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REVIEW

Self-assembled monolayers (SAMs) for electrochemical sensing

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Abstract The past, present, and future of the application of self-assembled monolayers (SAMs) in electroanalytical chemistry is reviewed. SAMs for electroanalytical applications have been introduced in the early 1990s and since then have been exploited for the detection of different species ranging from metal ions to biomolecules and microorganisms. This review describes the different types of monolayers, surfaces on which they have been assembled, the various analytes, which were determined, and the various electrochemical techniques employed. The prospective and perspectives of this topic are discussed.

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Introduction

The recognition that self-assembled monolayers (SAMs) mostly on conducting surfaces can be used as the sensing element of an electrochemical sensor has followed closely the first studies of SAMs. These 2D layers seem to be the ideal approach of tailoring a surface and therefore controlling electron transfer, which is the basis of an electrochemical sensor.

A sensor is a device that measures a physical quantity and converts it into a signal which can be read by an observer or by an instrument. The latter is usually made of at least three consecutive events (Fig. 1): recognition of the analyte, signal transduction, and signal readout. In electrochemical sensors [1–7] signal transduction involves current, potential or impedance measurements that convert changes at the electrode–electrolyte interface into an electrical signal. These changes can follow electron transfer, charge accumulation, adsorption, or any other event comprising interactions between the analyte and the electrode surface. Most of these interactions are sensitive to the surface nature and morphology and therefore can be altered by a thin coating, such as a monomolecular layer. Hence, the design of an electrochemical sensor, regardless of the transduction involved, will aim, on one hand, at maximizing the analyte–interface interactions, and on the other hand, suppressing the interference–interface interactions.

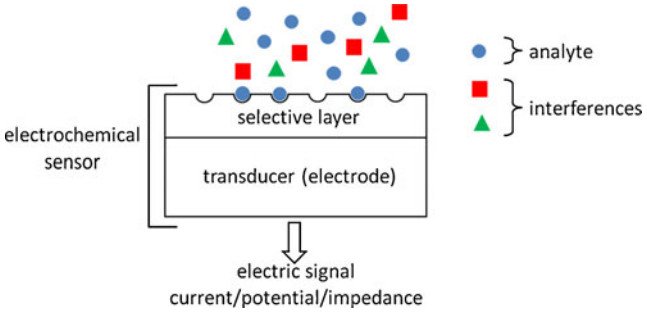

Fig. 1 Schematics of an electrochemical sensor

Analytes can span from atomic or small molecular species, such as metallic ions and gases to biological substances including macromolecules, such as enzymes and antibodies or antigens. To be able to architecture the electrode–electrolyte interface, and create proper recognition sites for such a variety of analytes, organic chemistry must be invoked. Hence, it is not surprising that electroanalytical chemistry took immediate advantage of the appearance of a simple approach for assembling organic layers on electrode materials such as gold and mercury.

This contribution aims to cover most of the reports in this area, namely, those studies whereby SAMs have been used as the recognition element, and as a result increased the sensitivity or selectivity or other properties of the electrochemical sensor. Hence, those studies where an SAM was used as a means of attaching a polymeric film or other components onto an electrode surface are not covered here. Moreover, we will discuss only systems where the organization of the SAMs was carried out on the electrode surface and therefore we will not cover, for example, Langmuir–Blodgett films. We are aware of a few previous reviews on this or related topics [8–12]. Reviewing the literature was accomplished primarily through ISI web of science database. Categorizing the different studies can be made on various bases, such as the type of analyte, the layer, the electrode material, or technique which was used. To facilitate the reading of this review, we have decided to focus mostly on the type of monolayer that was used, yet, we discuss also the electrode material and to some extent the nature of the analyte, and technique used in different subsections.

The monolayers

Historically, the first self-assembled monolayers to be reported were based on alkylsilanes [13]. These were assembled by the formation of a covalent bond between the monolayer and the surface. Much later other monolayers, such as thiols, have been introduced, and the terminology of self-assembly expanded and encompassed all sorts of layers and preparation methods. Thiol SAMs have become the most popular and common approach for assembling electrochemical sensors based on organic monolayers. Hence, we will begin by reviewing the application of thiol-based SAMs and continue with silane and other families of organic molecules that are nowadays used in electroanalytical chemistry.

Thiols

Sulfur compounds are known for their reactivity towards noble metals and other surfaces. Thiols adsorb spontaneously onto metals such as silver [14–16], platinum [15–17], palladium [18] and mercury [19–22], and on semiconductors, e.g., InAs [23] and GaAs [24]. However, the adsorption of thiols on gold, which forms an exceptionally strong bond, makes this system the most commonly used [9, 24, 25]. Gold surface does not have a stable oxide under ambient conditions [25], it is easily cleaned and adsorbs impurities weakly [26]. The thiol groups chemisorb onto the gold surface via the formation of a S–Au bond to form a densely packed, highly ordered monolayer. The mechanism of covalent bond formation was investigated by us [27] and is believed to involve charging and discharging steps while releasing H_2, as described in Fig. 2. The strong affinity of –SH groups to gold surface lies on the "soft" nature of both gold and sulfur atoms [26], as opposed to relatively "hard" atoms introduced by other groups such as acids or amines. For this reason, functionalization of gold surfaces using thiols with terminal groups can be efficiently achieved.

Mercury is commonly used as a substrate for thiols' self-assembly as well [28–31]. This electrode exhibits strong interactions with thiols (which are also called mercaptans due to their high affinity toward mercury) [9]. Moreover, mercury, because of its liquid state, is atomically flat.

The preparation of thiol monolayers various metals involves a very simple protocol. The desired substrate is dipped into the required dilute solution of the thiols [32]. The layer is formed spontaneously under open-circuit potential. The deposition is usually carried out in either protic (ethanol, water) or aprotic (acetonitrile, hexane) solvents at ambient temperature and under continuous stirring for periods that vary between a few minutes to several days [9]. The process is followed by thorough

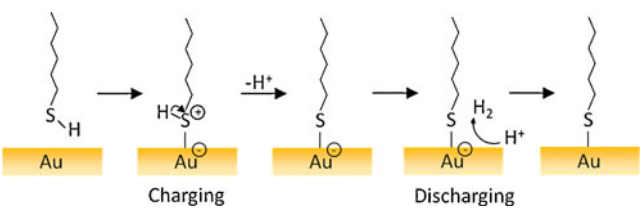

Fig. 2 Schematics of the adsorption of thiols on gold

washing of the substrate with the same solvent and drying, often using a jet of dry argon [32].

Extensive work has been devoted to the understanding of the mechanism of layer formation. It is thought to comprise two steps [9, 26]. Initially, there is a rapid attachment of the –SH group to a gold atom with formation of an S–Au bond. The initial fast adsorption step is followed by a much slower process of organization of the thiols when the alkyl chains are assembled together to maximize the van der Waals interactions between them.

These steps result in a well-assembled monolayer in which the alkyl chains of the thiols are in all trans-conformation, tilted at an angle of 30° from the normal to the metal surface in a $\sqrt{3} \times \sqrt{3}$ R30° adlayer [9, 25]. Moreover, and despite of the S–Au bond being reasonably strong, the adsorbed alkanethiols still have the ability to move around the surface [25]. These movements allow the alkanethiols to diffuse towards defects of exposed gold sites to maximize the coverage of the surface and to obtain a densely, highly organized, stable monolayer.

The formed layers can be examined by different macroscopic and microscopic surface techniques such as XPS, FTIR, wettability measurements, electrochemistry, and scanning probe microscopies [9]. The different studies scrutinize the experimental factors affecting the formation and packing density of the monolayers. The structure of the monolayers strongly depends on the substrate and its morphology [9, 33]. Usually, the roughness of the substrate is of a similar order or greater than the size of the adsorbate [25]. Cleaning procedures and pretreatment of the surface are essential for fabricating atomically flat gold surfaces. Common pretreatments are chemical treatment in piranha solution, electrochemical oxidation, and reconstruction in electrolytes like H_2SO_4 and flame annealing.

The concentration of the thiol solution also plays a crucial role in determining the quality of the formed layer. Formation of ordered monolayers usually requires a dilute solution, whereas a high concentration favors multilayer formation [32]. Other parameters controlling the deposition process are the temperature [34, 35], pH [36, 37], and the architecture of the electrode [38, 39].

The stability of the layer strongly depends on the nature of the adsorbate. The strongest binding occurs between gold and thiol groups, but other species such as disulfides, thiones, thioesters, etc. have been used [26].

As mentioned, the compactness of the layer relies on the intermolecular interactions between the adsorbate molecules [9]. Longer aliphatic chains will lead to stronger van der Waals interactions and hence produce more ordered SAMs with higher integrity (less defects) and thermal stability. Molecules, such as 16-hexadecanethiol, lead to well-packed quasicrystalline monolayers, whereas shorter thiols, such as 6-hexanethiol, yield liquid-like monolayers. For this reason, hydrogen bonding [40] or π–π interactions [14] exhibit even better thermal stability.

The simple procedure for SAM formation, the high stability, and the strong affinity of the thiols towards a variety of electrode materials [32] are the reasons for the wide application of thiols in electroanalytical studies. The use of monolayers in electroanalytical applications requires stability over a wide potential window. This was studied by Beulen et al. [41] who found that adsorbed thiols exhibit only a limited potential window between approximately −0.8 and −1.4 V versus SCE.

At more negative potentials thiols are reductively desorbed (Eq. 1):

$$R - S - Au + e^- \rightarrow R - S^- + Au_{(s)}, \quad (1)$$

where the potential of reductive desorption depends on the nature of thiol, i.e., chain length, head group repulsion, etc. For example, more hydrophobic thiols exhibit more negative desorption potentials [10].

At anodic potentials, an oxidative desorption of thiols occurs. The mechanism of the oxidation is somewhat unclear and might involve cleavage of the C–S bond, oxidation of sulfur to sulfate, and formation of RCO_2^- [10]. In spite of the instability in extreme potentials, the exhibited potential window has been compatible with many electrochemical applications [25].

Another limitation of using SAMs of thiols for electroanalytical applications derives from the necessity of a conducting interface. For this reason, usually short chain alkanethiols are used, which enable, on one hand, electron transfer across the layer, but on the other hand, reduce the stability of the interface. The most commonly used thiols have been cysteamine, 3-mercaptopropanoic acid, 2-mercaptoethanesulfonic acid, mercaptoethanol, and others.

Thiol-based SAM sensors have been used to monitor pH, inorganic species, and organic molecules using both chemical and biological recognition elements. Thiols can be used in electroanalytical devices in five main approaches (Fig. 3): (1) functionalized thiols, whereby the thiol bears functionality typically at the other end of the molecule; (2) functionalization followed by attachment, where a complex entity, e.g., cyclodextrin, is thiolated prior to adsorption; (3) attachment followed by modification, i.e., functionalization of a thiol-based SAM; (4) attachment of a mixed layer composed of two or more different thiols; and (5) attachment followed by incorporation.

Functionalized thiols This is a very common approach (Fig. 3a) as it takes advantage of commercially available thiols. The requirements of the thiol are straightforward: the X group should not interact with either the thiol or the surface, although alkanedithiol, for example, have also been

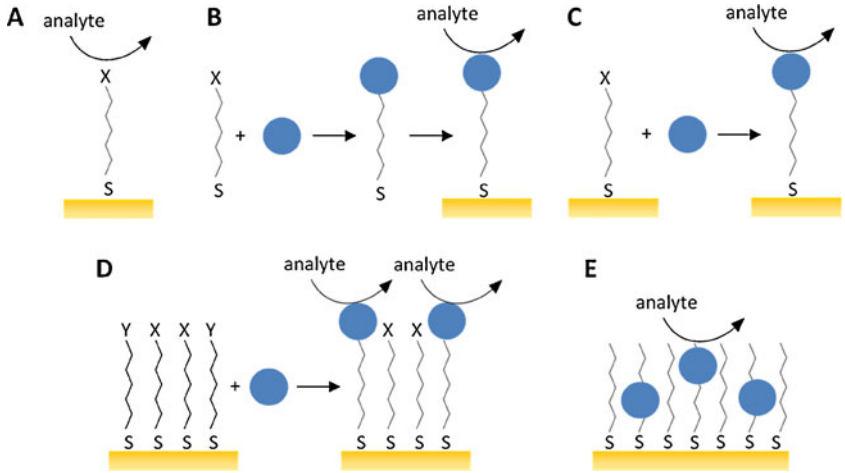

Fig. 3 Schematics of the different approaches for assembling thiol-based SAMs. **a** Functionalized thiols, **b** functionalization followed by attachment, **c** attachment followed by functionalization, **d** attachment of a mixed layer, and **e** attachment followed by incorporation

used successfully for the detection of Cd^{2+} [42]. In addition, the alkyl (or in some cases the aromatic) chain should be relatively short to avoid blocking of electron transfer. The functionality, X, should be stable and have the highest possible selectivity towards the desired analyte.

The advantages of this approach are clear, simple and cheap to implement, and of very high sensitivity [22, 43]. On the other hand, the disadvantages of this concept are that mainly only small analytes such as metallic ions (Cu^{2+}, Fe^{3+}, Hg^{2+}, and lanthanide ions) or small organic molecules (dopamine, ascorbic acid, epinephrine, and uric acid) can be addressed because of the relatively small distance between the functional groups. Moreover, the ability to form multidentate functionalities requires elaborated synthesis, and the cooperative interaction between a few thiols is not simple due to the high density of the layer and its relatively rigid structure.

The most common functionalities that have been used include carboxylic acids and more specifically 2-mercaptoethanoic acid, 3-mercaptopropanoic [44–48] acid, thioglycolic [49, 50] acid, glutathione [51–53], thiolactic acid [51–55], lipoic acid [56, 57], and mercaptosuccinic acid [58–61] although longer—up to ten carbons have also been reported [22, 62]. Cysteine [37, 63–71] and its derivatives, such as penicillamine [72–74] have also been extensively used.

Conventional n-alkanethiols were used for the determination of hydrophobic compounds such as proteins [75], hydrophobic drugs [76], and organic ordnance molecules [77]. Other functional groups, such as amine (using cysteamine [78] or amino-functionalized aromatic thiols [43, 79–82]) and sulfonate (using mercaptoalkanesulfonic acid) [83–85] are also commonly introduced. Table 1 summarizes many of the reported studies using this "functionalized thiols" approach.

Simple commercially available thiols can also be applied for constructing disorganized layers [84–87]. This is accomplished by using thiols with a large mismatch between the head group and the tail to form a selectively permeable layer. This feature of disorganized layers opens the way to using them as selective filters for species in correspondence to the nature of the film. For instance, Herzog et al. [84, 86] used disorganized monolayers to protect the electrode surface from the adsorption of surfactants while simultaneously allowing the underpotential deposition and stripping of metals ions. Hydrophobic layer allowed the penetration of organic molecules [87] while a charged hydrophilic layer was used for the selective penetration of metallic complexes of opposite charge [85].

Functionalization followed by attachment The second approach involves "wet chemistry" that is functionalization of the thiol prior to its adsorption (Fig. 3b). This allows applying the conventional and versatile organic synthesis in solutions, the isolation, purification, and characterization of the monolayer precursor before assembling the SAM. Since the thiol group is a rather good nucleophile, synthesis is often carried out after protecting the thiol by either formation of the disulfide (R–S–S–R) or introducing other thiol-protective groups, such as acetyl, benzoyl, and 2-methoxyisobutyryl [88]. A different approach is to maintain inert atmosphere during the synthesis and using dry solvent (e.g., dimethyl formaminde) [89]. Table 2 details numerous examples whereby different molecules were thiolated prior to their assembly on gold surfaces. It can be seen that the nature of the functionalized molecules is very broad and includes organic species, such as cyclodextrin and calixarenes as well as biomolecules including DNA and proteins. The SAMs based on these thiolated substances were used for detecting a variety of aqueous soluble species ranging from metal ions to bacteria.

Attachment followed by modification The third approach complements the previous one and is widely used. The strong binding of thiols onto gold and other surfaces

Table 1 Functionalized thiols and their electroanalytical applications

Thiol	Analyte	Reference
Mercaptoalkanoic acids	pH	[62]
	Metal ions	[44, 46, 48, 62]
	Catecholamines	[45, 47]
Other carboxylate functionalized alkanethiols	Metal ions	[50–53, 57, 58, 61]
	Catecholamines	[49, 54, 55, 59, 60]
	Proteins	[56]
Cysteine and derivatives	Metal ions	[63, 66, 69, 71, 74]
	Catecholamines	[37, 67, 70, 72, 73]
	Large organic/biomolecules	[64, 65, 68]
n-Alkanethiols	pH	[311]
	Organic molecules	[75–77, 312]
1,n-Alkanedithiols	Metal ions	[42, 313]
Cysteamine	Catecholamines	[78]
Amino-functionalized aromatic thiols	Metal ions	[43, 314, 315]
	Organic/biomolecules	[79–82]
Mercaptoquinone derivatives	Metal ions	[316]
	Organic molecules	[316, 317]
	Proteins	[318]
Mercaptoalkane sulfonic acids	Metal ions	[83–85]

provides an effective way to use these molecules as primers for immobilization of further organic and biologic compounds with different functions [10] (Fig. 3c). The layer remains chemically intact even after coupling with the immobilizing molecules [32]. Moreover, only a minor amount of modifier is needed for immobilization on the functionalized SAM [32]. Furthermore, either a single or multirecognition elements can be introduced to the electrode using more than one type of recognition molecule which operates cooperatively [25].

The immobilized feature can be attached to the layer through covalent links (such as amide bonds and Schiff's base formation [90, 91]) either directly to the functionalized thiol monolayer [35, 92–99] or by the assistance of bridging

Table 2 Thiolated compound-based SAMs and their electroanalytical applications

Thiolated compound	Analyte	Reference
Cyclodextrin	Metal ions	[19, 319]
	Electrochemically active organic analytes, e.g., catecholamines, TNT	[320–323]
	Electrochemically inactive organic analytes (e.g., glucose)	[324–326]
DNA probe	DNA hybridization	[136–139, 273, 327]
	Proteins	[140, 143, 308]
	Virus and bacteria	[144, 328, 329]
Calixarene	Metal ions, catecholamines	[220, 330, 331]
Metallic complexes	pH	[126]
	Inorganic analytes	[278]
	Organic analytes	[275, 298]
Proteins	Nitroaromatic compounds, antigens	[332, 333]
Polymers and macrocyclic polymolecules	Metal ions	[299, 334, 335]
	Nonelectroactive organic analytes	[145, 336]
	DNA	[337]
Organic compounds	pH	[338]
	Metal ions	[339, 340]
	Organic analytes	[341–344]

TNT troponin T

molecules (most common—glutardealdehyde [100–107]). The attachment of DNA or other probes is often carried out in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) and *N*-hydroxysuccinimide (NHS) [108–112]. Other noncovalent coupling comprises electrostatic [90, 91, 113–118] and hydrophobic/hydrophilic interactions. Metallic complexes are often bound to the electrode through coupling reactions [119–123]. The immobilization can also be driven by affinity interactions, such as receptor–protein recognition and antigen–antibody

Table 3 Functionalizations of thiol-based SAMs and their electroanalytical applications

Modifier	Analyte	Thiol	Reference
Proteins			
Glucose oxidase	Glucose	Carboxylate-terminated thiols	[102, 103, 127, 345–347]
		Amino-terminated thiols	[127, 348]
Cytochrome C	NO, O_2^-, H_2O_2	Carboxylate-terminated thiols	[349, 350]
		Mixed hydroxyl/amino and carboxylate-terminated thiols	[92, 128, 133–135]
		Penicillamine/cysteine	[351, 352]
		n-Alkanethiols	[353]
Other oxidases (e.g., tyrosinase, horseradish peroxidase, alcohol oxidase, etc.)	Alcohols, catechol, catecholamines, H_2O_2, lactate, etc.	Carboxylate-terminated thiols	[354–357]
		Amino-terminated thiols	[104, 106, 358, 359]
		Mixed hydroxyl/amino and carboxylate-terminated thiols	[128, 353]
Dehydrogenases (e.g., fructose dehydrogenase, superoxide dismutase)	Alcohols, uric and gluconic acids, fructose, O_2^-	Carboxylate-terminated thiols	[100, 101]
		Thiol-substituted nucleobases	[360]
		Amino-terminated thiols	[361, 362]
Hemoglobin	H_2O_2	Amino-terminated thiols	[363]
		Phosphonic acid-terminated thiols	[364]
Peptides	Metal ions	Carboxylate-terminated thiols	[35, 98, 365–368]
Nucleic acids			
ssDNA	DNA hybridization	Carboxylate-terminated thiols	[97, 108–110]
		Amino-terminated thiols	[369]
dsDNA	Electroactive/nonelectroactive organic molecules and drugs	Azide-terminated thiols	[370, 371]
		Amino-terminated thiols	[115]
		Avidin	[125]
PNA	DNA hybridization	Carboxylate-terminated thiols	[111, 306]
		Amino-terminated thiols	[112, 372]
Antibodies	Proteins, toxic antigens, bacteria	Carboxylate-terminated thiols	[38, 93, 124, 284, 294, 373–375]
		Amino-terminated thiols	[38, 105, 309, 376–378]
		Sulfonate-terminated thiols	[310]
		Thiol-terminated thiols (dithiols)	[379]
Nanoparticles			
Au NPs	Catecholamines, proteins, peptides, DNA, H_2O_2	Thiol-terminated thiols (dithiols)	[380–384]
		Amino-terminated thiols	[107, 117, 385–390]
CNT	Aromatic compound, DNA	n-Alkanethiols	[285]
		Amino-terminated thiols	[300]
Prussian blue NPs	H_2O_2	Cysteine or dithiols	[391]
Metallic complexes			
Iron complexes	Organic (e.g., hydrazine) and inorganic (e.g., SCN^-, H_2O_2) compounds	Hydroxyl-terminated thiols	[121]
		Thiolated pyridine	[122, 123]
		Cysteine	[118]
Cobalt complexes	H_2O_2, cysteine	Hydroxyl-terminated thiols	[119–121]
Copper complexes	Catecholamines	Carboxylate-terminated thiols	[113]

PNA peptic nucleic acid

pairs. Biotin–avidin is one unique example, leading to this type of surface immobilization [32, 124, 125]. Table 3 provides many examples of this approach. It can be seen that a wide variety of modifiers, e.g., proteins and nucleic acids, have been attached by coupling to activated thiols and have been used to determine different analytes. It should be noted that this approach allows introducing different enzymatic or other highly selective recognition factors for maximizing the analyte–SAM interactions.

Attachment of a mixed layer The fourth approach is based on the formation of a multicomponent SAM as a result of adsorption from a mixture of thiols [25] (Fig. 3d). The monolayer can be functionalized prior or after attachment of the thiols.

One advantage of such mixed system is the ability to construct integrated molecular systems where several components are incorporated within a single monolayer [25, 126–132]. Yet, the principal application of mixed monolayers is to allow large recognition elements to be spaced apart from each other. Furthermore, by varying the composition of a mixed SAM, the density of attachment points, and hence the surface loading of recognition molecules, can be controlled while blocking bare areas of electrode. One example is the controlled immobilization of cytochrome C. This recognition element can be covalently bound to carboxylic moieties. Hence, a spacer having either amine [133, 134] or hydroxyl [92, 135] end groups was used. Another example is the attachment of thiolated DNA probes. These are often used for the determination of large biological molecules, such as target DNA [136–142], proteins [140, 143], and viruses [144] and hence a spacer is necessary to maximize the interactions with the analyte. Table 4 details the studies where DNA and other modifiers were immobilized onto a mixed layer of functionalized alkanethiols.

Attachment followed by incorporation An additional approach comprises the incorporation of a recognition element into an SAM of thiols. An SAM of long chain alkanethiols produces a highly packed and ordered monolayer, which mimics a membrane-like microenvironment, useful for immobilizing biological (antibodies, enzymes, nucleic acids) and organic molecules [32] (Fig. 3e). For example, Radecka et al. [145] embedded macrocyclic polyamine molecules with long alkyl chains within 1-dodecanethiol SAM for the detection of adenine nucleotides.

Silanes

Silane layers applied to electroanalytical devices have been used in many applications. As mentioned, silanization was the first reported method for formation of organized SAMs, as introduced by Sagiv et al. [13]. They demonstrated that alkyltrichlorosilanes on polar surfaces, i.e., bearing hydroxyl groups, lead to the formation of chemically bonded organized monolayers. Introducing silanes onto the electrode surface is straightforward and involves the covalent attachment of a silane precursor, i.e., derivatives of either trialkoxy- or trichlorosilane, through nucleophilic attack of an activated hydroxyl group (Fig. 4). For this reason, oxides, such as SiO_2 [146–148] or indium tin oxide (ITO) [149–152] are often used, but other metals could be used as well. For example [153], Ti was anodically treated to obtain TiO_2, which was further treated with NaOH solution, to increase the presence of –OH groups on the surface.

Silanization requires the immersion of the electrode into a dry solution of the desired silane, tailoring the conditions in accordance with the desirable outcome: at room temperature [147, 148, 152–156] or under slight heating [146]; the solvent can be either toluene [146–148, 152, 153, 156], ethanol [146, 154], or acetone [155]; the silane concentration varies from 1% [146, 152, 155] up to 20% [147]; and the duration of silanization can vary from 30 min [148, 153] to overnight and longer [155]. This ability shows the high flexibility of the process and the ease of obtaining high yields. On the other hand, it is not surprising that the literature is full of different protocols that are used to form SAMs from even the most conventional silane precursors, such as octadecyltrimethoxysilane and octadecyltrichlorosilane.

Surveying the literature of electroanalytical studies using silane layers reveals that, similar to thiols, there have been a few major approaches used for functionalizing the interface. These include: attachment followed by functionalization, i.e., modification of pre-attached silane layer; functionalization followed by attachment, whereby the silane is modified

Table 4 Different SAMs based on mixed thiol and their electroanalytical applications

Modifier	Functionalized thiols	Spacer	Reference
Antibody	Amino-terminated thiols	Hydroxyl-terminated thiols	[105]
Cytochrome C	Carboxylate-terminated thiols	Hydroxyl-terminated thiols	[92, 135]
	Carboxylate-terminated thiols	Amino-terminated thiols	[133, 134]
DNA	Carboxylate-terminated thiols	Hydroxyl-terminated thiols	[306]
	Azide-terminated thiols	Hydroxyl-terminated thiols	[370]
Au NPs	Dithiols	n-Alkanethiols	[381]

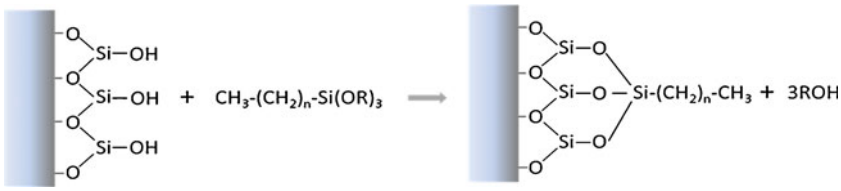

Fig. 4 Scheme of the silanization process

prior to self assembly onto the surface; and attachment followed by incorporation (Fig. 5).

Attachment followed by functionalization Most electroanalysis-related studies employ alkylsilanes, which possess a functional modification on the far end (Fig. 5a). This approach has been recently reviewed by Schubert et al. [157]. One important advantage is that it is possible to apply a broader range of chemical reactions to the silane monolayer as they are much more stable, physically and chemically, compared with other SAMs, such as thiol-terminated monolayers [157]. Silane precursors cannot bear many of the possible functionalities, such as acidic groups, e.g., carboxylic acids, sulfonates, phosphonates, etc., yet amines, thiols, and alcohols can readily be attached onto oxides by this approach and used as anchors for further immobilization of additional functionalities onto the interface. Accordingly, the mostly applied functionalities have been amines [146, 150, 153, 154] and epoxy groups [147, 152, 155, 156], which were utilized for attaching biologic species, such as proteins [147], DNA [150], or antigens [153–156], primarily through the formation of amide bonds.

Other chemical functionalizations were introduced onto the silane layer through nucleophilic substitution reactions. For instance, bromine-terminated surfaces were reacted with various nucleophiles, such as –SCN, $–NH_2$, $–SO_3^-$, and other, as a means of introducing additional surface functionalities [157]. This opened a window for the immobilization of many recognition elements, such as cyclodextrins [158] and metallic complexes [159].

Functionalization followed by attachment While in most cases, modification takes place after silanization of the electrode, it is also possible to functionalize the silane prior to surface modification (Fig. 5b). Synthetically, this allows to not only introduce different more sophisticated functionalities, but also makes it possible to carry out much better purification and analysis of the precursor prior to attachment onto the electrode surface. For example, Sharme et al. [148] coupled silane-modified polyethylene glycol (PEG) through a single-step coupling reaction. The PEG–silane was further used to modify a Si electrode. The thin PEG interfaces were proven to be very efficient in controlling protein fouling using fibrinogen as the model protein. Metallic complexes can also be introduced onto silanes prior to attachment. Gupta et al. demonstrated the synthesis of an osmium bipyridyl complex functionalized with a trimethoxy group which was used for the attachment onto silicon substrate [157, 160].

Attachment followed by incorporation A third option is to incorporate an external selective factor into an inert matrix of a silane layer [161, 162] (Fig. 5c). This method takes advantage of the so-called "disorganized self-assembled monolayers" (mentioned above), which are purposely assembled with low organization to afford the incorporation of additional molecules onto their matrix. The embedded amphiphilic molecules lead to a better flexibility of the layers, which can now adopt the best conformation for higher selectivity. Moreover, the incorporated amphiphiles are allowed to diffuse laterally in the monolayer and easily interact with the analyte. For example [161], macrocycle tetramethylcyclam ligands were introduced into a disorganized monolayer of octadecylsilane attached onto an ITO electrode for selective recognition of Cu^{2+} ions.

Another aspect of integrating silanes in electrochemical analysis is modifying an electrode through the sol–gel technique [5, 163, 164]. Sol–gel for sensing application has been reviewed by Walcarius [5], Lev [165], and others. Since sol–gel materials almost always result in thicker films and cannot be referred as self-assembled monolayers, we shall not review these studies.

Examining the various studies where silanes were used for assembling electroanalytical systems suggests a few advantages as well as disadvantages of this family of

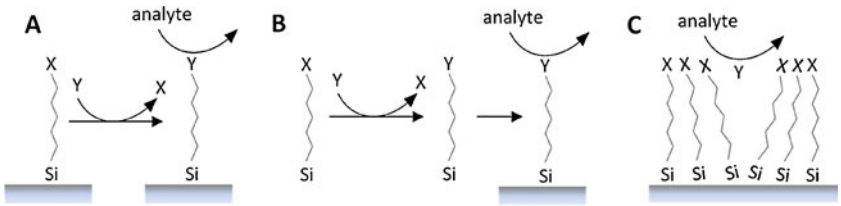

Fig. 5 Schematics of the different approaches for functionalization of surface through silanization. **a** Attachment followed by functionalization, **b** functionalization followed by attachment, and **c** attachment followed by incorporation

molecules. Clearly, the advantages stem from the covalent binding between the surface and the silanes. This results in highly stable and robust layers that can in principle withstand harsh conditions. Moreover, the silanization process is simple, does not require sophisticated equipment or extreme conditions, and is fairly generic. On the other hand, the high reactivity of silanes makes it difficult to end with a monolayer rather than multilayers, which often blocks electron transfer and are less permeable towards the analyte. Furthermore, this reactivity limits the "functionalization followed by attachment" approach mentioned above. Finally, attachment can be applied to hydroxylated surfaces, which is not always the case in particularly for noble metals such as Pt and Au. Obviously, the best surface for silanization in terms of electrochemical applications is silicon, yet, it requires a thin oxide film, which avoids employing many of the electrochemical methods, e.g., voltammetry and amperometry. Hence, it is very likely that we will witness more electrochemical sensors based on silane monolayers on Si that employ other electrochemical techniques, e.g., potentiometry and impedance, and particularly will be integrated as part of solid-state devices such as field effect transistors.

Diazonium

Modification of surfaces with aryl diazonium salts has been reviewed in detail by Downard [166], Pinson [167], and Gooding [25]. Briefly, the covalent attachment of molecular species to surfaces via the electrochemical reduction of aryl diazonium salts was first reported in 1992 by Pinson, Savéant, and coworkers [168]. The essence of this approach involves the formation of a covalent bond between electrogenerated species in the solution and the electrode surface. This process is usually termed electrografting. Specifically, the grafting process comprises the electroreduction of diazonium salt [167], ArN_2^+, in aprotic media (mostly acetonitrile) [168–181] or in an acidic aqueous medium (such as H_2SO_4 or HCl, pH <2) [182–185] and in the presence of NBu_4BF_4 as a supporting electrolyte. Reduction of the salt takes place by applying negative potential to the surface, which serves as a cathode. Reduction can be effective by either cyclic voltammetry or controlled potential electrolysis [183]. The reduction involves a one-electron mechanism producing aryl radical, accompanied by the release of a stable nitrogen molecule. Such aryl radicals are unstable and react immediately with the electrode surface to form a covalent bond. The cathodic reduction potentials of diazonium salts are relatively positive, typically around 0 V versus SCE, most likely due to the stabilization by the aryl group [25, 167, 186]. The stability of the aromatic group prohibits its further reduction and therefore enhances the reaction with the surface. The grafting process, which typically takes from seconds to no more than a few minutes [167, 181] is described in Fig. 6.

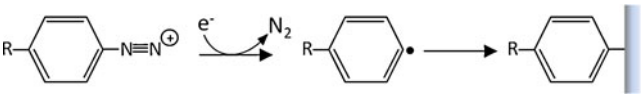

Fig. 6 Electrochemical grafting mechanism of aryldiazonium salts

There are several parameters that control the grafting process and influence the structure of the deposited films. Among them are: the applied charge (or potential) [171, 176], reduction duration [176, 187], media [171], salt concentration [180], electrode [166], the substituent in the para position of the aryl diazonium salt [25], etc. For instance, Brooksby and Downard [171] applied electrochemistry and AFM and concluded that the film thickness increases with deposition time up to a limiting value of five layers (ca. 4–6.5 nm for different modifications). Also, films prepared in acidic aqueous medium were found to result in lower limiting thickness and surface coverage than those prepared in acetonitrile. This was attributed to growth of inherently more blocking films as supported by examination of the response towards $Fe(CN)_6^{3-/4-}$ couple [171].

Modification of electrodes by aryldiazonium reduction has some clear advantages. First, the preparation of diazonium salt is well established in the organic chemistry literature and involves a one-step synthesis from a wide range of aromatic amines. This allows modifying the surface with a wide array of functionalities for a variety of applications. In addition, the reduction of diazonium salts leads to the formation of a strong covalent bond between the electrode and the desired modifier. Researchers reported on stable modified electrodes for long-term storage, even under extreme conditions such as sonication in aggressive organic solvents.

Moreover, a large variety of materials can be modified by this method: carbon [168, 173, 174, 176–179, 183–186, 188], metals [170, 175, 177, 181, 188], and semiconductors [167, 169, 181]. In order to create metal–carbon bonds, one should work with surfaces as free from oxides as possible. For this purpose, it is necessary to polish the surface very carefully. Liu and Gooding [177, 188] reported that electrochemical reduction of 4-carboxyphenyl diazonium salts on gold electrodes yielded more stable layers (i.e., longer storage and withstanding higher repeated cycling abilities) than n-alkanethiol self-assembled monolayers, probably due to stronger binding energy [167].

Removing of oxide is also necessary in the case of silicon. For modifying Si by reduction of diazonium, hydrogenated silicon should be used. In this case, the grafting mechanism involves attack of the Si–H bonds on the surface by the aryl radical to produce a silyl radical. The

modification is a result of the recombination of both radicals to form Si–C bonds [189].

An additional advantage is the cathodic reduction potentials of diazonium salts. As mentioned above, and in contrast to many of the other methods (such as electrochemical oxidation of amines or carboxylates or oxidative electrolysis of hydrazides [167]), the potential is mild (<0 V versus SCE) and can therefore be performed on oxidizable substrates such as iron and other reactive metals.

The formation of the organic films can easily be confirmed and characterized using different electrochemical and spectroscopic techniques. For example, nitrophenyl groups are excellent reporting groups for electrochemical studies [167, 179] as they show a quasireversible typical voltammogram of a nitrophenyl group.

For electroanalytical applications, the discussed method exhibits an important property as it does not lead to surface roughening and large background currents. Moreover, the layers provide a wider potential window for electrochemical applications than other layers such as thiols [177, 188]. The organic layer can also protect the electrode surface from fouling by protein adsorption [166, 173].

However, this method bears a major disadvantage as well. The electrodeposition of aryl diazoniums has been known to produce films from submonolayer up to multilayers [166, 167, 169, 175, 176, 181, 190]. Namely, there is a good possibility for further attacking of the ortho position of grafted aryl groups by remaining radicals in the solution to form multilayers [25]. The latter are not desirable in order to achieve maximum communication via electron transfer [175]. However, different investigations [166] have shown that it was possible to obtain either monolayers or multilayers by controlling the different parameters (mentioned above). For example, potential sweep methods lead to thicker films than fixed potential depositions [175].

Limoges and Dequaire [166, 184, 185] were the first to use grafting of screen-printed graphite electrodes by diazonium reduction as the first step in the fabrication of electrochemical biosensors. Diazonium-modified electrode can be found in electroanalytical applications in two manners, either as a charged layer [173, 174, 182] or as a substrate for further functionalization [175, 177, 179, 183–185, 188, 191–194]. In the first approach, the electrodes can be modified with p-phenylacetate groups by electrografting of the corresponding diazonium salt [174]. For example, at pH 7.4, the layer is negatively charged. This can lead to electrostatic attractions between the surface and dopamine, which is monocationic in this pH, and repulsion towards ascorbic acid, which is still in its anionic form under these conditions. Electrostatic interactions at the electrode interface are crucial to dopamine adsorption [182] and permit the detection of concentrations down to nanomolar level of this neurotransmitter.

For functionalizing the electrode with further modifications, there are two commonly used diazonium ions: 4-nitrophenyl and 4-carboxyphenyl. After grafting to an electrode, the nitro ($-NO_2$) group of the 4-nitrophenyl can be electrically reduced (in protic media) to amino ($-NH_2$) [178], which can, in turn, bind to a large selection of compounds, such as pyrroloquinoline quinine for NADH detection [175], oligonucleotides for viral DNA sensing [185], protein such as acetylcholine [193], or glucose oxidase [194] for biosensing applications or Co(II)tetracarboxyphthalocyanine complex for thiocyanate catalytic oxidation [179] through amide bonds. The carboxylic moiety of 4-carboxyphenyl could also be used for further covalent modification through amide bonds as well. Liu et al. [35, 177] used oligopeptides for the selective detection of Cu^{2+}, Cd^{2+}, and Pb^{2+}. Proteins could also be immobilized in the same manner [192]. Carboxylic groups were also used for the accumulation of metallic ions, such as Cu^{2+} and therefore applied for the detection of contaminants in aqueous media [183]. Most of these and other modifications are generally assisted by EDC and NHS used as coupling (cross-linking) agents.

Other layers

Primary and 2° amines have been coupled to electrode surfaces, mainly glassy carbon electrode (GCE), via oxidation of the amine head group [166]. The mechanism was studied by Barbier, Pinson, and coworkers [195] and is believed to involve the loss of a proton to form an amine radical cation, followed by further grafting of the radical onto the surface.

The main factor affecting layer formation is steric effects. Higher molecular weight amines require higher concentrations or repeating cyclic scans, most probably due to conformational disorder in the alkyl chain which deters the access of the amine to the active sites on the surface. For this same reason, 2° amines, although exhibiting a well-defined oxidation process, lead to low surface coverage. This is attributed to the substituents hindering the access as well [166]. The ease of electrochemical formation of SAMs based on primary and relatively short amines offers a significant advantage that so far has not been exploited. In other words, it seems that short and primary amines, which are superior in terms of facile electron transfer, would form also better SAMs.

However, amines are less common in electroanalytical applications. One reason is the questionable stability of the formed layer. The grafted monolayers of amines are easily oxidized into imine or iminium ions which are readily hydrolyzed by water molecules resulting in the cleavage of the layer.

Moreover, ω-functionalized amines, in particular diamines, often lead to either ring structures, where both functionalities

are bound to the electrode surface or to the formation of multilayer structures (through polymerization process). These impede further modification of the interface.

Generally, the amines used are mostly polyamines [196–201] that were grafted onto GCE or Au and were used for detection of metal ions and small organic species. The attachment of organic amines have also been applied for introducing additional functionalities onto the electrode [202–204].

Other functional groups, such as alcohol [15, 205, 206], sulfonates [15, 191], phosphanate [207], and hydrazines [15, 208, 209] have also been used for assembling SAMs in electroanalytical applications on different electrode surfaces.

The electrodes

A wide variety of electrode materials have been used for assembling SAMs. Noble as well as reactive metals, semiconductors, e.g., Si, GaAs, and conducting (mostly doped) metal oxides, such as ITO, have been employed. The formation of SAMs on noble metals, such as Au and Pt, lay on chemisorption, whereas SAMs on reactive metals, semiconductors, and metal oxides were formed as a result of covalent binding or in some cases electrostatic interaction mostly via surface oxides. The following sections describe the formation of SAMs categorized according to the substrate where the emphasis is the mechanism of formation and applications. We focused on the most commonly used surfaces.

Silicon

Silicon, when doped and conducts, can also serve as a working electrode. There have been attempts and studies on the formation of SAMs directly attached onto silicon [189, 210, 211]. This usually involved radical mechanism. The stability of such layers and elimination of oxide formation requires a highly dense monolayer, which naturally would completely block electron transfer. Therefore, bare silicon onto which SAMs were attached has not found, so far, wide applications in electroanalytical chemistry. On the other hand, SAMs on Si could be applied for electrochemical sensors via impedance spectroscopy, potentiometry, and other methods which are sensitive to changes in the interfacial charge and conductivity. For example, Yang et al. [212] used n- and p-Si(111) as a substrate for antigen–antibody binding. The silicon substrates were immersed in NH_4F to produce H-terminated surface for modification by amino-functionalized alkene SAM (through addition reaction onto the double bond). Glutardialdehyde was used as a linker between the SAM and the antigen IgG.

The native oxide layer of Si can be utilized for sensors based on metal–oxide–silicon field effect transistors [146, 147, 154, 213]. The analysis often relies on changes in the surface conductivity upon recognition, as measured by frequency dependent through AC impedance spectroscopy and DC I–V measurements. The oxide is usually obtained by thermal oxidation of a silicon substrate. Silanization is used to modify the insulating surface, where a variety of functionalities can be introduced, such as amine [146, 154], epoxy [147], and hydroxy [213]. The SAM can be used as the recognition factor [146] but is often employed as a linker for further immobilization of proteins [147], antibodies, and antigens [154].

A nice example of using SiO_2 as a substrate for an electrochemical sensor was demonstrated by Yang and Kong [214]. Highly sensitive sensors based on capacitance changes have been developed for the detection of heavy metal ions by utilization of SAMs on silicon oxide surfaces between interdigitated electrodes. The sensor was highly sensitive due to the preconcentration of the metal ions of and allowed the detection of Cu^{2+} down to 1.0×10^{-13} M.

Silicon technology is extremely advanced due to microelectronics and therefore miniaturization of electrochemical sensors based on SAMs on Si could be integrated as part of the existing technology. Hence, a major advantage of silicon as a substrate for SAMs is the ease to miniaturize its dimensions down to micro- and nanoscale features [148]. There are also applications where Si-based nanoobjects, such as Si nanowires have been used as substrates for SAMs. For example, Cattani-Scholz et al. [213] biofunctionalized silicon nanowires by an SAM of hydroxyalkylphosphonate for DNA detection.

Metals

A variety of metals have been used for assembling SAMs. This includes the noble metals, such as Pt, Au, and Pd and some of the more reactive metals, such as Ag and Hg. Naturally, a noble metal offers a wider potential window in aqueous and nonaqueous solutions and therefore is preferable. Moreover, stable well-defined, i.e., single crystals, oxide-free surfaces can be formed and maintained in ambient. On the other hand, noble metals are not expected to react with organic functionalities and bind strongly to the monolayer. Reviewing the literature and in particular the electroanalytical applications reveals that the most commonly used metal is by far gold due to the strong and quite unique interaction with thiol groups. This was detailed above (see section "Thiols").

There are very few studies where SAMs were formed on Pt [215–219]. Thiols, amines, and pyridines were reported to adsorb onto Pt and form stable SAMs, yet we are aware of only one report dealing with electroanalytical chemistry. Specifically, Niu et al. [217] reported that 4-pyridyl hydroquinone adsorbed on a platinum electrode through

the pyridine nitrogen forming stable SAMs. The electrocatalytical oxidation of hydrazines was performed by the modified electrode. The overpotential of hydrazines was decreased markedly at the modified electrode, and the latter was used in a flow system.

Similarly, we are aware of only a few studies of SAMs on silver that were electroanalytically oriented [56, 220]. Although carboxylic acids are strongly adsorbed on Ag (covered by an oxide) and also thiols are claimed to be strongly adsorbed on this metal, the potential window is quite limited to negative potentials, and its surface cannot be easily renewed like Hg. One example, which utilizes a silver surface for SAMs, was reported by Zhang [56]. Specifically, the direct electrochemistry of hemoglobin was studied by cyclic voltammetry and flow injection analysis on a silver electrode modified by an SAM of lipoic acid. Experimental data show that the layer promoted the redox process of hemoglobin and linear relationship between the oxidative peak current, and the concentration of this substance was obtained in the range of 5.0×10^{-7}–1.5×10^{-5} M.

The uniqueness and advantages of a mercury surface that are due to its flatness, electronic conductivity, and high affinity toward many organic functional groups, have well been recognized and applied for the formation of two-dimensional organized systems. As a result, the adsorption of numerous organic compounds on electrified Hg interfaces has been studied [221–230], and theories accounting for the effect of the interfacial potential on the organization of the adsorbates have been developed.

In spite of the fact that SAMs on solid electrodes can easily be studied, it is evident that these surfaces, e.g., gold, cannot be atomically flat over large areas. As a consequence, the resulting monolayers accommodate defects such as pinholes and grain boundaries [231–233]. Moreover, the lattice structure of the solid substrate, rather than intermolecular forces, governs the organization of the adsorbed molecules. On the other hand, liquid mercury offers a reproducible atomically flat surface on which many adsorbed molecules can form a perfect condensed film, where the interactions between adsorbed molecules determine the organization of the 2D array of molecules.

The affinity of thiols toward mercury is well documented [21]. Nonetheless, most of the studies focused on short, water-soluble thiols such as cysteine [234–237] and thiouracil [238, 239], whereas the formation of SAMs of alkanethiols on mercury has attracted only little attention [21, 22, 29, 30, 240–244]. Specifically, Demos and Harrison [241], Majda and his coworkers [30], and us [20, 21] reported on the formation of an extremely impermeable, low-defect density alkanethiol monolayer on mercury.

Hence, Hg has the advantages of both noble metals due to its well-defined surface and reactive metals for the ease of formation of SAMs. Nevertheless, it seems that the toxicity and infirmity of mercury have distracted scientists from applying it for sensing. One of the very few studies using SAMs on Hg for electroanalytical applications was reported by us [22]. We have shown that ω-mercaptoalkanoic acid monolayers on mercury thin films exhibit high selectivity towards Cd^{2+}. We found that shorter ω-mercaptocarboxylic acids provided superior sensitivity. Optimizing the electrode response resulted in a detection limit of 4×10^{-12} M of Cd^{2+}. Thiolated recognition elements, e.g., cyclodextrin, have also been assembled on Hg and used for the detection of inorganic ions [19].

Carbonaceous materials

Carbonaceous materials are highly widespread in electroanalytical studies. This family of electrodes bears several advantages as they exhibit a wide range of kinetic properties and are electrochemically inert over a wide potential window [245]. In addition and far more interesting, the carbon surface enables adsorption of a variety of compounds by both the nonspecific physisorption and the specific chemisorption [182, 245]. Specifically, these electrodes bear high complexation capacities compared to metallic materials, resulting in a higher sensitivity of the surface. As will be discussed below, the modifiers are typically bound to the carbonaceous surface through strong covalent bonds, yielding a stable system even under extreme conditions, such as high temperatures and sonication in various solvents [25, 166]. Additionally, carbonaceous materials are relatively reasonably priced and therefore suitable for industrial applications and as components in disposable systems [246].

There are several types of carbonaceous surfaces used as substrates for SAMs in electroanalytical applications. The most common electrode is GCE [245] as it is isotropic, very hard with low porosity, good stability in corrosive media, and high conductivity. GCE is easily covered by organic contaminations. Those can be removed by polishing the GCE followed by anodic polarization. The surface of GCE is relatively undefined and consequently has many catalytic sites [247]. The heterogeneous topography of the surface complicates electron transfer from and to the GCE, increases the capacity and background current of this electrode and adversely affects the detection limit for sensing applications. The undefined structure of a GCE surface also leads to poor reproducibility, especially after modification, as different GC electrodes, even from the same type, reveal different behavior [166]. Reproducibility can be obtained only when using the same electrode or

newly fabricated electrodes with identical material and fabrication procedure.

Other common electrodes are screen-printed carbon electrodes [183, 184, 196, 248, 249], carbon paste electrodes (CPE) [250, 251], carbon fibers [182, 252], highly ordered pyrolytic graphite (HOPG) [178, 186, 247, 253], doped diamonds [254–256], and carbon-containing composites [257–259]. Each electrode has its own advantages and drawbacks. For example, HOPG is the only carbon electrode with a well-defined structure as it is built from crystallographic planes. The highly organized structure can lead to a better understanding of electron transfer. Moreover, the crystallographic planes can be cleaved, exposing a fresh basal (surface) plane for further use. However, the lack of functional groups on the surface and the lower reactivity of basal plane carbon compared to the edge carbon (as in GCE), make this material less suitable for modifications. It is believed that much of the catalytic activity, electron transfer, and chemical reactivity of graphitic carbon electrodes are at surface defect sites [247].

CPE is made of a homogenized paste of finely dispersed coal and a water-immiscible binding liquid like paraffin or petrolatum [245]. On one hand, CPE has a well-developed surface with high adsorptive abilities; on the other hand, it exhibits high background currents caused by adsorption and percolation of oxygen into the paste. This effect can be slightly reduced by applying either positive or negative potentials.

Doped diamonds have some very special material properties, such as extremely high hardness, thus opening up new opportunities for work under extreme conditions, e.g., at high anodic potentials or in chemically aggressive media [254]. The drawback is their relatively high price as they are made of hardly accessible materials, whose preparation requires high temperature and pressure. An optional solution is to grow a thin layer of the doped diamond on top of lower priced substrates using gas or plasma phase deposition procedures [256].

Carbon fibers possess very large surface areas compared to disk electrodes and therefore exhibit high sensitivity. However, working with carbon fibers requires solving the problem of structural ordering which influences the reproducibility of measurements [245].

A main drawback of carbonaceous electrodes is their tendency to adsorb interfering molecules and contaminations. For example, in biologic media, these electrodes tend to be fouled by proteins. Furthermore, the analyte itself can be physisorbed onto the electrode surface, which might disrupt the recorded signals. Therefore, it is necessary to protect the interface in a way that would allow only the recognition interaction to occur.

Modification of carbon electrode with functional coatings can greatly improve their sensing properties. The common modifications found in electroanalytical studies are organic layers. Other modifications, such as sol–gel [260], silica [261–263], or mesoporous silica [264–266] are also optional for carbon surfaces, but due to their somewhat bulky structure we will not discuss them in this review.

There are few main approaches to covalently modifying carbon surfaces with organic monolayers [166]. The earliest approach, suggested by Barbier and Pinson [195], is oxidation of primary amines, yielding amine radicals which can couple with the carbon via formation of C–N bonds [203, 257, 259, 267–269]. In order to form C–C bonds, either reduction of aryl diazonium salts [35, 168, 174, 177–179, 182–186, 188, 268] or oxidation of arylacetates [270] can be applied. Both mechanisms involve the release of a stable molecule, $N_{2(g)}$ and $CO_{2(g)}$, respectively, resulting in reactive aryl radicals near the surface. Less common is the electrolysis of hydrazide derivatives under oxidative or reductive conditions [208, 209].

All the abovementioned methods involve the formation of radicals in the solution. Alternatively, and exclusive to carbonaceous materials, it is possible to alter the functionality of the electrode surface, which can further react and bond to the modifying species in the solution. Formation of surface aromatic radicals was originally obtained by heat treatment under vacuum or Ar plasma etching and mechanical abrasion [166]. Nowadays, surface radicals are electrochemically generated by anodizing the carbon electrode under high positive potential (2 V versus SCE) [205, 206]. In an anhydrous solution of primary alcohol, the aromatic radicals on the surface undergo nucleophilic attack by the alcohol to form an ether (C–O–C) linkage.

There are few studies that use silanization for modifying carbon electrodes. For silanization to occur, hydroxyl groups must exist on the surface. Therefore, this method is applicable for doped diamond electrodes [271] where hydroxyl groups can be introduced to the electrode surface by either anodic polarization or oxygen plasma treatment. Dai et al. [272] and Hoa et al. [155] demonstrated silanization of GCE. Surface hydroxyl groups are electrochemically formed by anodizing the electrode in a slightly acidic solution (pH 5.0). Weaker bonding is also optional through physisorption of the layer. For example, Bath et al. [182] modified carbon fiber electrodes by physisorption of 2,6-anthraquinone disulfonic acid.

The analyte

SAMs have been used in electroanalytical chemistry for the detection and determination of analytes spanning from metal ions, through organic molecules, to biomolecules.

Table 5 The analytes, the SAMs, and the substrates used in electroanalytical applications

Analyte	SAM	Electrode	Reference
Inorganic analytes			
H^+	Carboxylate-terminated thiol	Gold	[62]
	n-Alkanethiol	Gold	[311]
	Cysteine	Gold	[392]
	Thiolated recognition elements	Gold	[126, 338]
Cu^{2+}	Carboxylate-terminated thiol	Gold	[35, 46, 48, 52, 58, 98, 99, 301, 365, 368, 393]
	Amino-terminated thiol	Gold	[91, 394]
	Cysteine/penicillamine	Gold	[63, 66, 69, 71, 74]
	Sulfonate terminated thiol	Gold	[83, 84]
	Amine-terminated dendrimer	Gold	[202]
	Carboxyphenyl diazonium	Gold	[177]
	Carboxyphenyl diazonium	SPCE	[183]
Cd^{2+}	Carboxylate-terminated thiol	Gold	[44, 62, 365, 366, 395]
	Carboxylate-terminated thiol	Mercury	[22]
	Thiol-terminated alkanethiol (dithiol)	Gold	[42]
	Carboxyphenyl diazonium	Gold	[177]
Pb^{2+}	Carboxylate-terminated thiol	Gold	[48, 365, 367]
	Amino-terminated thiol	Gold	[394]
	Thiolated recognition elements	Gold	[319, 335]
	Carboxyphenyl diazonium	Gold	[177]
Cr (VI)	Thiolated pyridine	Gold	[43, 315]
$Fe^{2+/3+}$	Carboxylate-terminated thiol	Gold	[61]
	Sulfonate-terminated thiol	Gold	[85]
Hg^{2+}	Carboxylate-terminated thiol	Gold	[50]
	Imidazole-terminated thiol	Gold	[314]
	Thiolated DNA	Gold	[141]
Lanthanides	Carboxylate-terminated thiol	Gold	[51, 53, 57]
Alkali metals	Carboxylate-terminated thiol	Gold	[396, 397]
	Thiolated recognition elements	Gold	[299, 398]
	n-Alkanethiol	Gold	[399]
Alkaline earth metals	Thiol-terminated alkanethiol (dithiol)	Gold	[400]
	n-Alkanol	GCE	[206]
Other metal ions (UO_2^{2+}, Zr(IV), Ag^+)	Carboxylate-terminated thiol	Gold	[340, 393]
	Amino-terminated thiol	Gold	[401, 402]
	Hydroxyl-terminated thiol	Gold	[403]
	Thiolated recognition elements	Gold	[220, 339]
H_2O_2/O_2^-	Amino-terminated thiol	Gold	[106, 107, 363, 390, 404]
	Cysteine	Gold	[118, 352, 361, 362, 391]
	Mixed hydroxyl/amino and carboxylate-terminated thiols	Gold	[92, 128, 133–135]
	n-Alkanethiol	Gold	[353]
	Phosphanate-terminated thiol	Gold	[364]
	Thiolated recognition elements	Gold	[278]
	Amino-functionalized recognition elements	GCE	[192]
	Amino-terminated amine (diamine)	Gold	[405]
Other inorganic analytes: ions (CN^-, NO_2^-, PO_4^{3-}, SCN^-) and molecules (O_2 and NO)	Carboxylate-terminated thiol	Gold	[350, 406]
	Amino-terminated thiol	Gold	[123, 407, 408]
	Penicillamine	Gold	[351]

Table 5 (continued)

Analyte	SAM	Electrode	Reference
	Thiolated recognition elements	Gold	[409]
	Thiolated recognition elements	Mercury	[19]
	Nitrobenzene diazonium	GCE	[179]
Organic analytes			
Dopamine and other catecholamines	Carboxylate-terminated thiol	Gold	[45, 47, 54, 55, 59, 96, 410]
	Amino-terminated thiol	Gold	[78, 81, 90, 342, 343, 411]
	Cysteine/penicillamine	Gold	[67, 70, 72, 73, 359]
	Thiolated recognition elements	Gold	[131, 298, 322, 331]
	Mixed amino and carboxylate-terminated thiols	Gold	[386, 387]
	Thiol-terminated thiol (dithiol)	Gold	[381]
	Phosphanate-terminated thiol	Gold	[412]
	Hydroxyl-terminated thiol	Gold	[413]
	Carboxyphenyl diazonium	Carbon	[174, 182]
Uric and ascorbic acids	Carboxylate-terminated thiol	Gold	[47, 49, 60, 113, 414]
	Amino-terminated thiol	Gold	[343, 411]
	Cysteine	Gold	[117]
	Thiolated recognition elements	Gold	[131, 322, 360]
	Mixed amino and carboxylate-terminated thiols	Gold	[386, 387]
	Carboxyphenyl diazonium	GCE	[174]
Glucose, fructose, and derivatives	Carboxylate-terminated thiol	Gold	[100–103, 116, 345–347, 355, 415, 416]
	Amino-terminated thiol	Gold	[103, 286, 348, 417, 418]
	Thiolated recognition elements	Gold	[324, 419, 420]
	Mixed thiol and carboxylate-terminated thiols	Gold	[127]
	Aminophenyl diazonium	Diamond	[115]
	Amino-terminated silane	TiO_2	[153]
Amino acids	Carboxylate-terminated thiol	Gold	[357]
	Hydroxyl-terminated thiol	Gold	[119, 121]
	Thiolated recognition elements	Gold	[275, 321]
	Phosphanate	ITO	[207]
Toxins and pesticides	Amino-terminated thiol	Gold	[38, 122]
	n-Alkanethiol	Gold	[75, 285]
	Thiol-terminated thiol (dithiol)	Gold	[313]
	Epoxysilane	ITO	[152]
	Nitrobenzene diazonium	SPCE	[193]
Drugs	Carboxylate-terminated thiol	Gold	[375]
	Amino-terminated thiol	Gold	[79, 115]
	2-Alkanethiol	Gold	[371]
	Avidin	Gold	[125]
Explosives	n-Alkanethiol	Gold	[77]
	Thiolated recognition elements	Gold	[323, 332]
Acids (carboxylic, fatty, cafeic acid, etc.)	Carboxylate-terminated thiol	Gold	[65]
	Amino-terminated thiol	Gold	[114, 421]
	n-Alkanethiol	Gold	[422]
	Thiolated recognition elements	Gold	[336]
	Cysteine	Gold	[414]
Amines (urea, catechin, spermidine, atrazine, phenothiazine, adenosine, adenine dinucleotide, etc.)	Carboxylate-terminated thiol	Gold	[423]
	Thiol-terminated thiol (dithiol)	Gold	[380]
	Hydroxyl-terminated thiol	Gold	[424]

Table 5 (continued)

Analyte	SAM	Electrode	Reference
	Mixed azide and carboxylate-terminated thiols	Gold	[370]
	Thiolated recognition elements	Gold	[125, 145, 344]
Mono and polyalcohols and phenols (primary alcohols and phenols, quinines, catechol, dopa, dopac, etc.)	Carboxylate-terminated thiol	Gold	[354, 414]
	Amino-terminated thiol	Gold	[104, 129, 130, 358, 425]
	Thiol-terminated thiol (dithiol)	Gold	[382]
	Cysteine	Gold	[37]
Bio analytes			
Proteins	Carboxylate-terminated thiol	Gold	[124, 284, 373, 426]
	Carboxylate-terminated thiol	Silver	[56]
	Amino-terminated thiol	Gold	[385]
	Cysteine	Gold	[376]
	Thiol-terminated thiol (dithiol)	Gold	[379, 383]
	n-Alkanethiol	Gold	[427]
	Thiolated recognition elements	Gold	[140, 143, 273, 308, 333]
	Amino-terminated amine (diamine)	GCE	[203]
	Epoxysilane	SiO_2	[147]
	Silanized PEG	SiO_2	[148]
Peptide	Carboxylate-terminated thiol	Gold	[414]
	Amino-terminated thiol	Gold	[309]
	Thiolated recognition elements	Gold	[428]
DNA	Carboxylate-terminated thiol	Gold	[97, 108–111, 356, 429]
	Amino-terminated thiol	Gold	[82, 112, 300, 307, 369, 389]
	Cysteine	Gold	[372]
	Hydroxyl-terminated thiol	Gold	[430, 431]
	Thiolated recognition elements	Gold	[132, 136–139, 142, 327, 337, 432]
	Amino-terminated silane	ITO	[150]
	Aminophenyl diazonium	Carbon	[185]
Bacteria	Carboxylate-terminated thiol	Gold	[95, 306]
	Amino-terminated thiol	Gold	[105]
	Thiolated recognition elements	Gold	[310, 328, 329, 433, 434]
	Epoxysilane	GCE	[155]
Viruses	Thiolated recognition elements	Gold	[144, 435]
Antigens	Carboxylate-terminated thiol	Gold	[93, 374, 436]
	Amino-terminated thiol	Gold	[377, 378]
	Epoxysilane	SiO_2	[156]
NADH	Amino-terminated thiol	Gold	[80, 94]
	Cysteine	Gold	[64]
	Nitrophenyl diazonium	Carbon	[175]
	Hydrazine	Carbon	[208]
Steroids	Thiolated recognition elements	Gold	[301, 326]
Vitamins	Amino-terminated thiol	Gold	[68]
	Cysteine	Gold	[388]

NADH nicotinamide adenine dinucleotide, *SPCE* screen-printed carbon electrodes

Every possible interaction between the monolayer and the analyte has been exploited; coordination chemistry, electrostatic interactions, hydrogen bonding, hydrophobic, and hydrophilic interactions and evidently, enzyme–substrate and antigen–antibody interactions. One of the advantages of SAMs is the ability to control their organization, which affects and tunes the monolayer–analyte interactions. In general, increasing the selectivity of the monolayer usually

requires a more complex (and therefore larger) functionality at the end pointing outward of the SAM. Table 5 divides much of the reported work into three categories: inorganic species, organic compounds, and biomolecules.

The electrochemical techniques

Electrochemistry is used as a means of transducing the chemical interactions between the monolayer and the analyte into an electrical signal. The sensitivity depends to a large extent on this transduction. The choice of the electrochemical technique is dictated by a few factors such as the substrate, the analyte, the required sensitivity, medium, etc. We often find that the same species, e.g., metallic ions, can be detected by different electrochemical techniques, using different approaches based on SAMs. Electrochemistry is an inherently sensitive technique due to the Faraday constant, which enables the detection of the charge or current of much less than a monolayer of electroactive species. Hence, most studies have used either voltammetry or amperometry, which are based on measuring the current, as the detecting method in conjunction with SAMs. The combination of SAMs as the selective element and voltammetry techniques, e.g., square wave voltammetry, resulted in extremely high sensitivity [22, 46, 66, 96, 263, 273, 274]. SAMs have also been used to enhance the underpotential deposition and stripping peaks [44, 48, 83, 275–277]. Voltammetry methods have been very popular in cases where electron transfer was facile, namely, upon applying short chain and disorganized SAMs. There are numerous reports where SAMs have been used as the molecular glue (or spacer) for attaching biomolecules, such as enzymes. Amperometry is often used in biosensors based on SAMs, whereby catalytic activity of the monolayer takes place [278–283]. Recently, we find an increase in the number of studies where carbon nanotubes and metallic particles are attached onto solid electrodes via SAMs, and detection is carried out amperometrically [198, 246, 249, 280, 281, 283–293].

On the other hand and as mentioned above, the application of different SAMs on Si, SiO_2, and other semiconductors and metal oxides have been combined with potentiometry, which is based on potential change and does not involve the flow of charge. When either the layers are formed on an insulator, e.g., SiO_2, or electron transfer is blocked due to the application of highly dense and long chain functionalized alkanes, voltammetry and amperometry cannot be used. Yet, the interfacial properties, such as charge and work function are still altered by adsorption. Hence, there have been numerous studies aiming at using SAMs as the selective factor in MOSFET or other miniaturized devices where detection is based either on potentiometry or on I–V measurements, which are affected by the selective adsorption of different analytes on SAMs assembled on a dielectric insulator [50, 146, 147, 294–297].

A particularly appealing and common technique is electrochemical impedance spectroscopy, which has been very often applied for detecting electrochemically inactive species by SAMs modified electrodes [81, 93, 125, 143, 298–305]. Different approaches have been used. The charge transfer resistance of different electroactive species, which was affected by the selective attachment of analyte onto the SAMs, has been monitored. Alternatively, the capacity of the interface, which was influenced by the association of the monolayer with charged species, was followed. Impedance spectroscopy allowed analysis of interfacial changes originating from biorecognition events at electrode surfaces and therefore has been very often employed for the determination of DNA fragments [96, 124, 303, 306, 307], antigen–antibody interactions [153, 155, 271, 296, 304, 305, 308–310], etc. The reported detection limits of these systems have been remarkably low.

Perspective and prospective

The first studies using SAMs for electroanalytical chemistry appeared in the early 1990s. Since then, a few hundreds of papers in this topic have been published. The term "self-assembled monolayer" has been used for almost any type of monolayer regardless if the layer was organized or not. It is almost impossible to review and categorize the literature and keep updated in this constantly growing field, yet it is possible to draw a few conclusions and predict to some extent the development that is envisaged:

1. Clearly, SAMs offer some significant advantages in electrochemical sensors. Their ease of preparation and implementation attracts more and more studies. There are almost no limitations as to the nature of analyte that can be detected by electrochemical means, be it electrochemically active or inactive.
2. The main approaches for assembling such sensors are either functionalizing the monolayer precursor before or after attachment onto the surface. These two approaches provide high versatility, yet require good organic synthetic tools and experience.
3. We are witnessing an enormous number of studies that utilize nano-objects, such as nanoparticles and nanotubes attached onto solid electrodes via self-assembled monolayers. In these cases, the monolayers are used as either simple spacers or in some cases for introducing also recognition elements. It is envisioned that these

complex systems where nano-objects, biomolecules, and SAMs are integrated for amplifying the highly selective measurement of different species, will substantially increase.

4. It is predicted that SAMs will eventually be integrated in silicon technology. Organic molecules will be the bridge between micro- and nanoelectronics and sensing and diagnostic devices. It is hard to foresee the future of medical diagnostics without SAMs.
5. In spite of the many advantages that SAMs offer, they suffer from lack of robustness. This has avoided so far the implementation of monolayers, such as Langmuir–Blodgett films in real-world applications. Hence, it is evident that in order to use SAMs in many applications, ways to increase their robustness must be developed. Two possible approaches comprising cross-linking or thickening can be suggested. Cross-linking means the formation of monomolecular polymeric films. Several studies undertaking this approach have already appeared. The other approach is to bridge SAMs and polymers in terms of thickness. Increasing the thickness of SAMs to 10–20 nm will allow using them in electrochemical sensors and at the same time will increase their stability.

Finally, it is evident that the application of self-assembled monolayers in electroanalytical chemistry has still not peaked. It is very likely that we will witness many more exciting studies and new ideas where these monomolecular layers are integrated in electrochemical sensors. There is still a lot of room at the nanometer scale of the interface.

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