metal and oxide substrates to form amino, hydroxyl, carboxylate, or phosphate groups. The hydrocarbon chain and the terminal functionality allow flexibility of design, and specialized synthetic strategies similar to organometallic synthesis are necessary.

As one example, let us describe the effective use of SAM of 1,4-benzene dimethanethiol (BDMT) to link Zr^{4+} from an aqueous solution of appropriate zirconium salt to subsequently form microcrystalline, monoclinic zirconia at room temperature by potentiodynamic method (Fig. 2). The experimental methodology includes a dithiol SAM first formed on vacuum-deposited, 200-nm-thick Au film on glass slides (Cr buffer) followed by immersion into aqueous $ZrOCl_2$ solution to covalently link Zr^{4+} ion on the SAM surface. After thorough washing, these Zr-attached samples were used as working electrodes in a 1 *M* aqueous KCl solution, and the potential was cycled between –1.1 and 0.7 V vs saturated calomel electrode (SCE) several times to get crystalline zirconia (Fig. 3). The process of monolayer formation and the subsequent covalent attachment of Zr^{4+} from aqueous solution to the SAM-covered surface was followed by XPS and cyclic voltammetry *(31)*. The striking feature of the crystal confirms the ability of SAM to control morphology of ceramic materials as also confirmed by similar results of $CaCO_3$ crystal growth on SAM surface *(56)*.

Biosensors Using SAM

Since SAMs can serve as an interface layer between a noble metal surface and a species present in solution or vapor state, its advantages for utilization toward molecular recognition (or chemical sensing) are clear (Fig. 4). First, the high selectivity offered by biomolecules such as antibodies, nucleic acids, and enzymes or even organized systems such as whole cells can be favorably used for molecular recognition if monolayers are formed by these molecules. More significantly, immobilization of these biomolecules using SAM requires only a minimum amount (monolayer), and the biomolecules still maintain their biologic activity. Similarly a variety of transduction modes such as electrochemical, optical, or piezoelectric can be used for biologic sensing of the analyte molecules depending on the amount, environment, and response time. Lastly, a control over the immobilization process (e.g., biotin-avidin chemistry) as well as the orientation of the biomolecules (microtiter plate immunoassay) allows tremendous flexibility in design *(39,57)*. A few selected examples illustrating the application of SAMs for biosensors are given in Table 2.

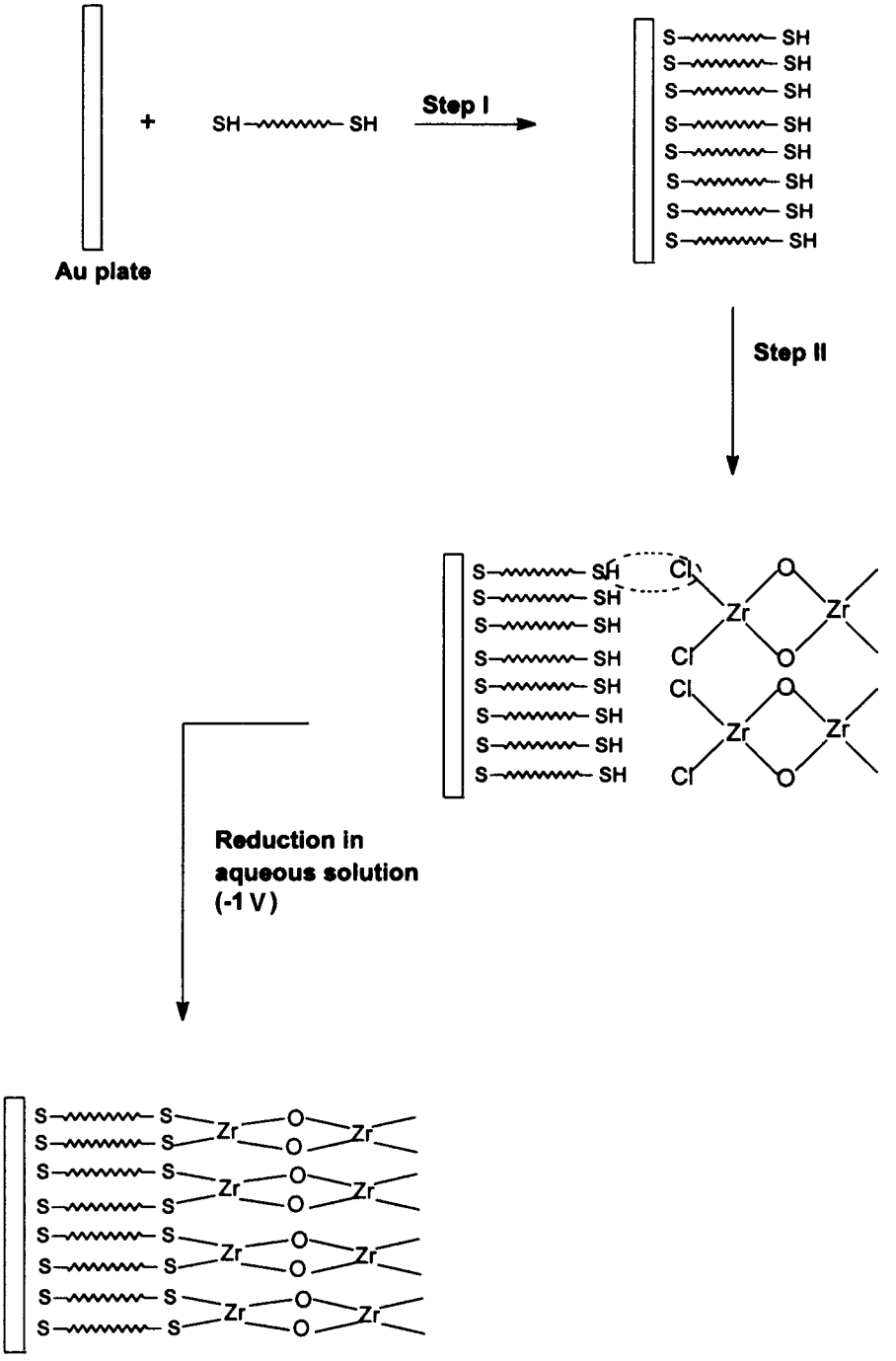

Fig. 2. Tentative scheme for the mechanism of ZrO_2 formation on Au surface modified with 1,4-benzenedimethanethiol after keeping the Au substrates subsequently in m*M* ethanolic solutions of BDMT and aqueous $ZrOCl_2$ solution. After Zr linkage on SAM functionalized surface, the potential was cycled between –1.1 and 0.7 V in 1 *M* aqueous KCl solution.

<Au: Pls. give units.

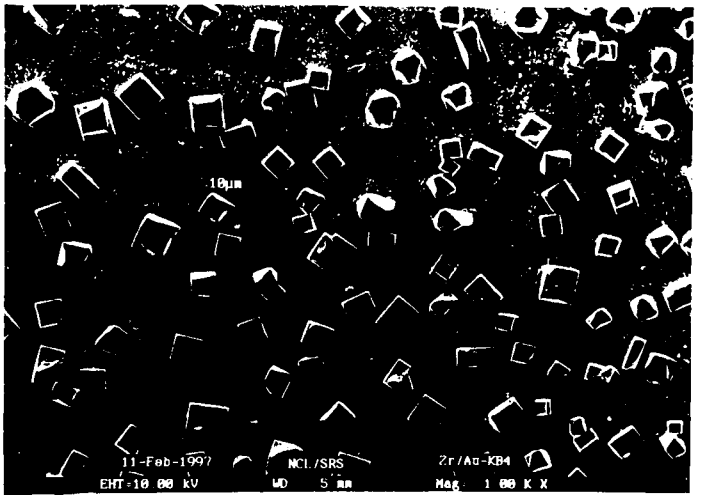

Fig. 3. Scanning electron micrograph of microcrystalline ZrO_2 on Au surface derivatized with BDMT after potentiodynamic cycling in a potential range of –1.1–0.7 V vs SCE.

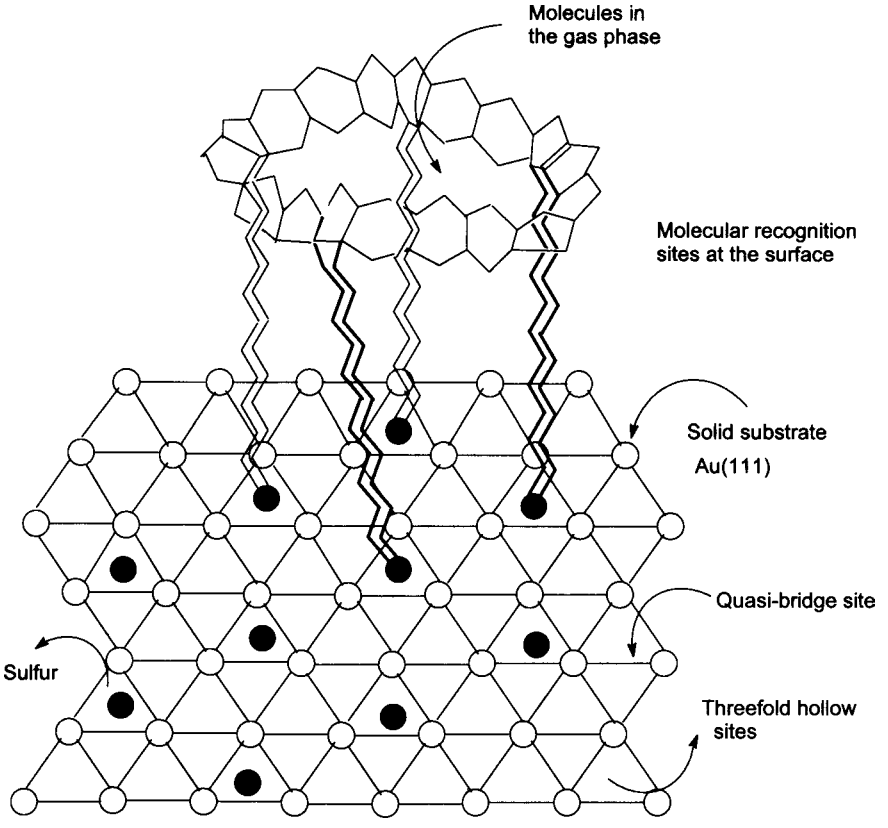

Fig. 4. Schematic representation of the molecular structure and interaction of self-assembled monolayer on an Au(111) surface with the molecules from gas phase.

Table 2
Selected Applications of Self-Assembled Monolayers for Biosensors

SAM type	Analyte molecule/enzyme/cells	Ref.
Octanethiol, propanethiol, 3-mercaptopropionic acid, 11-mercaptoundecanoic acid	Murine 3T3 fibroblasts/ osteoblast cells	*(58)*
Phospholipid monolayers	S-layer protein from *Bacillus sphaericus* CCM 2177/from *Bacillus coagulans* E38-66/VI	*(59)*
Biotin-terminated mercapto compounds	Streptavidin	*(60,61)*
Thioacetic acid, mercaptopropionic acid, 4-aminothiophenol	Immunoglobulin G (human IgG)	*(62)*
Methyl- and hydroxyl-terminated alkanethiols	Endothelial cell	*(63)*
Thiol-terminated lipophilic SAMs	Lipid membranes	*(64)*
Carboxylic acid–terminated SAM $HS(CH_2)_nCOOH$	Cytochrome-*c* via corbodiimide/ dopamine with ascorbic acid	*(65,66)*
ω-Hydroxy alkanethiol with glucose oxidase crosslinked by glutaric acid	Glucose	*(67)*
Ferrocenyl hexadecane thiol and aminoethanethiol	Glucose oxidase (GO_x), DNA	*(68,69)*

One of the important biosensors developed using SAM includes an amperometric sensor in which, cytochrome-*c* is immobilized on a carboxylic acid–terminated SAM surface ($S[CH_2]_nCOOH$ with *n* as 15 or 11) using a carbodiimide reaction *(38)*. Dopamine sensors in the presence of ascorbic acid have also been developed using carboxylic acid–terminated SAMs, based on the fact that at neutral pH, negatively charged SAM repels ascorbic acid while the positively charged dopamine can be detected without any interference *(66)*. Several redox enzymes such as glucose oxidase have been linked to SAMs for the fabrication of biosensors, and normally a redox mediator such as a ferrocene derivative is used for electrical communication. The application of SAM for biosensors recently has been reviewed with several newer examples including electrochemical detection systems of specific DNA sequences and surface plasmon resonance methods with antigenic peptide-containing SAMs *(39)*.

The stability, uniform surface structure, and relative ease of varying the functionality make SAMs particularly suitable for developing applications in the area of biosensors. The SAMs of alkanethiols on gold are probably one of the best currently available surfaces for accomplishing the functionalization and patterning necessary for fabricating biosensors and

also have several advantages such as flexibility and stability. A convenient way of tailoring surfaces at the molecular level is the inclusion of some well-known receptor molecules in the monolayer to use as a support for molecular recognition at the surface through the formation of inclusion complexes by host-guest interaction.

Conclusion

Although the concept of a single molecule or a supramolecular assembly functioning as a bioelectronic device has been demonstrated several times recently, the utilization of biotechnology for making a fully integrated form of biochip or biocomputer still has to surmount several obstacles. Some of the difficulties can be ameliorated by designing suitable molecular architectures using self-assembly. Potential applications of SAMs in biomolecular electronics include single electron transistors, biomimetic coatings, optoelectronic molecular devices, smart biocomposites, and magnetic storage materials. Since the energetics of several biologic processes are governed by electrostatic interaction or geometric constraints, this can be controlled by designing suitable SAM-forming molecules. Some of the organo-inorganic nanocomposites have unusual properties, and the thin film fabrication and nanopatterning possibilities offer excellent future prospects for developing faster, cheaper, and smaller devices.

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