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Silicon and Silicon-related Surfaces for Biosensor Applications

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1. Introduction

Biosensing systems, such as enzyme, immunosensors, and DNA microarrays, are widely used in the field of medical care and medicine manufacturing [Spochiger-Kuller, 1998]. Recent developments in these devices require a high performance integrated micro-multi-biosensing system, which can be employed for the recognition of an individual biomolecule and the analysis of bioreactions at the single molecular level. Constructing a highly sensitive biosensing system, precise fabrication of the electrode parts for molecular recognition is of significant importance. In these context, organic monolayers have self-assemble ability onto surfaces [Ulman, 1991]. Monolayer-modified electrode is suitable as the template for ordered immobilization of biomolecules. On the other hand, it is preferable that the detection system can detect the signal immediately, with a high sensitivity.

Formation of covalently-bound organic monolayers has been particularly developed in the last two decades. The main benefit of organic monolayers is to add functionality to inorganic surface via the adaptable tailoring of surface properties. These monolayers keep the bulk features of the material (electrical, optical, magnetic, mechanical and structural), while their surface properties (wetting, passivation, bioresistance, biochemical affinity, etc…) can be tuned through a nanometer-sized grafting.

This chapter provides substantial information on modification of silicon and silicon-related surfaces by organic monolayers to get the reader acquainted with the different techniques employed in tailoring the surface properties towards biosensing capability.

2. Silicon and silicon related surfaces

2.1 Silicon surfaces

Silicon was discovered by Berzelius in 1824 and isolated as amorphous brown powder. Crystalline silicon was first prepared in 1854 as a grey material with metallic luster. Normally, silicon is prepared by reduction of silica, using different reducing agents. Silicon has a crystal structure similar to diamond, with Si-Si bond length of 2.3 Å [Cotton & Wilkinson, 1999].

Cleavage of a silicon crystal results in a large variety of surfaces. Several investigations on these surfaces have been carried out under ultra high vacuum (UHV) conditions [Hamers & Wang, 1996]. The surfaces are characterized by their Miller indices, which refer the plane thorough which the crystal was originally cleaved.

2.2 Surface orientations of silicon

The most common surface orientations of commercially available silicon are Si(100) and Si(111), *See Fig. 1.*
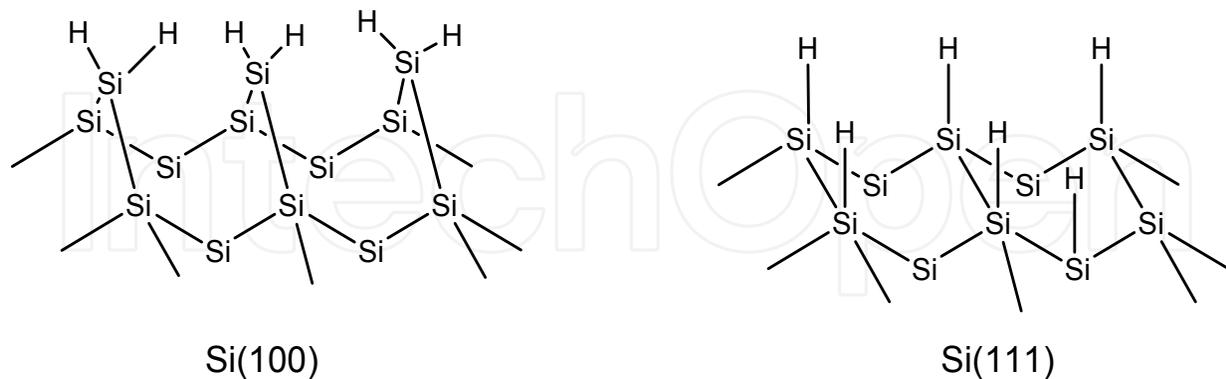

Fig. 1. Hydrogen-terminated Si(100) and Si(111) surfaces.

Upon exposure to air both become rapidly coated with a self-limiting, thin native oxide (SiO$_2$) that can be removed thermally under UHV conditions or chemically by immersion in aqueous fluoride-containing solutions [Buriak, 2002 & Leftwich, et al., 2008 & Sieval, et al., 2000a & Wayner & Wolkow, 2002]. Typically, Si(100) wafers are treated with 2.5% HF to yield dihydride-terminated Si(100) surfaces that are on the nanometer scale still rough. In contrast, Si(111) yields atomically flat terraces with monohydride-termination, (*See Fig. 2*) because during etching in argon-saturated 40% NH$_4$F solution the initially rough Si(111) surface will spontaneously smoothen as a result of the differences in reactivities of different crystal faces [Allongue, et al., 2000]. Both hydrogen-terminated Si surfaces are sufficiently stable that they can be handled in air for short periods of time (tens of seconds), allowing wet-chemical modification routes like the formation of organic monolayers. Because the lattice constant of thermally grown silicon dioxide (SiO$_2$) matches best with the crystal plane of Si(100), for electronic devices that use the oxide as an electrical insulator Si(100) is the most used crystal orientation, since these results in the lowest concentration of defects at the SiO$_2$-Si interface. However, due to its atomic flatness and nearly defect-free hydrogen-termination, Si(111) is the best substrate for new hybrid organic monolayer-silicon devices [Hamers & Wang, 1996].

2.3 Silicon-related materials

A special attention has given in recent years to the formation of organic monolayers on other surfaces than silicon, namely, silicon-rich silicon nitride (Si$_x$N$_4$, $3.5 < x < 4.5$) and silicon carbide (SiC). The exceptional mechanical and chemical robustness of Si$_x$N$_4$ and SiC make these substrates attractive for applications where harsh conditions and/or when prolonged exposure are applied. Moreover, Si$_x$N$_4$ and SiC have properties that differ from those of materials commonly used for the formation of organic monolayers (gold, glass, or silicon), and the chemistry presented herein thus provides the scientist or engineer with more choices in the selection of a suitable substrate.

Stoichiometric silicon nitride (Si$_3$N$_4$) can form robust insulating coatings, but this material can develop a very high surface stress that negatively affects its mechanical properties. In comparison, silicon-rich silicon nitride displays very low residual stress, and can form

homogeneous coatings by chemical vapor deposition (CVD) [Andersen, et al., 2005]. The composition of the material can be controlled by tuning the proportions of the compounds used as precursors in the CVD process (usually NH_3/SiH_2Cl_2). This material is indeed used commonly, for example, for the coating of micro-fabricated membranes or microelectromechanical systems (MEMS).
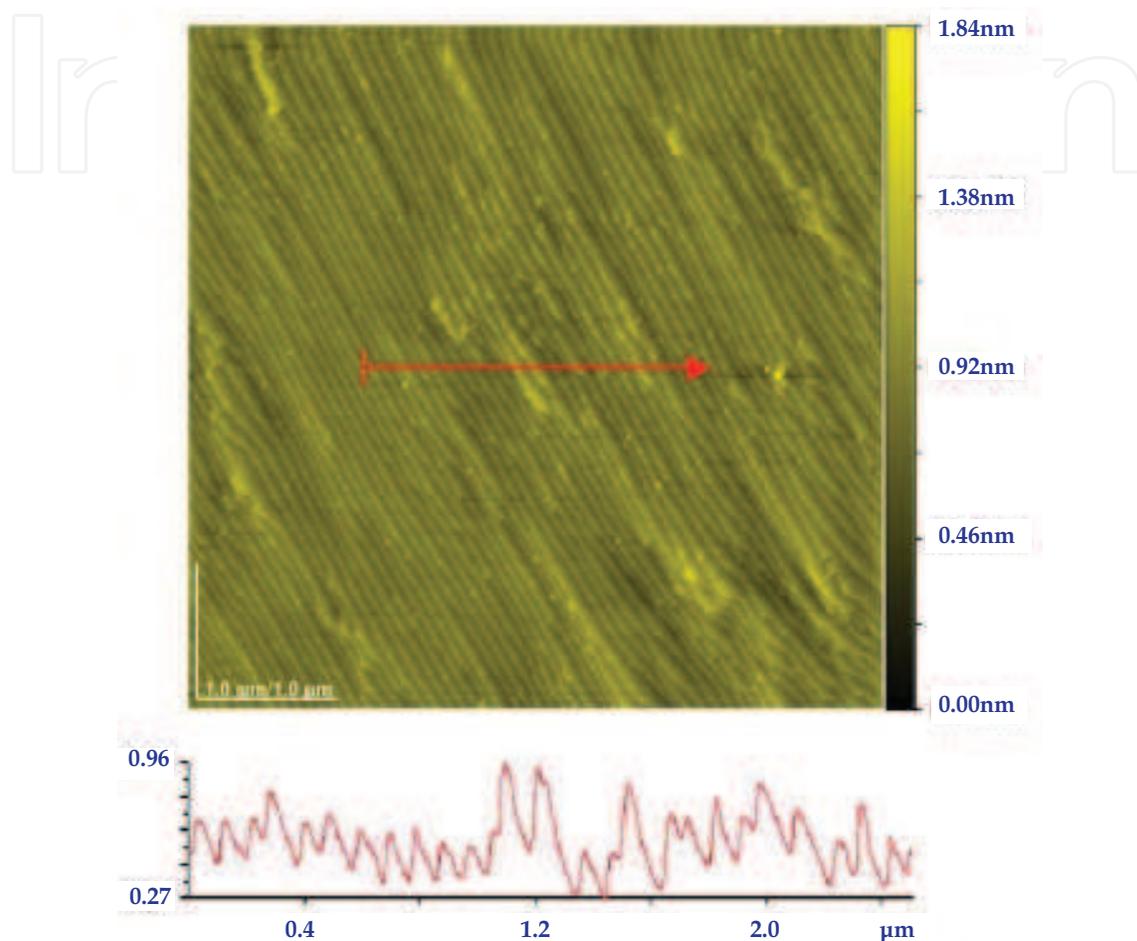

Fig. 2. H-terminated Si(111) surface, and section analysis along a line across the surface.

Silicon carbide had long been perceived as a potential replacement for silicon in electronic applications, but it was only in 1989, with the founding of CREE Inc., that SiC LED's (light emitting diodes) and high quality wafers became widely available due to the breakthrough of "step-controlled epitaxy"[Saddow & Agarwal, 2004]. Since then, the quality and availability of SiC materials have been steadily improved, and applications in high-power electronics and sensors are increasingly investigated. Application of Si_xN_4 and SiC can even be enhanced if effective surface modification techniques are becoming available.

3. Organic monolayers on solid substrates

Organic monolayers are layers that are precisely one organic molecule thick, and which are attached in a dense packing on a solid substrate. The attachment can be weak or strong, and can rely on either physical adsorption (e.g. electrostatic interactions) or chemical adsorptions (formation of chemical bonds). From the time when the revolutionary work on organic

monolayers on gold [Nuzzo & Allara, 1983], glass [Maoz & Sagiv, 1984] and oxidized aluminum [Allara & Nuzzo, 1985], the field of organic monolayers has grown tremendously, and nowadays organic monolayers on numerous metals, oxides and semiconductors have been reported in literature. With these extremely thin organic films (typical thickness ca. 2-5 nm) the surface properties of the underlying substrate can be precisely controlled, and therefore organic monolayers find rapidly increasing application in many fields of interest, including surface hydrophilicity and lubrication, surface passivation, chemical and biological sensing, and molecular electronics [Love, et al., 2005a & b & Onclin, et al., 2005a & b].

Organic monolayers of alkylthiols on gold and alkylsilanes on oxidized surfaces are obviously the most extensively studied systems (Fig. 3a and b) [Love, et al., 2005a & Onclin, et al., 2005b & Ulman, 1996]. Due to the high affinity of the thiol group for the gold surface, the self-assembly of alkylthiol monolayers on gold is a highly flexible process, which is clearly displayed by the wide variety of functional and rather complex monolayers that have been prepared [Love, et al., 2005a]. In addition, the semi-covalent nature of the Au-S bond allows diffusion of already absorbed chains along the surface, and as a result well-ordered and nearly defect-free monolayers can be obtained in a simple and reproducible manner [Love, et al., 2005a & Ulman, 1996]. However, the semi-covalent Au-S bond is also the shortcoming of these monolayers, because its limited strength provides alkylthiol monolayers with only moderate thermal and chemical stability. This stability, both thermally and chemically, is significantly increased by the use of a covalent C-Si-O linkage to an oxide, as results from the attachment of alkylsilanes onto oxide surfaces [Onclin, et al., 2005b].

The increased stability comes at a price, however, as the preparation of alkylsilane monolayers on oxidized surfaces is highly dependent on the reaction conditions, and therefore considerably less simple and reproducible than achievable for alkylthiols on gold. In addition, while organosilane-derived monolayers can be prepared with a wide variety of functional moieties, their long-term applicability remains less than ideal since the interfacial Si–O bonds are susceptible to hydrolysis.
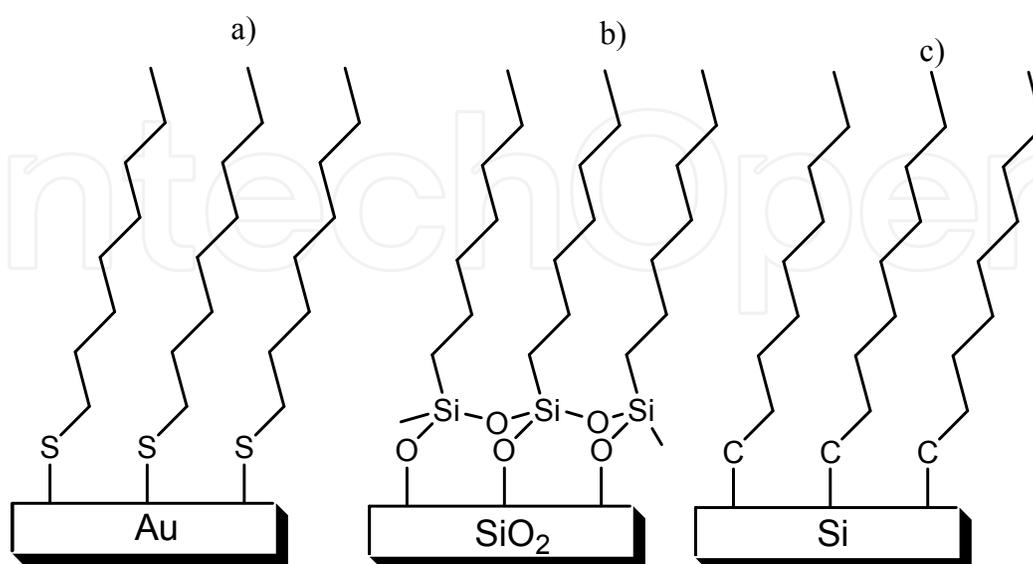

Fig. 3. Some examples of organic monolayers: (a) alkylthiols on gold, (b) alkylsilanes onto glass, and (c) 1-alkenes on oxide-free silicon.

4. Monolayers on oxide-free, hydrogen-terminated silicon surfaces

Due to the ongoing down-sizing of semiconductor devices, there is a significant interest in the surface modification of silicon. In this perspective, organic monolayers directly bound to oxide-free, hydrogen-terminated silicon are interesting candidates as they can easily be implemented in existing technology for the fabrication of silicon-based micro and nano-structured devices (Fig. 3c). The direct covalent linkage (Si–C bond) to the silicon surface provides a well-defined organic monolayer-silicon interface, and the nonpolar character of this strong bond make these monolayers thermally and chemically very robust [Linford, et al., 1995 & Sung, et al., 1997]. Moreover, because an intervening SiO_2 layer is essentially absent, direct electronic coupling between any organic functionality and the silicon substrate is possible, which provides an opportunity to enhance the device performance compared to SiO_2-covered electronic devices [Aswal, et al., 2006 & Cahen, et al., 2005 & Hiremath, et al., 2008 & Salomon, et al., 2006 & Vilan, et al., 2010]. Furthermore, using a semiconductor instead of a metal as a substrate/electrode has the advantage that – depending on the desired electronic properties of the final device – semiconductors with different doping levels and doping types can be used [Boukherroub, 2005 & Cahen, et al., 2005 & Salomon, et al., 2006 & Salomon, et al., 2007]. As a result organic monolayers on oxide-free silicon have great potential in the field of biosensors, molecular electronics and photovoltaic devices [Har-Lavan, et al., 2009 & Maldonado, et al., 2008].

Since the first reports of Chidsey and Linford [Linford & Chidsey, 1993 & Linford, et al., 1995], numerous new methods have been reported, and nowadays organic monolayers on oxide-free, hydrogen-terminated silicon can be prepared under a variety of conditions with both 1-alkenes and 1-alkynes. Over the last ten years several reviews about this topic have appeared in literature [Boukherroub, 2005 & Buriak, 2002 & Shirahata, et al., 2005]. Although initially harsh conditions (neat 1-alkenes or 1-alkynes with radical initiators and heat) [Sieval, et al., 1998] were required for the modification of planar silicon surfaces, the last decade displays a trend towards milder reaction conditions. In 1999 Sieval et al. [Sieval, et al., 1999] already showed that instead of neat 1-alkenes also dilute solutions of 1-alkenes can be used for monolayer formation on H-Si(100) under thermal conditions. Subsequently, Cicero et al. [Cicero, et al., 2000] demonstrated monolayer assembly on H-Si(111) by UV illumination at room temperature, and Stewart and Buriak reported visible light-promoted modification of porous silicon with 1-alkenes and 1-alkynes [Stewart & Buriak, 2001 & 1998]. Not much later, it was shown by Sun et al. [Sun, et al., 2005 & Sun, et al., 2004] on planar silicon surfaces visible light can initiate monolayer formation, even in dilute solutions.

Nowadays, it is widely accepted that monolayer formation occurs via a radical-chain mechanism on the surface (Fig. 4), even during mild visible light-induced monolayer assembly at room temperature [Eves, et al., 2004]. However, the exact initiation mechanism of the radical chain reaction, especially under these mild reaction conditions, is not yet completely understood. Radical initiators [Linford, et al., 1995] and UV light [Effenberger, et al., 1998] are capable of breaking the H-Si bond homolytically, which yields silicon radicals (silicon dangling bonds) that can act as a starting point for the radical chain propagation (Fig. 4, route 1). In contrast, using thermal conditions [Sieval, et al., 2001 & Sieval, et al., 2000b] or visible light at room temperature [Eves, et al., 2004 & Sun, et al., 2005 & Sun, et al., 2004], insufficient energy for homolytic cleavage of the strong H-Si bond is available. Nevertheless, as evidenced by scanning tunnelling microscopy (STM) (*see Fig. 5*) monolayer formation still occurs via island growth [De Smet, et al., 2005 & Eves, et al., 2004 & Mischki,

et al., 2009]. This implies that propagation of the radical chain reaction still proceeds, but a different initiation mechanism must be active under mild reaction conditions.
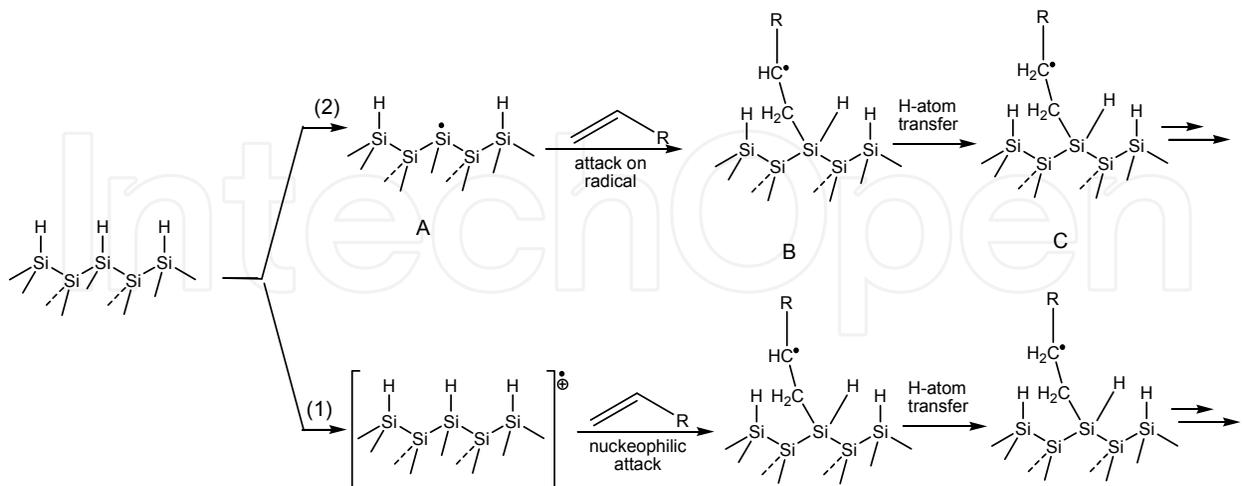

Fig. 4. The radical chain mechanisms for modification of H-terminated silicon surface with 1-alkenes (1) with radical initiators or UV irradiation and (2) with thermal activation or visible-light irradiation.
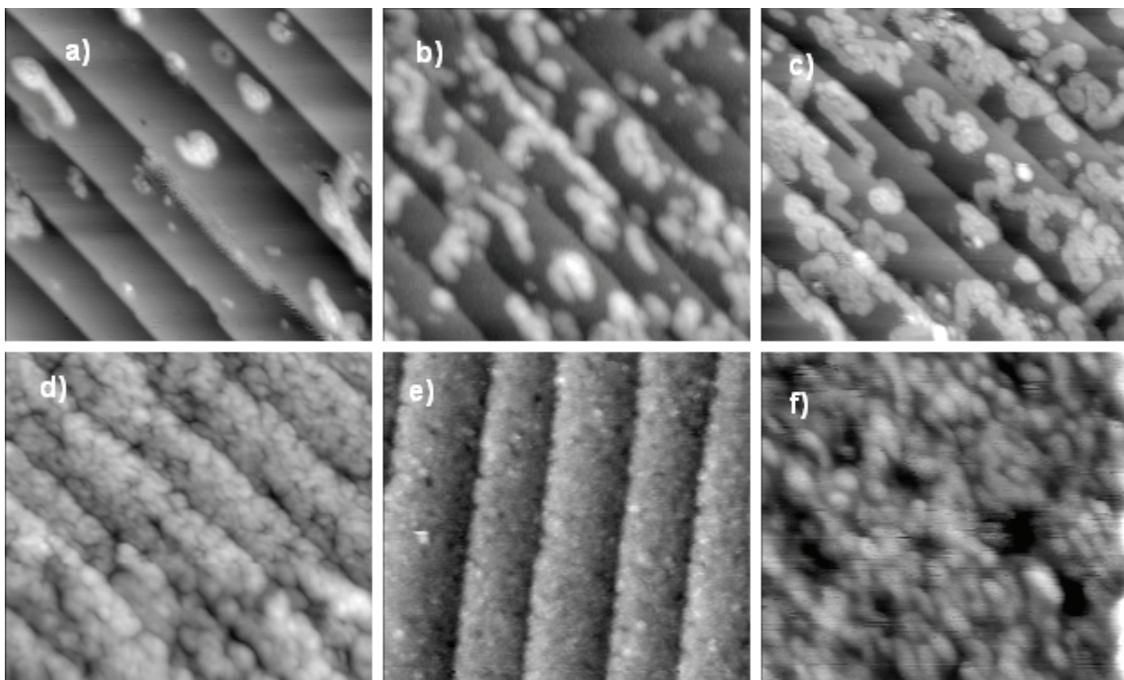

Fig. 5. STM images of hexadecyl monolayers on Si(111) surface taken at different time imtervals, a) 3 min., b) 15 min., c) 30 min, d) 2 h, e) 15 h and f) 24 h of irradiation with 447 nm [Eves, et al., 2004].

Inspired by the visible light-induced monolayer formation at room temperature, Sun et al. [Sun, et al., 2005] proposed an initiation mechanism based on photo-excited electron-hole pairs (excitons) near the silicon surface. These electron-hole pairs are susceptible to nucleophilic attack by a 1-alkene or 1-alkyne resulting in the formation of a Si–C bond and a

carbon radical at the β-position +1 ion (Fig. 3, route 2). This radical can then abstract a hydrogen atom from an adjacent H-Si site and leaves highly-reactive silicon radical at the surface. A new incoming alkene or alkyne molecule can react with this silyl radical and in this way propagate the radical chain reaction at the H-Si surface. However, we note that although the increasingly milder reaction conditions that were shown to work with 1-alkenes will extend the range of functional groups that can be attached directly onto Si [De Smet, et al., 2003], at the same time the quality and thus the stability of these organic monolayers is decreased with respect to those obtained under more harsh attachment conditions [Sun, et al., 2005].

5. Crucial issues for organic monolayers on silicon

For all potential applications the stability of the monolayer and its oxide-free monolayer silicon interface are the crucial issues. Both depend, in principle, on the exclusion of water and oxygen from the monolayer-silicon interface. If water and oxygen can get to the interface via some defects in the monolayer, they will react with the many remaining H-Si sites (45-50% of the H-Si sites remain after completion of an alkyl monolayer) [Cicero, et al., 2000 & Linford, et al., 1995 & Sieval, et al., 2001 & Sieval, et al., 2000c & Wallart, et al., 2005 & Yuan, et al., 2003] and some small oxide patches will be formed. These trace amounts of oxide facilitate hydrolysis-based degradation of the monolayer via an excavation mechanism, and introduce electrically active interface states that change the electronic properties of the underlying Si atoms drastically. Thus, the primary role of the organic monolayer is to provide a hydrophobic environment that is not readily penetrated by water and oxygen molecules, and therefore the densest possible packing of the monolayer is desirable. As monolayer formation occurs via a meandering radical chain reaction on the silicon surface, and because diffusion of already absorbed chains to improve the ordering – as observed for alkyl-thiol monolayers on gold [Ulman, 1996] – cannot take place due to the strong covalent Si–C bond, steric hindrance of the covalently bound chains prevents insertion of new chains. Consequently, filling the last pinholes in the monolayer is hard and thus organic monolayers on oxide-free silicon are in general less ordered and almost never completely defect free. As a result the oxide-free monolayer-silicon interface, generally, has a limited long-term stability [Faber, et al., 2005 & Seitz, et al., 2006]. Furthermore, because many functional groups (including -OH, -CHO, -NH$_2$, -Br, -SH) are reactive towards a H-Si surface [Asanuma, et al., 2005 & Boukherroub, et al., 2000 & Faucheux, et al., 2006], preparation of ω-functionalized monolayers on H-Si is considerably more difficult than, for instance, with alkylthiols on gold. Here, the use of protected precursors, which do not react with the H-Si surface and after completion can be deprotected to yield the desired functional monolayer, could offer an outcome [Böcking, Till, et al., 2007 & Fabre & Hauquier, 2006 & Sieval, et al., 2001 & Strother, et al., 2000]. However, often quite harsh deprotection conditions are required that consequently affect the quality of the monolayer-substrate interface. As mentioned above, also the use of milder reaction conditions could be helpful. A nice example is the carboxylic acid (-COOH) functionality, which binds to the H-Si surface at elevated temperatures [Linford & Chidsey, 1993], whereas under mild photochemical reaction conditions carboxylic acid-terminated monolayers with only small to negligible indications of upside-down attachment were reported [Perring, et al., 2005]. Nevertheless, hydrogen bonding causes acid bilayer formation, which makes these monolayers hard to clean while for further functionalization an additional activation step via carboxylic anhydrides or N-hydroxysuccinimide (NHS) chemistry is still needed [Fabre & Hauquier, 2006 & Fabre, et

al., 2008 & Hauquier, et al., 2008 & Strother, et al., 2000]. In addition, we note that the last years some interesting ω-functionalized monolayers are prepared, which showed no signs of upside-down attachment, are easy to clean, and allow further functionalization in a single step [Böcking, T., et al., 2006 & Ciampi, et al., 2007 & Li, et al., 2010 & Ng, et al., 2009 & Scheres, et al., 2010 & Yang, M., et al., 2008]. Finally, in view of the broad range of available patterning techniques [Garcia, et al., 2006 & Woodson & Liu, 2007] it is somewhat remarkable that thus far, only a limited number of patterning routes for organic monolayers on oxide-free silicon has been reported. In particular, because monolayer formation on H-Si can be initiated with UV or visible light, mainly photolithographic procedures were applied [Voicu, et al., 2004 & Wojtyk, et al., 2001 & Yin, et al., 2004]. In addition, micro-contact printing (μCP) – a fast and simple patterning technique, which is frequently used for alkylthiols on gold and alkylsilanes on oxide surfaces [Xia & Whitesides, 1998] – is currently not feasible with 1-alkenes and 1-alkynes directly on H-Si, due to the extended reaction times required for monolayer formation and related difficulties to remain a oxide-free monolayer-silicon interface. Only recently a number of elegant soft lithographic [Jun, et al., 2002 & Mizuno & Buriak, 2008 & Perring, et al., 2007] and scanning probe [Niederhauser, et al., 2001 & Niederhauser, et al., 2002 & Yang, L., et al., 2005 & Yang, M., et al., 2009] methods for patterning of organic monolayer on oxide-free silicon were published.

6. Organic monolayers on the surfaces of silicon-rich materials

Alkene-based monolayers were also formed on flat Si_xN_4 [Arafat, et al., 2007 & Arafat, et al., 2004], (Fig. 6) and 6H-SiC and polycrystalline 3C-SiC [Rosso, et al., 2008b] using thermal conditions close to those used for the surface modification of silicon. Good quality monolayers were obtained with several simple alkenes (e.g. water contact angles up to 107° for hexadecene-derived monolayers on both SiC and Si_xN_4, Table 1). The UV-induced formation of monolayers of semi-carbazide on H-terminated Si_5N_4 surfaces prepared under UHV conditions was also reported by Coffinier *et al. [Coffinier, et al., 2007].* In addition, methyl- and ester-terminated monolayers were also formed on $Si_{3.9}N_4$ [Arafat, et al., 2004] and 3C-SiC substrates [Rosso, et al., 2008b & Rosso, et al., 2009], using wet etching with HF and UV irradiation in the presence of alkenes, under ambient conditions of temperature and pressure. Semi-carbazides and esters can be easily converted to amine [Coffinier, et al., 2007] and acid groups [Rosso, et al., 2009], respectively, which can serve for further attachment of biomolecules or biorepelling molecules and polymers [Asanuma, et al., 2006 & Coffinier, et al., 2005 & Love, et al., 2005a].

The advantage of alkene-based monolayers is their stability, mainly due to the absence of a silicon oxide layer, and the presence of stable and non-polar Si-C bonds, in the case of Si [Linford & Chidsey, 1993] and Si_xN_4, [Arafat, et al., 2007] [Rosso, et al., 2008b] and stable C-O-C bonds in the case of SiC surfaces [Rosso, et al., 2008a]. Stability measurements revealed the outstanding stability of thermally produced 1-hexadecene monolayers on Si_xN_4 substrates, in acidic or basic conditions at 60 °C, with changes in contact angles of less than 5° after 4 h of such a treatment [Arafat, et al., 2007]. On SiC substrates, a good stability is also obtained after 4 h treatments in 2M HCl at 90 °C and at pH 11 at 60 °C, with resulting water contact angle values of 106° and 96°, respectively (coming from 108/109° for the original alkyl monolayer) [Rosso, et al., 2009]. Even after 1 h in 2.5% HF solution, under which Si-O-Si bonds dissolve rapidly, 1-hexadecene monolayers on SiC still displayed water contact angles of 99°, which indicates the presence of a stable hydrophobic coating.

Compound (concentration)	$\theta \pm 1°$
$CH_2=CH-C_{20}H_{41}$ (0.4 M)	102
$CH_2=CH-C_{16}H_{33}$ (Neat)	107
$CH_2=CH-C_{16}H_{33}$ (0.4 M)	104
$CH_2=CH-C_{14}H_{29}$ (Neat)	107
$CH_2=CH-C_{14}H_{29}$ (0.4 M)	106
$CH_2=CH-C_{12}H_{25}$ (0.4 M)	105
$CH_2=CH-C_{10}H_{21}$ (0.4 M)	106
$CH\equiv C-C_{16}H_{33}$ (0.4 M)	104
$CH\equiv C-C_{14}H_{33}$ (0.4 M)	103
$CH_2=CH-(CH_2)_8CO_2CH_2CF_3$ (0.4 M)	85

Table 1. Water contact angle $\theta°$ of different monolayers on $Si_{3.9}N_4$ surface.
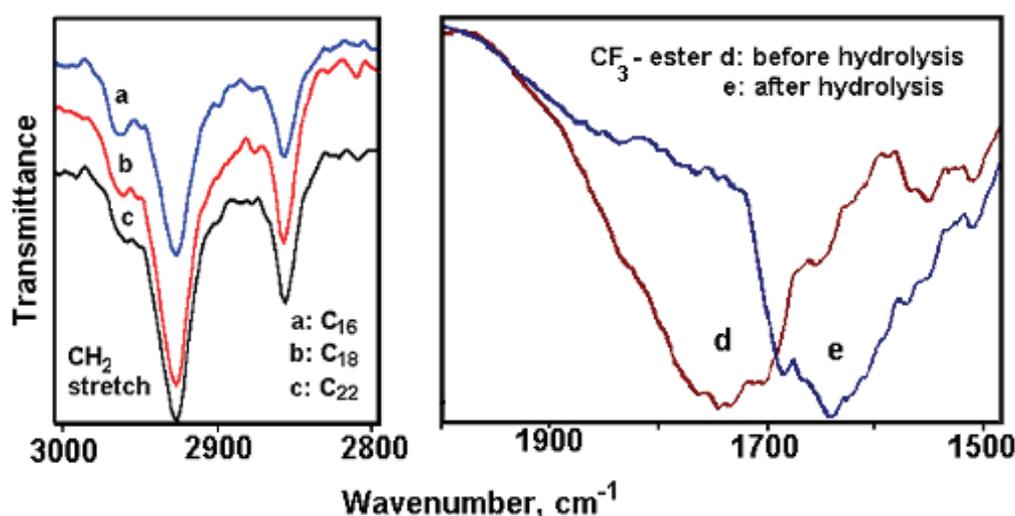

Fig. 6. Infrared reflection absorption Spectroscopy (IRRAS) data of modified Si_3N_x. (left) CH_2 vibrations after reaction of Si_3N_x with different 1-alkenes. (right) C=O vibrations after reaction of Si_3N_x with $CH_2=CH-(CH_2)_8CO_2CH_2CF_3$, before (d) and after (e) hydrolysis with 0.25 M potassium *tert*-butoxide [Arafat, et al., 2004].

Hydrogen-free diamond surfaces were also reacted under UHV conditions [Buriak, 2001 & Hovis, et al., 2000 & Knickerbocker, et al., 2003] with alkenes via a [2+2] cycloaddition or Diels-Alder mechanism. Hydrogen-terminated diamond surfaces could be functionalized with alkenes under UV irradiation [Knickerbocker, et al., 2003 & Strother, et al., 2002]. The reaction forms new carbon-carbon bonds, ensuring a robust grafting of monolayers. The same modification can be applied to amorphous carbon [Ababou-Girard, et al., 2007 & Ababou-Girard, et al., 2006]. Functional molecules, including DNA could be grafted in this way to diamond surfaces [Knickerbocker, et al., 2003] and the hybridization with complementary DNA strands could be monitored on the surfaces. In this case, the surface reactivity differs from that of silicon: the reaction initiation on diamond and amorphous carbon surfaces is due to their negative electron affinity [Nichols, et al., 2005] Upon irradiation with sub-band gap wavelengths, electrons are ejected from the surface into the surrounding alkenes, causing the formation of charged reactive species in the liquid close to the diamond surface [Wang, et al., 2007].

7. Biodetection based on organic monolayers on surfaces

Numerous examples of biodetection using organic monolayers have been described: for example, those based on fluorescence [Cattaruzza, et al., 2006], Raman scattering [Yonzon, et al., 2004], ellipsometry [Arwin, 2000 & 2001], infra-red [Liao, et al., 2006] or simply [Masuda, et al., 2005] have used the specificity of monolayer-functionalized surfaces. The geometry of the sensor also has a remarkable importance for the realization of the devices. Besides classical transmission and reflection modes, the need for compact sensors has favored the development of systems based on optic fibers and waveguide materials to transport light from the source to the binding area and to the detector [Sharma & Gupta, 2007]. Miniaturized microfluidics sensors, for example, can use silicon oxide or silicon nitride as waveguide and immobilization platform. In particular, Si_xN_4 is widely used, for example, as waveguide material in refractometric [Karymov, et al., 1995] or fluorescence [Anderson, et al., 2008] detection.

Among all optical techniques, one type of surface-based detection technique, surface plasmon resonance (SPR), has had magnificent success in the last 20 years [Phillips, K.S. & Cheng, 2007 & Phillips, M.M., et al., 2010]. Surface plasmon resonance (SPR) has been successful so far for many reasons include the easy cleaning and the infinite reuse of the sensor. Thiol based monolayers are normally grafted to gold or silver surfaces allow specific detection of DNA [Buhl, et al., 2007] or organic pollutants [Farré, et al., 2007 & Mauriz, et al., 2006] and pathogens [Chah & Zare, 2008] with coupling of DNA and antibodies. A significant improvement has been achieved with the formation of more multifaceted sensing architectures using the assembly of nanoparticles onto the gold surface of the SPR: the signal amplification caused by the coupling of the SPR signal with the localized surface plasmons of the metal or semiconductor nanoparticles (Fig. 7) has resulted in a 1000-fold increase in sensitivity, allowing the detection of picomolar concentrations, and approaches the performances of classical fluorescence based detection method of DNA hybridization [Hutter & Pileni, 2003].
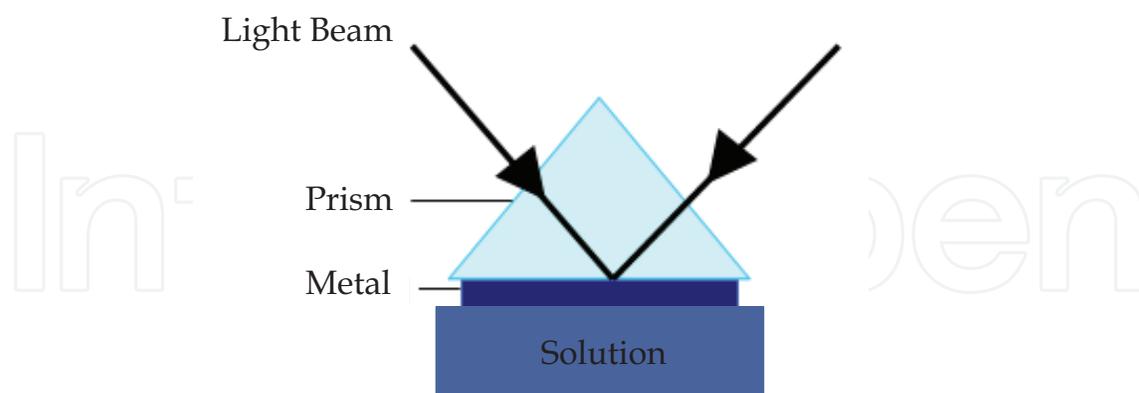

Fig. 7. SPR configuration for SPR detection: the light beam is directed towards the backside of a metal (gold or silver), by means of a prism. The front side of the metal is in contact with the solution to analyze. Adsorption of biomolecules on the metal changes the refractive index of the surface and decreases the intensity of the reflected beam.

The fluorescence of metallic or semiconducting nanoparticles has found their applications in biosensing and imaging [Bruchez Jr, et al., 1998 & Michalet, et al., 2005]. Similarly to SPR, the vibrating free electrons oscillations in metal nanoparticles can be together with

environmental factors result in variations in optical properties [Xu, et al., 2008]. DNA hybridization on surfaces modified with organic monolayers can cause the subsequent immobilization of functionalized nanoparticles (sandwich assay) [Bailey, et al., 2003]; their presence on the glass sensor can then be monitored directly, or after an amplification step, often carried out by reduction of the metal salt to increase the size of nanoparticles [Yang, N., et al., 2007].
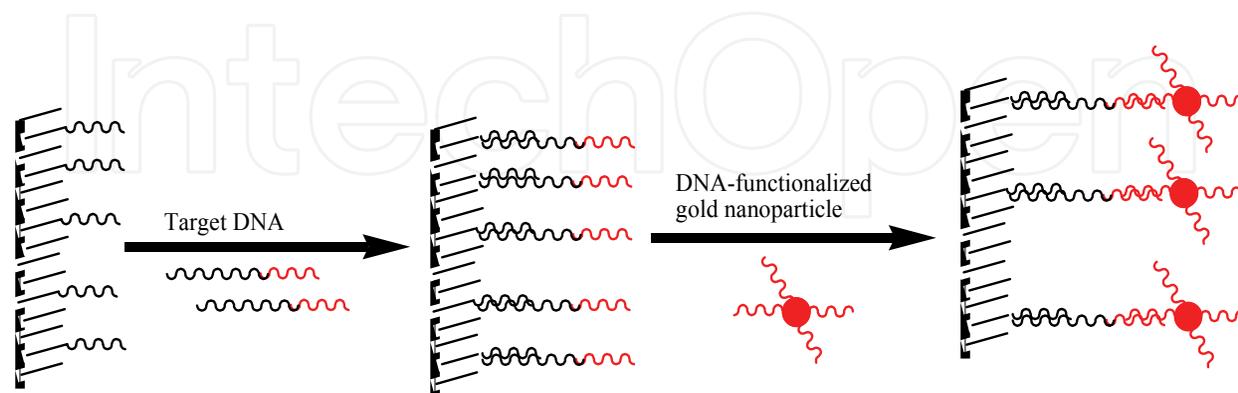

Fig. 8. Simplified SPR detection: nanoparticle-enhanced SPR.

In a similar way, the aggregation of metal nanoparticles functionalized with thiol-modified DNA single strands in the presence of the complementary DNA will cause a change in their melting behavior that can be observed by a change in their optical absorption, fluorescence or simply the visual aspect of the nanoparticles (Fig. 8) [Elghanian, et al., 1997]. Additionally, DNA, variations on this method have also enabled the detection of single amino acids or metal ions [Han, et al., 2006].

An additional use of monolayer-functionalized metal nanoparticles involves the coupling of their localized plasmon resonance (LSP) with fluorescence [Tam, et al., 2007] or chemiluminescence: the attachment of fluorescent molecules to metallic nanoparticles via organic monolayers can result in a dramatic increase in detection sensitivity, making single molecule detection and imaging possible (Fig. 9).

Another recent interesting sensing technique based on functionalized solid surfaces involves the use of photonic crystals, a type of mesoscopic structure formed by the periodical arrangement of nanosized objects. The resulting periodical variation of refractive index between bulk and void in the crystal causes the appearance of a photonic bang-gap: typically this causes sharp peaks in the transmission spectrum of the material. The position of these peaks is highly dependent on the refractive index in the voids of the crystal, allowing for an optical monitoring of adsorption processes at this location. Even the binding of small molecules on the highly developed surface of the crystals can cause a significant frequency shift in the resonant photonic crystal mode.

Several studies have investigated the use of surface-modified photonic crystals for biosensing applications; in particular, silicon can be used as a material for the fabrication of photonic crystals sensors, when combined with surface modification by hydrosilylation reactions with alkenes. Indeed, alkene-based monolayers can be readily formed onto the surface of porous silicon structures and the attachment and subsequent surface binding events can be monitored by the shift of the crystal optical band-gap [Alvarez, et al., 2009]. Such a silicon photonic crystal was developed to monitor the protease activity of biological samples [Kilian, et al., 2007], by immobilizing the protein angiotensine on the walls of the crystal: the

degradation of the protein caused by the presence of a protease induces a shift in the photonic band gap of the crystal.

Free-standing DNA-thiol coated gold nanoparticles
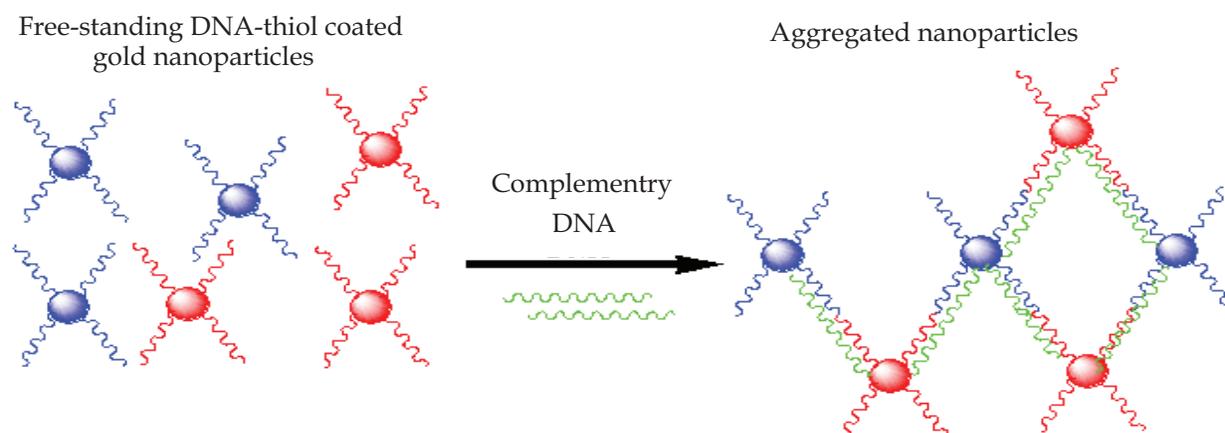
Aggregated nanoparticles

Complementry DNA

Fig. 9. Two types of DNA-functionalized gold nanoparticles, which carry different parts of the sequence to detect, aggregate when the target DNA is introduced, causing a shift in optical properties and melting behavior.

Besides optical techniques, electrical measurements have been intensively exploited for the development of biosensors. Metal and semiconductor surfaces coated with organic monolayers can be characterized by e.g. resistance, impedance or capacitance measurement [Chaki & Vijayamohanan, 2002]. The wealth of combinations of measurement modes and functionalized monolayers creates a large variety of sensor designs. Some examples of sensors include resistivity measurements to detect DNA hybridization [Hianik, et al., 2003], capacitance measurements to monitor the adsorption of nanoparticle-functionalized antibodies or the voltammetric detection of copper (II) ions on a gold electrode functionalized with a thiolderived sequence of chelating amino-acids (Gly-Gly-His, Fig. 10). Impedance measurements were also used to detect antibody–antigen interaction, by coating of silicon nitride surfaces with antibodies with an alkylsilane linker. The adsorption of rabbit immunoglobulin causes a change in the capacitance of the layer, which is used to monitor the interaction.

An important class of electrical biosensors is constituted by enzymatic electrodes: enzymes are immobilized onto metal electrodes and usually kept in presence of a red-ox mediator. In the presence of the analyte to detect (e.g. glucose [Alexander & Rechnitz, 2000], gluconic acid [Campuzano, et al., 2011], phenolic compounds [Liu, et al., 2006], the enzyme is converting the mediator into the other red-ox form, which is then detected at the electrode. Thiols have been extensively used to immobilize enzymes onto gold electrodes, often using acid-terminated monolayers and the subsequent formation of a strong amide bond with free amines of the enzyme. For enzyme electrodes, numerous studies describe the use of artificial bilayer membranes deposited onto electrodes: the two-dimensional liquid environment of lipid bilayers not only stabilizes the enzyme on the surface but also allows enough conformational freedom for the enzyme to function like in a natural membrane. Although artificial membranes are out of the scope of this review, it is important to highlight the positive role of covalent organic monolayers in the stabilization if these membranes. Compact linear alkyl monolayers, for instance, have been shown to stabilize bilayers membranes sitting on top of them [Zhang, et al., 2000]. In other studies, the integration of

some thiol compound within the bilayers also stabilizes the formation of synthetic membranes 303 or vesicles; such glycolipid-containing vesicles attached to gold electrodes, upon binding with concanavalin A, can decrease the typical reduction current of a solution of Fe(CN) (Fig. 11).

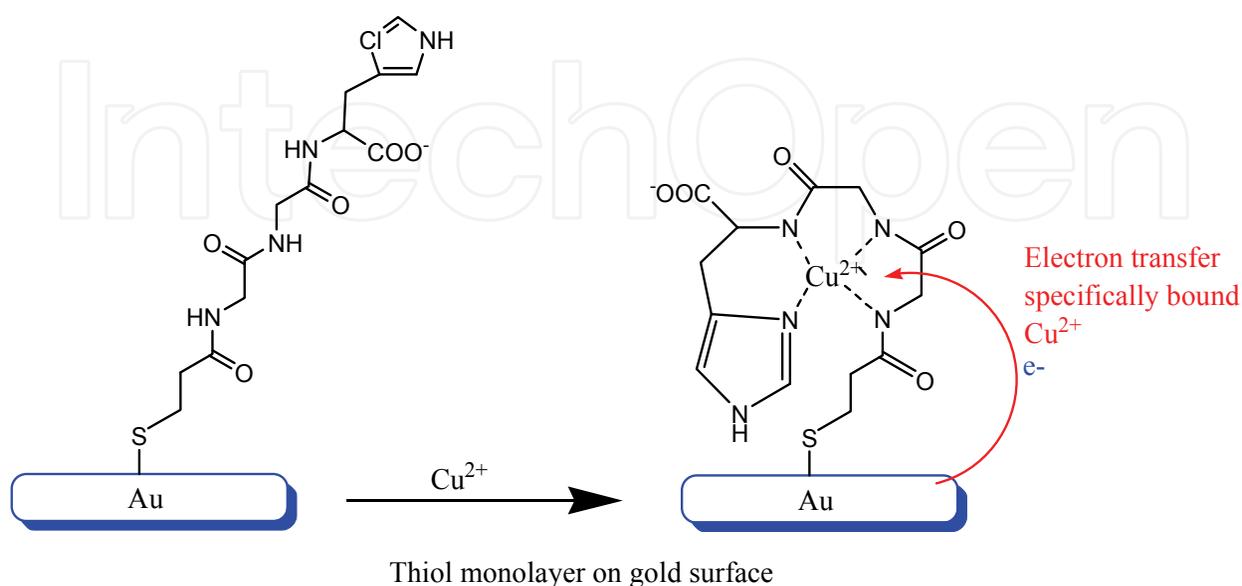Thiol monolayer on gold surface

Fig. 10. Specific binding of copper (II) ions onto gold electrode using a thiol-based monolayer of oligopeptide (Gly-Gly-His), the detection is carried out by voltammetry.
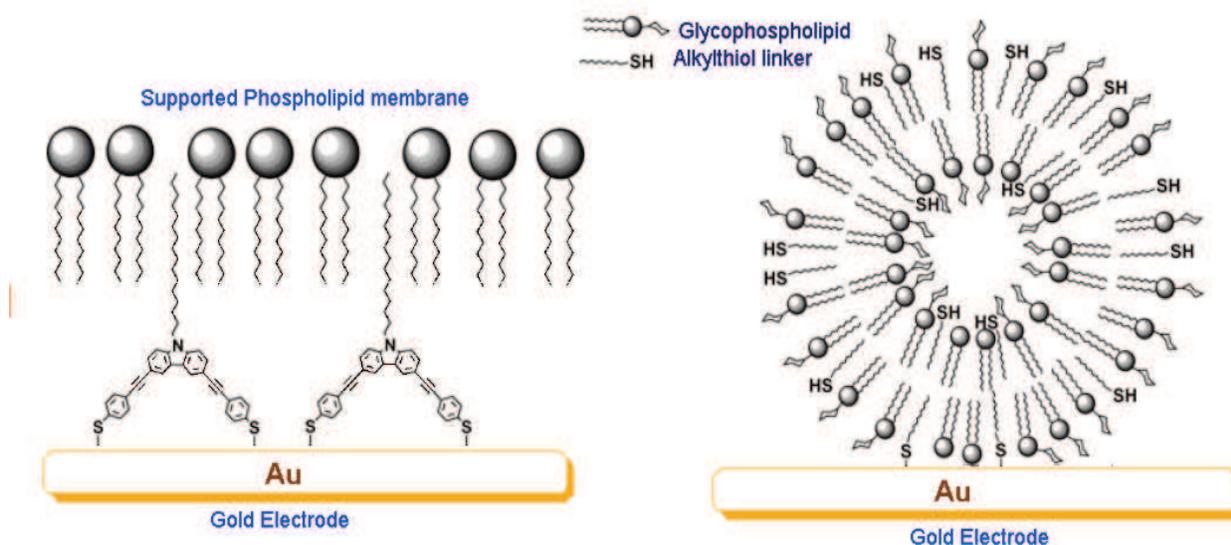
Fig. 11. Two examples of biomimetic membrane: a) bulky alkyl thiol linker to anchor flat phospholipid membrane and b) mixed vesicle prepared from glycophospholipids (for the specific binding of concanavalin A) and linear alkylthiol linkers.

The formation of covalent organic monolayers is an optimal way to control the surface of inorganic materials. The carefully designed bulk characteristics of a conducting, transparent or nanostructured inorganic device can be maintained even if surface properties need to be adapted to changing environments or applications. In this respect, they allow a

supplementary freedom in the design of nano- and microdevices. However, monolayers not only serve material science in this secondary function; they are nowadays at the center of new fields of research, such as nanopatterning or biocompatible surfaces.

So far, we have presented the general methods for the formation of covalent organic monolayers onto inorganic surfaces and a number of relevant applications where these nanometer-thick structures play a central role. Despite the wealth of applications, the fundamental aspects of monolayer formation are still undergoing intensive investigations; a basic internet query with ISI Web of Science on the topic "organic monolayers" shows an ever-increasing number of hits since 1990, which reaches almost 400 articles for the year 2008. Considering the current overwhelming trend in favor of nanotechnological research, which has brought an intense light upon a world dominated by interfacial effects, the interest in organic monolayers is likely to persist for a long time.

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Environmental Biosensors

Edited by Prof. Vernon Somerset

This book is a collection of contributions from leading specialists on the topic of biosensors for health, environment and biosecurity. It is divided into three sections with headings of current trends and developments; materials design and developments; and detection and monitoring. In the section on current trends and developments, topics such as biosensor applications for environmental and water monitoring, agro-industry applications, and trends in the detection of nerve agents and pesticides are discussed. The section on materials design and developments deals with topics on new materials for biosensor construction, polymer-based microsystems, silicon and silicon-related surfaces for biosensor applications, including hybrid film biosensor systems. Finally, in the detection and monitoring section, the specific topics covered deal with enzyme-based biosensors for phenol detection, ultra-sensitive fluorescence sensors, the determination of biochemical oxygen demand, and sensors for pharmaceutical and environmental analysis.

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