Ion recognition properties of self-assembled monolayers (SAMs)

Sheng Zhang,[b] Claudia M. Cardona[a] and Luis Echegoyen*[a]

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In the search for new sensors, self-assembled monolayers (SAMs) have gained intensive interest due to their nanometre size, highly-ordered structures, and molecular recognition properties. This article presents an overview of ion recognition at SAM-modified surface/solution interfaces, and brings up to date the most notable examples for the sensing of cations and anions. Sensing is achieved with SAMs containing redox active and inactive receptors using techniques such as fluorescence spectroscopy, cyclic voltammetry and electrochemical impedance spectroscopy.

Introduction

The first "self-assembled monolayers" (SAMs) were reported twenty years ago, and since then, these structures have become an important component in the field of materials science.[1] SAMs are highly ordered two-dimensional assemblies that form spontaneously on a variety of surfaces by the adsorption of organic molecules from solution or gas phases.[1] Well-studied self-assembling systems include silanes on silicon surfaces,[2] sulfur-containing molecules on gold[3a] and other metallic surfaces,[3b,c] and carboxylic acids on metal oxides.[4] Organosulfur SAMs on gold are generally formed by the adsorption of thiol, thioether, disulfide, or thioctic ester derivatives. These types of SAMs are particularly useful because of their high degree of structural order, ease of preparation, and the diversity of terminal functionalities that can be placed at the monolayer surface. These properties, in conjunction with the nanometre scale of these organic thin-film materials, make them great candidates for a wide range of potential applications in nano-science and nano-technology. Therefore, SAMs have become one of the best systems for studying the effect of molecular structure and composition on the macroscopic properties of materials, and they serve as a tool to design ultra thin materials with different physical and chemical characteristics. To date, there are a number of reviews on SAMs which illustrate their formation, structure, and characterization using electrochemical and scanning tunneling microscopy (STM) techniques.[5] More recently, interest in SAMs has shifted from the fundamental research

Dr Sheng Zhang was born in 1972, and obtained his PhD in 2001 from Peking University, China, under the supervision of Prof. Liangbing Gan and Prof. Chunhui Huang. He joined Prof. Jean-François Nierengarten's group at the University of Louis Pasteur (France) after he got his PhD. In 2002, he moved to Clemson University to work as a postdoctoral fellow with Prof. Luis Echegoyen and currently he is a research associate at the North Carolina State University with Prof. Christopher Gorman. His main research interests include monolayer sensing, nanoparticle assembly, fullerene chemistry, and electrochemical and photoelectrochemical materials.

Dr Claudia M. Cardona was born in Colombia, South America, in 1960. She obtained her PhD in 1999 from the University of Miami (UM), Coral Gables, under the supervision of Prof. Angel Kaifer. After three years postdoctoral work for Prof. Robert E. Gawley at NIEHS Marine and Freshwater Biomedical Sciences Center, UM, with an institutional NRSA NIH Postdoctoral Traineeship (2000–2001) and an individual NRSA NIH Postdoctoral Fellowship (2001–2003), she joined Prof. Luis Echegoyen's group (Clemson University) in 2004, initially as a postdoctoral associate, and most recently as an Assistant Research Professor. Her main research interests include the design of supramolecular receptors, the chemistry of endohedral metallofullerene and fullerene species, and the fabrication of electrochemical and photovoltaic materials.

Prof. Luis Echegoyen was born in La Habana, Cuba, in 1951. He obtained both his BSc and PhD degrees from the University of Puerto Rico in Rio Piedras in 1971 and 1974, respectively. After a one-year postdoctoral stay at the University of Wisconsin-Madison, subsequent appointments have included Chemist I, Nuclear Magnetic Resonance Spectroscopist at Union Carbide Corporation, Bound Brook, New Jersey, (1975–1977); Assistant Professor at the University of Puerto Rico, (1977–1980); Associate Professor at the University of Puerto Rico, (1980–1982); Adjunct Associate Professor at the University of Maryland, College Park, Maryland, (1982–1983); Program Officer, Chemical Dynamics Program, National Science Foundation, Washington, D.C., (1982–1983); Associate Professor at the University of Miami, Coral Gables, Florida, (1983–1987); Member of the Chemistry Advisory Committee-NSF (1986–1989); and Professor at the University of Miami, Coral Gables, Florida (1987–2001). In 2002 he was appointed to serve as Chair of the Department of Chemistry at Clemson University, in South Carolina. His research interests include fullerene chemistry, electrochemistry and supramolecular chemistry, with special emphasis on molecular electronics and endohedral fullerenes. He is the author or co-author of over 270 research articles.

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[a] *Department of Chemistry, Clemson University, Clemson, SC, USA. E-mail: luis@clemson.edu; Fax: +1 (864) 656 6613; Tel: +1 (864) 656 0778*
[b] *Department of Chemistry, North Carolina State University, Raleigh, NC, USA*

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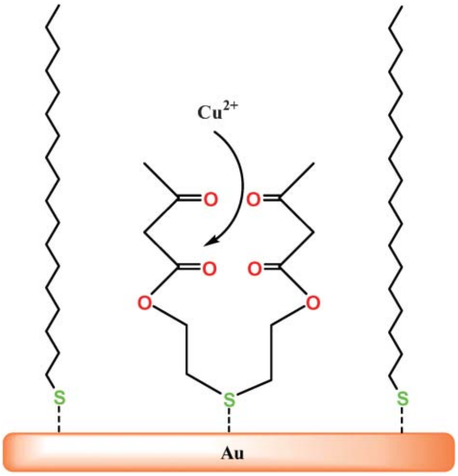
on their formation and structure to their potential applications in fields such as lubrication,[6] adhesion,[7] wetting,[8] quantum effects,[9] catalysis,[10] and recognition and sensing.[11]

Over the past decade, the design of molecular and ionic receptors, and the study of their sensing abilities have gained intensive interest and become a key research area in Supramolecular Chemistry, stimulated by the importance of these receptors in biological processes, food chemistry, environmental monitoring, and medical diagnostics. While extensive attention has been focused on the recognition of molecular and ionic species in bulk solutions,[12] the construction of thin-film receptors for molecular recognition of chemical or biological species has proven to be more effective. Such sensor arrays can be obtained by assembling different receptors on platforms such as glass slides, metal surfaces, and polymer supports. The combination of molecular recognition elements and SAMs generates a powerful tool to monitor the sensing process at monolayer/solution interfaces. In addition, incorporating SAMs in sensing devices offers several advantages[13] including ease of preparation, reproducibility, fast response, amplification of sensing, and pre-organization of receptors on the surfaces. This review will highlight recent advances in the recognition of ions at the interface of solutions and SAM-modified surfaces. The examples selected here are those that have led the way to establish the principles involved in controlling ionic recognition at interfaces, even when the conditions are somewhat far from being of practical utility. While the ultimate goal is to develop sensors for analytical applications in environmental and biological systems, the examples discussed here are of a more fundamental nature. Although organization and packing of individual molecules are important to determine some properties of SAMs, molecular recognition events depend mainly on the interaction between the immobilized receptors and the ions in solution, and not much on monolayer density and packing details. Consequently, little detail will be provided about SAM structures, concentrating on their ionic binding properties instead. Self-assembled monolayers designed for biosensing is beyond the scope of this article and the reader is referred to other specialized reviews.[14]

Recognition of redox active metal ions

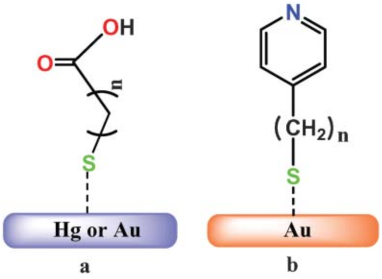
Sensing and sequestering metal ions from environmental samples is of critical importance due to their toxicity and longevity.[15] Detection of metal ions can be achieved by different approaches, but one of the most important methods is the use of electrochemical sensing arrays. For instance, highly selective receptors have been immobilized on gold electrodes to bind electrochemically active metal ions, which can be detected using cyclic voltammetry (CV).[16–26] One of the initial reports of an organized monolayer capable of selectively recognizing redox-active metal ions was published by Rubinstein and co-workers.[16] As illustrated in Scheme 1, they prepared mixed monolayers composed of thio-bis(ethylacetoacetate) (**TBEA**) and passivating molecules, such as *n*-octadecylmercaptan or *n*-octadecyltrichlorosilane, on gold electrodes. These mixed SAMs were capable of sensing divalent metal ions such as Cu^{2+} or Pb^{2+} on the electrode surfaces even in the presence of Fe^{2+} in 0.1 M aqueous H_2SO_4.



Scheme 1 Schematic representation of Cu^{2+} complexation with SAMs of **TBEA**.[16]

The selective binding of these metal ions to the **TBEA** monolayer was confirmed not only by electrochemical stripping experiments but also by non-electrochemical techniques such as ellipsometry and contact-angle measurements,[16b] and this selectivity was attributed to the complexation between these metal ions and the β-diketonate motif of the receptors. This report also demonstrated that the selectivity exhibited by the immobilized receptor was quite different from that observed in solution. One reason may be the effect of the externally applied potential which seems to provide part of the driving force for metal ion complexation to the immobilized receptor. Such receptors also proved to be very sensitive with detection limits of 10^{-7} M.

Thereafter, a series of redox-active metal ion sensors based on self-assembled monolayers were developed. Mandler and co-workers reported a method for the electrochemical determination of ultra low levels of Cd^{2+} in an acetate buffer solution using ω-mercaptocarboxylic acid monolayers on mercury and gold electrodes.[17] They found that shorter ω-mercaptocarboxylic acids provided superior sensitivity (Scheme 2a), and they employed both cyclic voltammetry and Osteryoung square wave voltammetry (OSWV) to determine the selectivity and sensitivity of these negatively charged monolayers. With a detection limit as low as 4 × 10^{-12} M, this method was successful in determining trace amount of cadmium in seawater.[17] Recently, they investigated further the binding of Cd^{2+} by SAMs of ω-mercaptocarboxylic



Scheme 2 SAMs of ω-mercaptocarboxylic acid monolayers on mercury and gold (a),[17] and 4-(2-mercaptoethyl)-pyridinium on gold (b).[19]

acids with CV and scanning electrochemical microscopy and concluded that binding of the metal ions by the monolayer affected the kinetics of electron transfer to a negatively charged redox probe in solution.[18] These authors also developed a highly sensitive and selective electrode modified by SAMs of 4-(2-mercaptoethyl)-pyridinium to recognize Cr^{6+} in fluoride buffer solutions at pH 7.8 with a detection limit as low as 0.02 nM (Scheme 2b).[19] The high selectivity of these surface immobilized receptors toward Cr^{6+} was attributed to both the positive charge of the pyridinium moiety and the hydrogen bonding between the pyridinium and chromate ions.

Electrodes modified with ω-mercaptocarboxylic acids have also been investigated by Shen and co-workers as Cu^{2+} sensors. They prepared SAMs of 3-mercaptopropionic acid (**MPA**) and obtained an enhancement in sensitivity and selectivity when the underpotential deposition effect was minimized during the stripping analysis of copper.[20] The structure of **MPA** (**1**) and other organosulfur compounds addressed in this section are depicted in Fig. 1. In turn, Nagoaka has employed SAMs consisting of 3,3′-thiodipropionic acid (**2**) and 1-decanethiol (**3**) for the determination of Cu^{2+} and Ag^{+} in aqueous systems in a sensitive and selective manner. Although both Ag^{+} and Cu^{2+} bind to the receptor, their different reduction potentials circumvented any interfering detection problems,[21] and after optimization of the experimental conditions, detection limits of 2×10^{-9} M and 6×10^{-8} M were obtained for Cu^{2+} and Ag^{+}, respectively. Detection of copper ions has also been pursued by Zeng and co-workers. They described the electrochemical response of gold electrodes, which were modified by SAMs of glutathione (**4**) to detect copper ions in an acetate buffer solution and found that the sensitivity and selectivity of the Au–glutathione electrode can be improved by including **MPA** (**1**) in these monolayers.[22] More recently, Kubota *et al.* developed a more sensitive copper ion sensor based also on SAMs of **1** with a detection limit of 1.8×10^{-14} M.[23] The excellent reproducibility and sensitivity of this sensor facilitated its application in determining the copper content in mineral water and sugar cane spirits.[23]

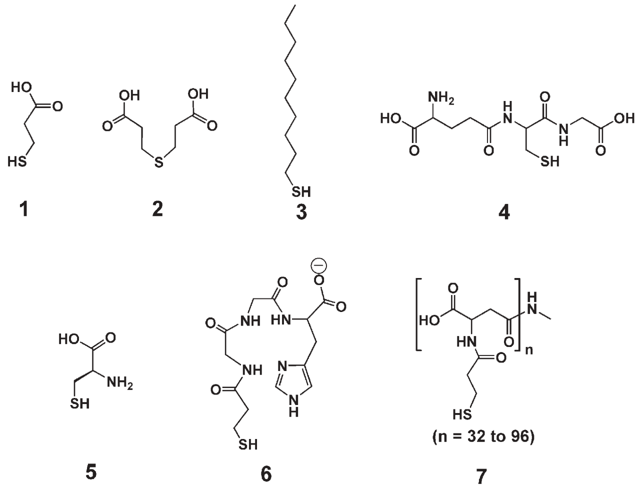


Fig. 1 Organosulfur molecules employed in SAMs on gold electrodes to detect redox-active metal ions.[20–26]

Simple amino acids or short peptides have also proven to be ery valuable in the detection of redox active metals. For example, gold electrodes modified with SAMs containing cysteine (**5**) have been investigated by several groups to detect copper ions.[24–26] Chen and co-workers have demonstrated the electrochemical sensing abilities of a cysteine monolayer for Cu^{2+} in aqueous media with a detection limit of 3.9×10^{-10} M.[24] Gold electrodes modified with cysteine monolayers are highly selective towards Cu^{2+} because the binding constant of cysteine with this metal ion is four orders of magnitude larger than with any other metal ion. In terms of reproducibility and sensitivity, the performance of their electrodes was affected by the surface concentration of cysteine and the pH of the copper(II) solution. These modified electrodes showed optimal performance at pH 5, the isoelectric point of the receptor, suggesting the predominance of the zwitterionic form ($HSCH_2CH(NH_3^{+})CO_2^{-}$) as the binding motif. The binding affinity of cysteine to Cu^{2+} decreases at pHs lower than its isoelectric point because the carboxylate moiety is then protonated and becomes unable to participate in the binding process. Thus cysteine-modified electrodes have proven to be very specific for Cu^{2+} sensing, and only nickel(II) ions, among all other possible ions, cause significant interference in its detection. Nevertheless, this interference can be prevented with the addition of dimethylglyoxime, which sequesters nickel ions, resulting in total selectivity for Cu^{2+}.

Hibbert and co-workers have also studied gold electrodes modified with SAMs of cysteine for the adsorptive stripping analysis of copper ion in solution and obtained very high selectivity and low detection limits.[25a] Techniques such as CV, chronoamperometry, and X-ray photoelectron spectroscopy were employed in the characterization of this system. This group has also achieved the redox sensing of Cu^{2+} with gold electrodes modified with the Gly-Gly-His (**GGH**, **6**) tripeptide with detection limits of sub-parts per billion (sub-ppb) in aqueous media.[25b] The complex formed between the surface confined **GGH** and copper ions was extremely stable as demonstrated by the lack of change in intensity of the Cu^{2+} redox wave upon multiple scans. This stability has been attributed to the binding motif in this system, which is composed of four nitrogen atoms coordinating, in a tetragonal manner, a copper ion. Such an arrangement was confirmed by electrospray ionization Fourier transform ion cyclotron resonance mass spectroscopy, and OSWV was employed to detect low levels of Cu^{2+} in environmental samples with these electrodes.[25b] Such an example illustrates the potential of electrodes modified with biomolecules to be employed as metal ion sensors. In their pursuit for lower detection limits, this group also assembled polymeric aspartic acid (**PLAA**, **7**) onto a **MPA**-modified gold electrode using an *N*-hydroxysuccinimide intermediate and carbodiimide coupling conditions,[25c] and detection limits as low as 0.2 ppb for copper ions in phosphate buffer solutions were obtained. Recently, Profundo *et al.* detected trace amount of Cu^{2+} ions in tap, spring, and sea water with gold electrodes modified with SAMs, also containing simple amino acids.[26] In this case, the complexing molecules were peptides such as D,L-penicillamine and thiodimethylglyoxime.

Recognition of redox inactive cations

Thus far, the metal ion binding events described were measured directly by the electrochemical response of the analyte in question. Detection of redox inactive metals can also be done directly if the properties of the receptor are altered upon binding, and if this variation can be detected. Such signal transduction can be achieved by electrochemical means either directly or indirectly as discussed in this section, or by other techniques such as fluorescence.

Direct measurement of the binding event can be done if the self-assembled monolayers contain a redox active species at the binding site. The electrochemical response of such species is a function of the degree of interaction with the redox inactive metal ion, and thus, it directly reports its presence. Bryce and co-workers have demonstrated this approach by utilizing redox-active monolayers capable of signalling the metal ion binding event directly *via* changes in their electrochemical behaviour. They incorporated a redox active species, tetrathiafulvalene (**TTF**), to the metal binding macrocycle at the 1,2-positions of the **TTF** species (**8**, Fig. 2), and these **TTF**-macrocycles were anchored to the gold surfaces using thiol groups.[27a,b] **TTF** has a characteristic electrochemical behaviour with two reversible one-electron redox couples both in solution and on SAMs.[27a,c] Upon exposure of these SAMs to redox inactive metal ions, an anodic shift of the first oxidation process was obtained which increased from 10–20 mV for Li^+ and K^+, to 45–55 mV for Na^+ and Ba^{2+}, to 60–90 mV for Ag^+ in acetonitrile.[27a] The authors attributed these shifts to the inductive effect on the polarizability of **TTF** imposed by the bound metal cation. However, the observed electrochemical responses were weak and poorly resolved, and these SAMs were also unstable, especially when the potential was scanned beyond the first oxidation potential.

Echegoyen and co-workers detected well behaved electrochemical responses with crown-1,2-**TTF** SAMs (**9**) when they employed multiple anchoring sites or when the crown ether moiety was connected instead at the 2,7-positions of the **TTF** framework (**10**).[28a–c] In both cases, the SAMs obtained were extremely stable over a large potential window (from neutral to **TTF**$^+$ to **TTF**$^{2+}$) unlike those observed before. In order to provide multiple anchoring sites, each molecule of the SAM was composed of a bisthioctic ester derivative of the crown-**TTF** compound, which in turn formed remarkably stable monolayers on gold surfaces due to the dual anchoring approach. These SAMs (Scheme 3) were characterized by a clear and reversible surface-confined electrochemical behaviour of the **TTF** moiety, and displayed anodic shifts of both one-electron oxidation processes upon binding Na^+ and K^+ in THF.[28a] When the crown ether portion is connected at the 2,7-positions of the **TTF** skeleton (**10**), the recognition properties of the ligand are optimized in homogeneous media.[28c] Echegoyen *et al.* demonstrated that such recognition capabilities were maintained when this unit was incorporated into SAMs and observed a pronounced response for Ba^{2+} in acetonitrile, even when anchored at just one site. These monolayers displayed a 40 mV anodic shift of the first oxidation process, and unlike previous examples, the second oxidation process remained undisturbed, which was attributed to an electrostatic-induced decomplexation of Ba^{2+} upon oxidation of the redox **TTF** unit. This result was consistent with observations made of the parent **TTF**-ligand in homogeneous media, as well as the **TTF**-pseudocrown receptor, **11**, designed by Sallé and co-workers to be employed in the detection of lead(II) ions in acetonitrile.[28d,e] SAMs of this receptor on gold electrodes as well as platinum surfaces modified with polymer films incorporating this **TTF** molecule demonstrated great stability.

Kim *et al.* also achieved voltammetric recognition of Ba^{2+}, but in an aqueous medium with carefully designed SAMs of redox-active calix[4]arenes containing diquinone units (**12**, Fig. 3).[29] The electroactive quinone moieties were introduced into the annular framework as ring members and they exhibit binding properties that are significantly different before and after the electrochemical reduction since the quinone groups also act as coordination sites for the bound metal cations. These SAMs exhibited specific selectivity for Ba^{2+} as compared to Sr^{2+} and Ca^{2+}, and displayed no electrochemical response to Mg^{2+}. The measured association equilibrium constant (K) of barium ions with the redox-active calix[4]arene monolayers was 9.8×10^4 M^{-1} at 25 °C.[29]

The examples discussed thus far employed CV as the technique to signal the binding of redox inactive metals by

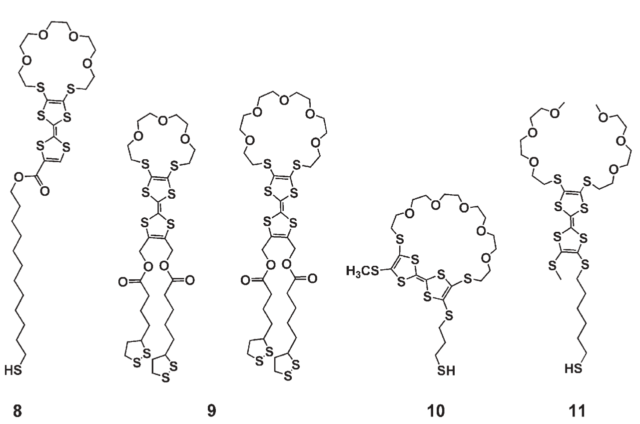
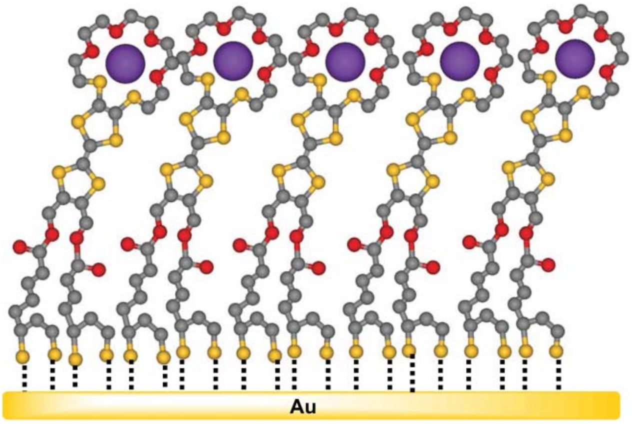


Fig. 2 Redox active macrocycles capable of binding and detecting redox inactive metal ions.[27,28]



Scheme 3 Scheme representing the binding of potassium (purple) by crown-1,2-**TTF** SAMs on a gold surface.[28a,b]

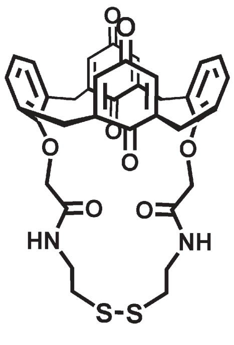


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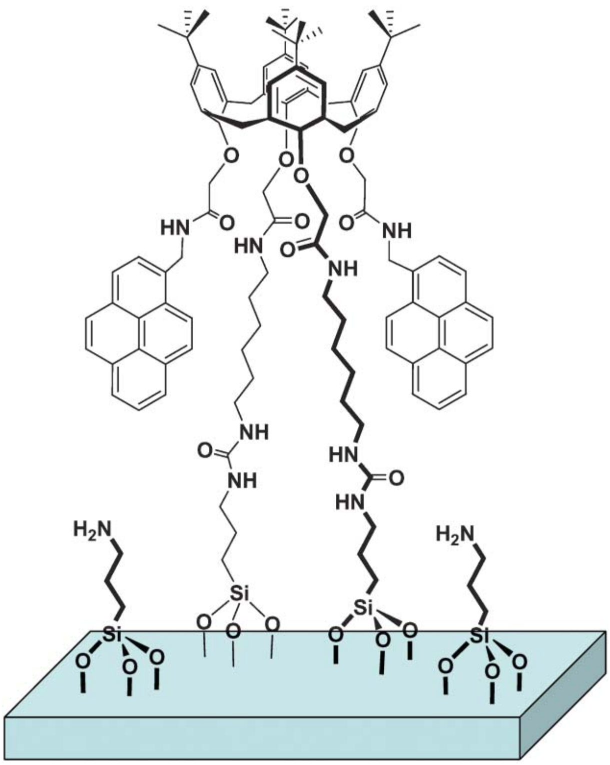
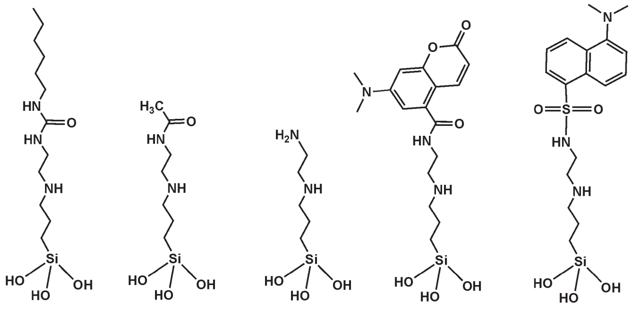
Fig. 3 Disulfide calix[4]arene composed of redox-active diquinone units.[29]

SAMs. Other principles and techniques, such as fluorescence, have been employed in this field because of higher sensitivity, but quenching of fluorescent monolayers by gold surfaces has rendered this type of assemblies ineffective for sensing applications. On the other hand, fluorescent-SAMs have been successfully fabricated on glass surfaces to selectively detect redox-inactive cations.[30] In one of these examples, a monolayer of a Na^+-selective fluoroionophore was prepared by the covalent coupling of the bis-isocyanate derivative of the receptor to a SAM of 3-aminopropyltriethoxysilane on a glass surface (Scheme 4).[30a] The structure of the ion receptor site was designed for Na^+ selectivity with a calix[4]arene cavity substituted with four amide units. Two of these amide moieties support two pyrene fluorophores, which report the complexation of the cation with the calix[4]arene by its effect on the fluorescent properties. The other two amide groups support the appendages that anchor the fluoroionophore to the glass surface. Binding of Na^+ ions in methanol is detected by an increase in pyrene excimer fluorescence probably due to a change in conformation of the calix[4]arene upon coordination of the cation, which in turn brings the pyrene units closer to each other giving rise to an increase in excimer emission. Other cations such as K^+ and Cs^+ failed to produce any significant changes in fluorescence. In another example, Reinhoudt and co-workers showed that in some cases there is no need for a pre-organized cavity as long as the SAMs are capped with functionalities containing fluorophores and recognition elements (**13**, Fig. 4). The interaction between the recognition elements, such as amides, ureas, or sulfonamides, and the metal cations produces changes in the polarity of their immediate environment, which are detected by the fluorophores.[30b] For instance, the quenching of the fluorophore (dansyl or coumarin) emission in acetonitrile reports the binding of the cation, and great selectivity for Pb^{2+} ions in the presence of Ca^{2+} and Zn^{2+} was obtained with this system. In a more recent example, Fang *et al.* reported pyrene-modified SAMs on glass surfaces capable of detecting and differentiating between organic and inorganic copper(II) salts in aqueous media, also by the quenching of the fluorophore.[30c]



Scheme 4 SAMs of Na^+-selective fluoroionophore on a glass surface.[30a]

Electrochemical impedance spectroscopy (EIS) has proven to be an effective tool in the understanding of interfacial ion recognition phenomena when both the guest ion and the host monolayer are electrochemically inactive. One of the advantages of this technique is its capability to detect any changes in the surface charge without disturbing the structure of the monolayer since it applies small potential sweeps, in the range of millivolts. Another great advantage is its ability to detect binding events in aqueous media, which resembles to a



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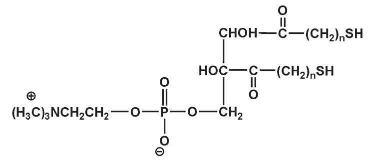

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Fig. 4 Molecules employed in SAMs to detect redox-inactive metal cations: 3-aminopropyltriethoxysilane molecules capped with fluorophores or recognition elements (**13**),[30b] and thiolated phospholipids (**14**).[32]

closer extent environmental and biological samples, and thus, it brings SAMs sensors closer to analytical performance. This technique reveals the electrochemical properties of a system and monitors binding events involving charged species through changes of the monolayer capacitance (C_{dl}) and charge transfer resistance (R_{ct}).[31] The R_{ct} of a monolayer in the presence of a redox active couple in solution, such as $[Ru(NH_3)_6]^{3+/2+}$, $[Fe(CN)_6]^{3-/4-}$, or *p*-benzoquinone, is dramatically affected by the incorporation of ionic charges in the monolayer. For instance, Chen and Huang observed a selective ion-gate effect with thiolated phospholipids, **14**, which were self-assembled as monolayers on the surface of gold electrodes.[32a] Since phospholipid molecules are amphiphilic with charged-polar headgroups, the structure and properties of these SAMs are very susceptible to the interaction with charged species. These SAMs undergo interfacial reorganization when they are exposed to alkaline earth ions in aqueous media due to the interaction of the metal ion with the charged headgroup of the monolayer, which causes the formation of ion-gated lipid channels. This conclusion was reached based on experiments conducted by AC impedance spectroscopy and voltammetric blocking of a redox probe molecule at a pH of 7.93.

Shervedani and Mozaffari described another example where gold electrodes were modified with SAMs terminated with phosphate groups.[32b] The complexation of these phosphate groups with uranyl ions, UO_2^{2+}, causes large increases in charge transfer resistance (R_{ct}) which allows for the impedimetric sensing of uranyl ions in aqueous media. Uranyl ions are often found in waste products from nuclear energy sites, and their detection in environmental samples has become of crucial importance.

Reinhoudt and co-workers were the first to show the significance of impedance spectroscopy to study the binding properties of SAMs containing non-redox active crown ethers as receptors for redox inactive metals in aqueous media (**15**, Fig. 5).[33] They corroborated their findings with X-ray photoelectron spectroscopy (XPS) and atomic force microscopy (AFM).[33c] The elegance of their work rests on the simplicity of their systems which self-assemble into monolayers with high concentration of macrocycles on the surface. This surface organization leads to a cooperative binding or "sandwich complexation" which accounts for the high affinity and selectivity of 12-crown-4-capped SAMs for Na^+ (K = 15800 M^{-1}) and of 15-crown-5-capped SAMs for K^+ (K = 27100 M^{-1}). Just recently, the same principles were applied on CdSe–ZnS quantum dots which were functionalized with 15-crown-5-monolayers and were capable of recognizing potassium ions in water with detection limits on the order of 10^{-6} by fluorescence spectroscopy.[34]

Echegoyen *et al.* showed that crown ether macrocycles are not needed as the receptors on SAMs in order to detect K^+ or Na^+ ions in aqueous media. Instead, bisthioctic ester derivatives of oligoethylene glycols (**16**, **17**) can be employed to form the monolayers with the idea that the ethylene glycol portion of the molecule, in between the two ending thioctic esters, can fold to form the binding domain on the surface, and the thioctic esters can secure this binding motif to the gold surface of the electrode.[35] These SAMs have shown remarkable stability and selectivity for K^+ or Na^+ suggesting that the ethylene glycol portion folds into pseudocrown ether structures. Monolayers containing hexaethylene glycol portions are selective for K^+ (**17**), and those containing pentaethylene glycol portions are selective for Na^+ (**16**). In this study, impedance spectroscopy played a crucial role in obtaining these results because the structural components of the SAMs are electroinactive. Blocking effects on the CV behaviour of a redox probe, $[Ru(NH_3)_6]^{3+/2+}$, confirmed the binding of the redox inactive metal ions in an aqueous system.

Echegoyen and co-workers also demonstrated that these types of pseudo-crown ether structures can in fact be formed during the assembling process of the monolayers in the presence of K^+ when a pre-organized motif was introduced in the polyether portion of the molecule.[36] An aromatic ring, a benzene (**18**) or naphthalene (**19**), fused to two triethylene glycol arms, introduces the rigidity and pre-disposition to bind the metal cations from an aqueous media. The monolayers with the naphthyl group were secured to the gold surface with

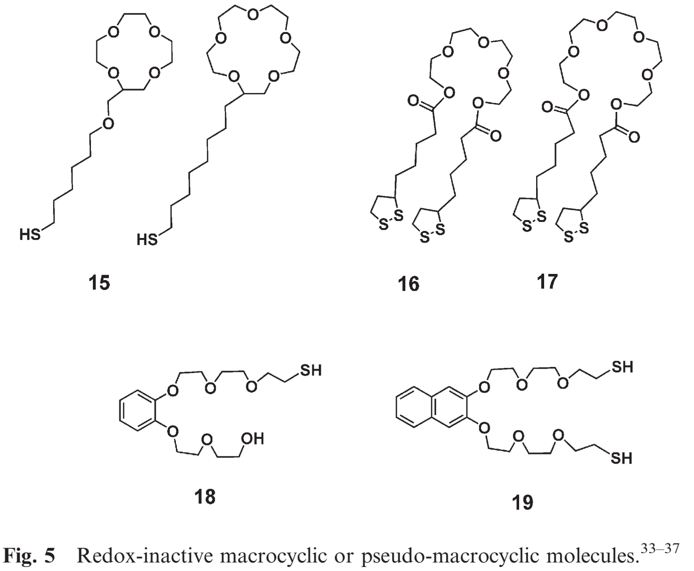

Fig. 5 Redox-inactive macrocyclic or pseudo-macrocyclic molecules.[33–37]

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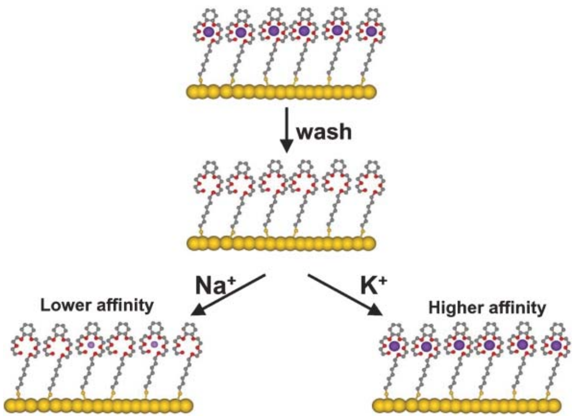
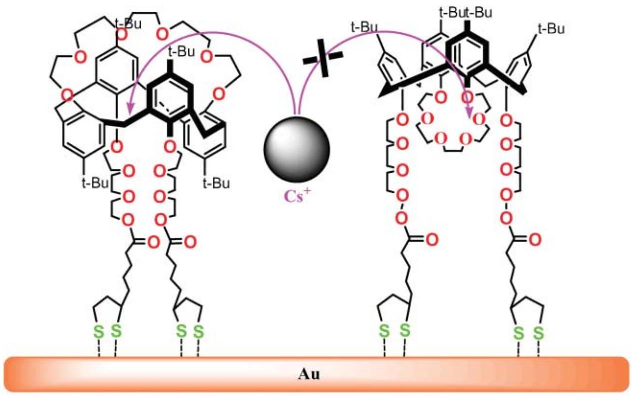


Scheme 5 Schematic representation of the K$^+$-imprinted SAMs.[36b]



Scheme 6 Schematic representation of selective Cs$^+$ recognition by SAMs of a calix[4]crown-6 derivative in 1,3-alternate conformation.[39]

two anchoring sites while those containing the benzene unit were anchored at just one site. Binding studies of the latter receptor (**19**) suggest two different binding states of K$^+$ in the monolayer.[36a] Strongly bound K$^+$ ions can be removed irreversibly and slowly in contrast to weakly bound K$^+$ ions, which exchange nearly reversibly and quickly. This templated monolayer also showed selective recognition of K$^+$ over other cations such as Na$^+$, Cs$^+$, Ba^{2+}, and Ca^{2+}, and some of these principles were employed in the development of gold nanoparticles capable of metal ion recognition, which thus far have proven successful in organic media.[37] The SAMs with the benzene group (**18**) had a higher degree of flexibility since they were anchored to the gold surface only at one site of the molecular units.[36b] When these monolayers were templated in the presence of K$^+$, the resulting binding sites were imprinted into the monolayers so that after removing the template cations, they retained the recognition motif and were capable of specifically binding K$^+$ ions over Na$^+$ (Scheme 5) when they were subsequently exposed to aqueous solutions of these cations. These types of monolayers represent the first example of binding sites of potassium cations imprinted into the SAMs when the monolayers assembled on the gold electrode in the presence of the metal cation.

Other binding motifs have been incorporated into SAMs to recognize redox inactive cations. For example, the highly selective calix[4]crown-6, in its 1,3-alternate conformation, has shown remarkable efficiency in extracting ^{137}Cs ion from radioactive waste,[38] and Echegoyen *et al.* have shown that this type of receptor retains its selectivity when incorporated into SAMs (Scheme 6).[39] Once again, impedance spectroscopy and cyclic voltammetry were employed to detect and compare the recognition properties of remarkably stable monolayers containing different conformational isomers of *p-tert*-butylcalix[4]crown-6 and *p-tert*-butylcalix[4]arene bisthioctic ester derivatives. SAMs derived from the cone isomer of *p-tert*-butylcalix[4]crown-6 derivative do not bind Cs$^+$; however, SAMs derived from its 1,3-alternate isomer recognized Cs$^+$ selectively.[39a] This selective recognition of Cs$^+$ was confirmed by both CV blocking experiments and EIS in aqueous media. This study clearly showed that the selectivity of the calix-crown SAMs is modulated by the change in conformation. These monolayers are also capable of differentiating between alkaline earth metal cations from alkali metal cations in aqueous solutions.[39b]

In addition to building monolayer sensors for redox inactive metal ions, the same group has recently developed a calix[6]crown-4 based sensor for redox inactive organic cations in aqueous media.[40] A conformationally fixed calix[6]arene cavity is very difficult to obtain because of its flexibility. Thus, the introduction of a crown ether bridge at the lower rim of the calix[6]arene was required in order to provide rigidity and lock the cavity in a frozen cone conformation (**20**, Fig. 6). Four thioctic ester appendages were also incorporated in this structure to serve as anchoring groups on the surface of a gold electrode, and such a system proved successful in the detection of anilinium ions using CV and EIS (Scheme 7). As shown in the right column of Scheme 7, the R_{ct} value is 52.6 kΩ in the presence of 80 mM of three different alkylammoniums, but addition of only 2 mM of anilinium chloride to the electrolyte resulted in a R_{ct} value of 145.6 kΩ, which indicates that anilinium chloride interacts with the monolayer much more strongly than the alkylammonium cations. The remarkably sensitive response for anilinium was attributed to the proper size fit and multipoint binding interactions between the

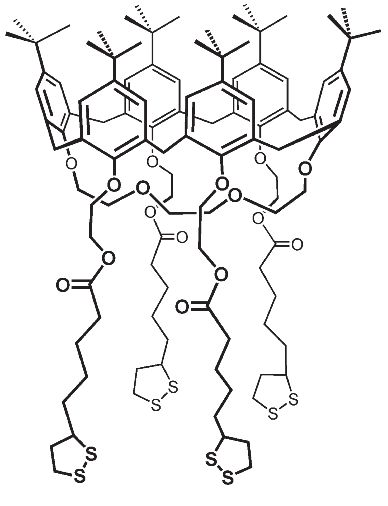


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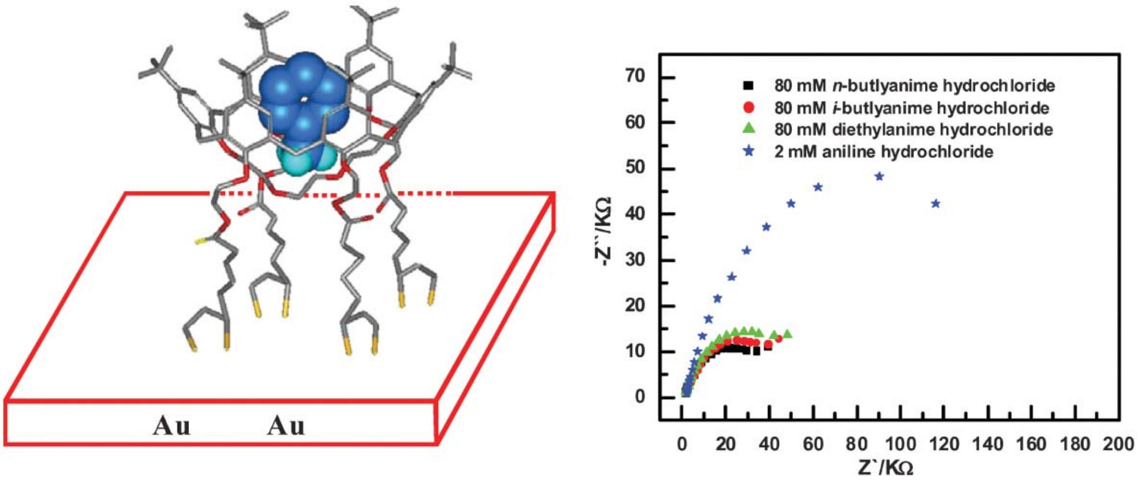
Fig. 6 Conformationally fixed calix[6]crown-4 receptor.[40]



Scheme 7 Schematic representation of anilinium recognition by SAMs of a calix[6]crown-4 derivative (left) and impedance response of $Ru(NH_3)_6{}^{3+/2+}$ at the monolayer modified gold electrode in the presence of 80 mM of alkyl ammonium cations and 2 mM of anilinium in aqueous media (right).[40]

host and the guest. Its binding affinity towards other biogenic aromatic amines such as dopamine was also investigated, and both CV blocking experiments and EIS showed that SAMs of this novel receptor exhibit much better recognition for dopamine than for the alkylammonium salts. This system could become a potential receptor for other aromatic amines of biological importance.

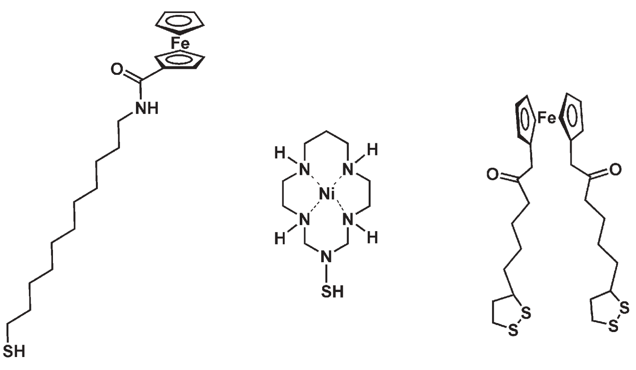
Recognition of anions by SAMs

The recognition and sensing of anionic species has recently gained more attention, and has emerged as a promising research area for the development of environmentally and biologically related anion sensors. Compared to the well-developed cation binding and sensing,[41] anion recognition both in bulk solutions and at monolayer/solution interfaces is a more challenging field due to their variable sizes, shapes, and strong solvation. Nevertheless, we will outline in this section some of the most interesting designs for anion recognition based on monolayers that have been reported recently.

In one of the first examples, Astruc and co-workers achieved the recognition of the dihydrogenophosphate anion in CH_2Cl_2 on a gold electrode derivatized with amidoferrocenyl alkylthiolate ligands (**21**, Fig. 7).[42] Upon addition of $H_2PO_4{}^-$ to the electrolyte solution, the oxidation potential of the corresponding SAMs shifted negatively by 0.29 V and the peak-to-peak separations became 244 mV, suggesting a significant structural reorganization upon dihydrogenophosphate complexation with the monolayer. In the case of other small inorganic anions such as Cl^-, Br^-, $NO_3{}^-$, and $HSO_4{}^-$, much smaller changes in the redox response were observed.

Gobi and Ohsaka prepared SAMs of a nickel azamacrocyclic complex (**22**) on gold electrodes to investigate anionic recognition in aqueous system.[43] The electrochemical response of these monolayers was susceptible to the type of anions present in solution due to a variety of coordination behaviours, as well as the anion concentration. Monolayers of the nickel complex exhibited a reversible oxidation peak at 0.82 V in 0.1 M aqueous $NaNO_3$, which shifted to 0.55 V in 0.1 M aqueous Na_2SO_4. This shift of the redox potential was reversible upon exchanging the SAM-modified electrodes between these two electrolyte solutions. Based on the concentration dependent electrochemical response, the binding constants of the macrocyclic complex with different anions were measured. Also, their electrochemical investigation indicated that the monolayer could distinguish between several different anions including $NO_3{}^-$, CF_3COO^-, $SO_4{}^{2-}$, $H_2PO_4{}^-$, $ClO_4{}^-$, $PF_6{}^-$, SCN^-, and even adenosine triphophate (**ATP**), a biologically important anion. In the latter study, for example, the redox potential of the Ni^{+2}-azamacrocyclic SAMs shifted cathodically by 250 mV upon the addition of 1 mM **ATP**.

The anion recognition properties of SAMs of 1,1′-bis(alkyl-*N*-amido)ferrocene, **23**, (**BAAF**) were studied by Beer and his co-workers in a 2 : 1 acetonitrile–chloroform solvent system.[44] In this work, a "surface sensing amplification" phenomenon was observed, which means that the anion binding affinities on the monolayer are orders of magnitude larger than those obtained in solution with the same receptors. They attributed the amplification effect to the pre-organization of the receptor on the electrode surfaces and to the relatively low dielectric constant of the monolayer receptor binding site. Upon addition of phosphate



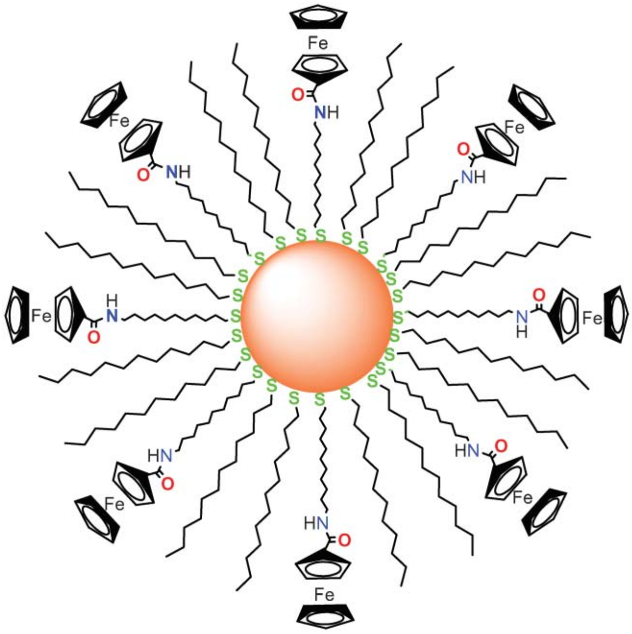
21 **22** **23**

Fig. 7 Structures of ferrocene derivatives,[42,43] and nickel complex with surface-anchoring groups.[44]

and chloride, the redox wave of the surface confined ferrocene derivative shifted cathodically and the peak-to-peak separation was increased, indicating a relatively slow rate of electron transfer and/or possible structural change within the monolayer induced by anion complexation. In terms of selectivity, these SAM-modified gold electrodes are able to recognize dihydrogen phosphate even in the presence of 100 fold excess of halide anions. Also, SAMs of **BAAF** are able to detect low levels of perrhennate in aqueous systems, as compared to their dihydrogen phosphate sensing in organic solvents. Perrhennate anion is used as a model to design receptors capable of detecting the radioactive pertechnetate anion, which is a pollutant derived from the nuclear industry.

In addition to the anion recognition conducted on the flat electrode surfaces, anion receptors have also been immobilized on gold nanoparticles in order to build three-dimensional anion sensing arrays. Beer and co-workers assembled disulfide-functionalized zinc metalloporphyrins (**24**, Fig. 8) on gold nanoparticles, which displayed a higher affinity for anions than the free metalloporphyrins in CH_2Cl_2, DMSO and aqueous DMSO solutions.[45] Such an enhancement in anion binding was attributed to the pre-organization of receptors and/or solvation effects.

The anion sensing properties of gold nanoparticles modified by ferrocene derivatives were also investigated in organic solution by Astruc and co-workers.[46] Gold nanoparticles were functionalized by mixed SAMs of dodecanethiol/(amidoferrocenyl)alkanethiol (**AFAT**) ligands with various chain length and different compositions (Scheme 8). **AFAT**-modified gold colloids are stable, soluble in CH_2Cl_2, and exhibit reversible redox behaviour with some adsorption. These **AFAT**-modified gold colloids have been used to sense oxoanions such as $H_2PO_4^-$ and HSO_4^- in CH_2Cl_2. The electrochemical behaviour of these particles do not display any significant potential shifts upon addition of chloride, bromide, or nitrate anions. However, upon titration with dihydrogen phosphate, a new quasireversible redox wave appeared at a more negative potential (220 mV) while the initial wave decreased. After the addition of 1 equivalent of this anion, the original wave had completely disappeared. No matter how the **AFAT** ligand is modified, the new redox peak always appears, and the potential shift is affected by the stereo-electronic characteristics of the aminoferrocene terminal group.[46a] In addition, Astruc *et al.* assembled tri- and nona-ferrocenyl thiol dendrons (**25**, **26**, Fig. 9) onto gold nanoparticles and investigated their anion sensing properties. Such nanoscopic supramolecular assemblies exhibit selective recognition of $H_2PO_4^-$ and **ATP** anions over Cl^- and HSO_4^- in CH_2Cl_2.[46b] These ferrocene-dendritic receptors also displayed new oxidation waves upon titration with $H_2PO_4^-$ and **ATP**, with a more than 200 mV cathodic potential shift compared to the initial oxidation wave.



Scheme 8 Schematic representation of amido-ferrecene derivative functionalized gold nanoparticles for anion sensing.[46a]

In all of the above cases, electrochemically active groups were incorporated at the receptor site to monitor the anion sensing processes. In order to develop new sensing systems in aqueous environments, simpler assemblies of anion receptors have been pursued on electrode surfaces without the need for

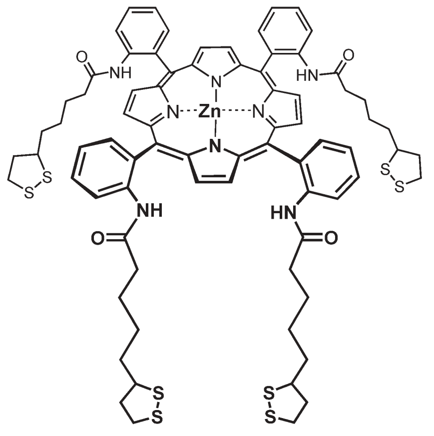


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Fig. 8 Zinc-metalloporphyrin with thioctamide appendages.[45]

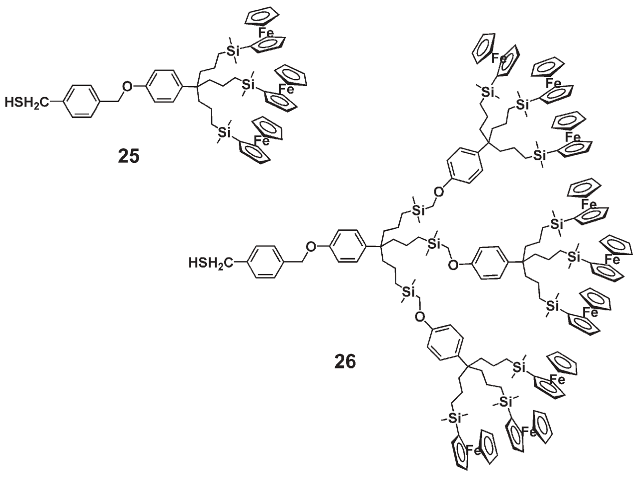

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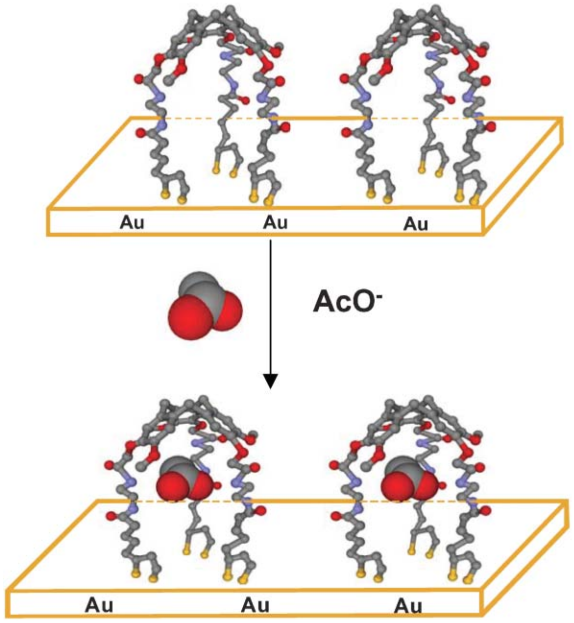
Fig. 9 Tri- and nona-ferrocenyl thiol dendrons employed in anion sensing.[46b]



Scheme 9 Schematic representation of AcO^- recognition by SAMs of a CTV–trisamide derivative (**CTVTE**).[47]

electroactive reporting groups. With this aim, impedance spectroscopy was recently employed to investigate anion sensing at the interface of SAM-modified electrodes containing cyclotriveratrylene (**CTVTE**) receptors in aqueous solutions (Scheme 9).[47] **CTVTE** was prepared and assembled on gold surfaces, and these SAMs were characterized by cyclic voltammetric blocking experiments, impedance spectroscopy, and electrochemical desorption. Electrochemical impedance proved to be as efficient and convenient technique to detect anions in aqueous solutions as it did in the case of cation detection. These modified gold electrodes show a drastic increase of the R_{ct} values when $Fe(CN)_6^{3-/4-}$ was used as the redox probe upon titration with acetate anions. Fig. 10a shows that addition of AcO^- to the electrolyte resulted in an increase in the $R_{ct,}$ from its initial value of 162 kΩ in the absence of AcO^-, to a limiting value of 329 kΩ when the acetate concentration reached 15 mM, which indicated a substantial build-up of negative charge on the surface due to anion binding. The electrostatic repulsion between the negatively charged redox probe and the negatively charged SAM surface gives rise to the increase of R_{ct}. When the probe was changed to a positively charged one, $Ru(NH_3)_6^{3+/2+}$, the R_{ct} values decreased from 33.9 kΩ in the absence of AcO^- to 10.9 kΩ in the presence of 20 mM of acetate anion (Fig. 10b), thus confirming the accumulation of a negative surface charge upon anion binding. $H_2PO_4^-$ showed some interference in the detection of acetate anions, but other monovalent anions, such as Cl^-, Br^-, NO_3^-, and HSO_4^-, do not bind appreciably to the **CTVTE** receptor either in solution or on the surface of the gold electrodes. The novelty of this work rests on the introduction of both negatively and positively charged probes to detect binding of anions with impedance spectroscopy in aqueous media.

A calix[6]crown-4 derivative (**C6C4TE**) with thioctic ester groups was also shown to interact with anions through hydrogen bonding.[48] As illustrated in Scheme 10, SAMs of **C6C4TE** exhibited a selective F^- binding ability in aqueous media. Impedance spectroscopy was again employed to monitor the anion recognition at the interface of the electrolyte solution and the SAM modified gold electrodes. These receptor-immobilized surfaces exhibit a higher affinity for F^- than for other anions such as Cl^-, Br^-, NO_3^-, HSO_4^-, $H_2PO_4^-$, and AcO^-.

As confirmed by the last two examples, assembling anion receptors on solid substrates and conducting molecular recognition at the monolayer/solution interface provides an effective method for anion sensing in aqueous solutions.

Conclusions and outlook

In conclusion, we have seen that over the past few years SAM-modified surfaces have been successfully designed to detect ionic species at solution interfaces. Employing SAM-modified electrodes for ion sensing has resulted in some elegant examples that incorporate sophisticated receptors on the electrode surfaces. These successful examples clearly demonstrate that chemical tailoring of electrodes provides useful sensor arrays, and that self-assembly plays a very important role in these designs. Recognition of redox active and inactive

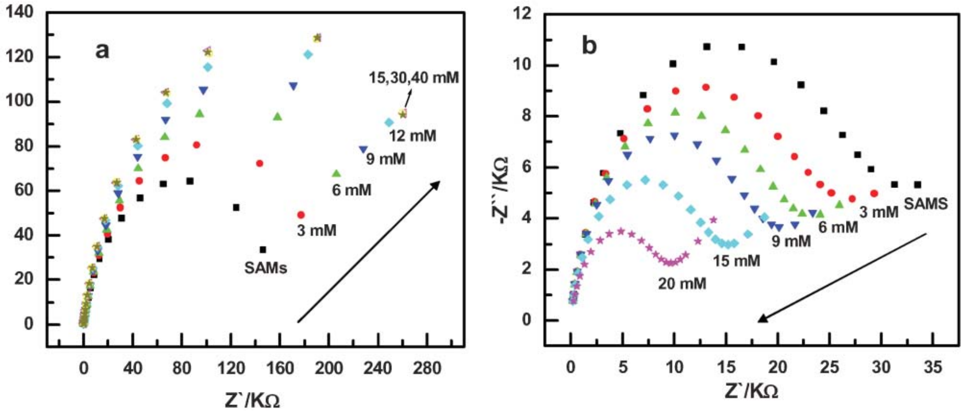


Fig. 10 Impedance response of $Fe(CN)_6^{3-/4-}$ (a) and $Ru(NH_3)_6^{3+/2+}$ (b) at the electrode modified by SAMs of CTV–trisamide receptor in the absence and presence of increasing $[AcO^-]$.[47]

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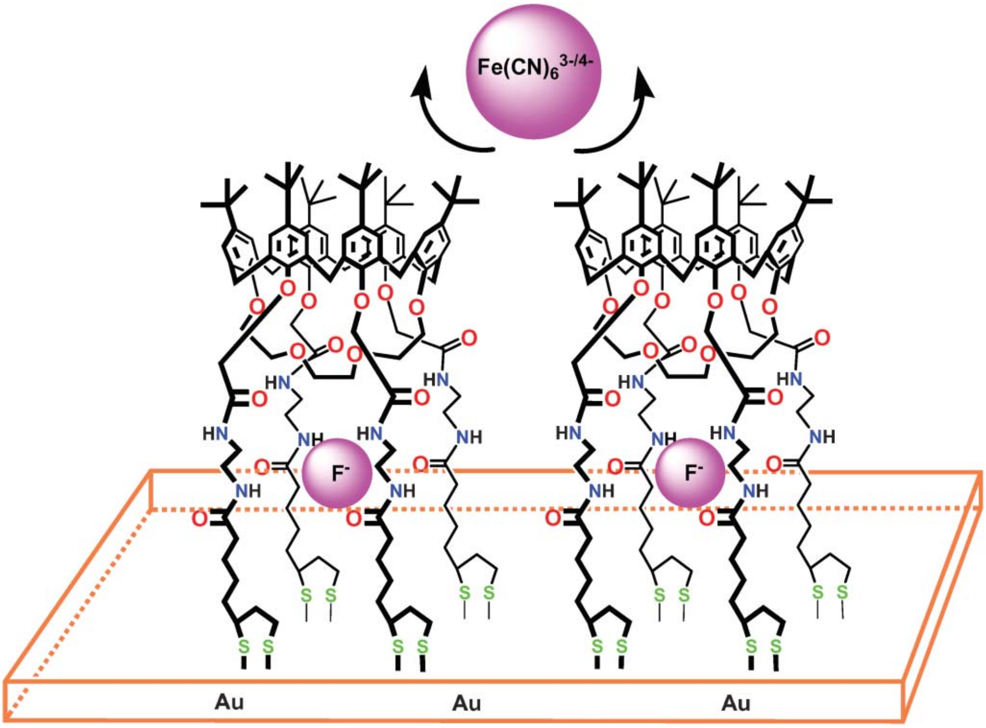

Scheme 10 Schematic representation of F$^-$ recognition by SAMs of a calix[6]crown-4 thioctamide derivative (**C6C4TE**).[48]

metal ions was readily achieved with SAMs of redox inactive and active receptors such as carboxylic acids, pyridines, amino acids, peptides, crown ethers, tetrathiafulvalenes, and calixarenes. In comparison to monolayers designed for cation recognition, employing SAMs in anion sensing has been a relatively unexplored field. However, recent results show that anion recognition by SAMs is feasible, especially in aqueous environments, and probably more effective than anion detection in homogeneous solutions. Progress in ion sensing in aqueous media has brought this field one step closer to potential application in the areas of environmental and biological analysis.

In the case of electrochemical monolayer sensing, currently most of the investigations employ cyclic voltammetry and, sometimes, pulse voltammetric techniques. Impedance spectroscopy is a rapidly developing electrochemical technique for the characterization of SAM-modified electrodes. Impedance spectroscopy has become an attractive tool to detect biorecognition events at the modified electrode surfaces because it provides detailed information on resistance and capacitance changes, which signal the recognition interactions,[5a] and this technique is expected to continue to evolve for the measurement of redox-inactive ions. The use of impedance spectroscopy measurements on SAM modified electrodes offers advantages for ion recognition such as: (1) ion sensing can be easily conducted in aqueous systems; (2) receptors can be designed exclusively for ion binding without consideration of the need to incorporate electrochemical or fluorescent active groups, thus broadening the options for the development of more selective and sensitive anion sensors; and (3) practical ion sensors are possible by assembling receptors on surfaces.

As discussed earlier, monolayer sensors exhibit potential commercial applications, but extensive research is still needed before these are viable. Stability, sensitivity and selectivity are issues to be addressed. To overcome the thermal instability and reductive or oxidative desorption of SAMs, more stable self-assembled monolayers need to be constructed. Therefore, it is important to develop new assemblies with more robust structures, perhaps by adding more interactions,[49] such as hydrogen bonding, within the existing systems and/or employing receptors with more anchoring groups.[28a,50] Even though sensors based on monolayers are very sensitive, optimizing their sensitivity is fundamental to further improve their commercial viability. Such optimization could be achieved by utilizing microarrays of individual sensing groups.

To enhance both sensitivity and selectivity, novel sensing arrays incorporating metal or semiconductor nanoparticles, dendritic structures, and nanotubes are expected to extend two-dimensional sensing arrays on electrode surfaces to three-dimensional recognition systems. Since the previously mentioned gold nanoparticle anion sensors[45,46] developed by Beer *et al.* and Astruc *et al.*, there have only been a few reports on three-dimensional sensors. Recently, a colorimetric alkali ion sensor was constructed by immobilizing crown and carboxylate moieties on spherical gold nanoparticles.[51] A cooperative effect was observed in which the sensing efficiency of the crown ether on gold nanoparticles can be dramatically affected by the presence of the carboxylate group. Employing new analytical techniques and developing new sensing technologies will also be helpful to optimize these systems. Crego-Calama and Reinhoudt *et al.* have recently developed a simple but efficient method to prepare cation or anion sensing SAMs.[52] They employed combinatorial chemistry in the construction of small molecule microarrays by simply assembling the mixed monolayers of receptors with binding functionalities and fluorophores on glass substrates. Through this strategy, selective ion sensing is easily achieved without the need to design receptors independently. In addition, the rapidly developing probe microscopy techniques, such as STM and AFM, will make it possible to detect host-guest interactions at the molecular level. This is the case of the microcantilever sensors which have been derived from the microfabricated cantilevers used in atomic force microscopy,[14a] and have been recently adapted to detect metal ions.[53]

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