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Chemosensor devices: voltammetric molecular recognition at solid interfaces

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This article reviews progress in modifying electrode surfaces with functional organic molecules which act as signalling units upon molecular recognition of a guest molecule or ion. This process triggers a change in the physicochemical properties of the host assembly which can be monitored by an electrochemical response. Topics covered include: molecular recognition in conjugated polymers; molecular recognition in monolayers formed by Langmuir–Blodgett and self assembly techniques; incorporation of recognition sites ('molecular gates') in otherwise passivating monolayers; ion channel sensors. Representative redox moieties include: polythiophene and polypyrrole derivatives, paraquat, ferrocene, tetrathiafulvalene, metalloporphyrins, C_{60}, $Ru(NH_3)_6^{3+}$ and $Fe(bpy)_2(CN)_2^0$. Issues relevant to the development of practical, commercially-viable sensors are considered.

1. Introduction

Molecular recognition is a corner-stone of supramolecular chemistry.[1] Within this field the study of chemosensor devices is an important topic. A chemosensor is a molecular system for which the physicochemical properties change upon interaction with a chemical species in such a way as to produce a detectable signal. A device can, therefore, be based on molecular recognition phenomena where the specific binding of an analyte to a sensor material (the receptor) is transduced to the signalling unit, which then responds by undergoing a change in its electronic state. This is monitored and measured by different spectroscopic, electrochemical or structural techniques. Most investigations based on this idea have concerned molecular recognition in solution, and signal transduction using luminescence[2] and electrochemical[3] techniques have been reviewed. However, the knowledge of these specific host–guest interactions and their application to sensing devices in thin films, especially thin solid films, is less well developed. Recently, molecular recognition in Langmuir monolayers and Langmuir–Blodgett films has been reviewed.[4] The importance of investigating such processes in films is without question, as these systems are relevant to the construction of practical devices. Signal detection by both voltammetric and amperometric devices involves measurement of current. With the development of modern instrumentation, especially pulse techniques, both modes of operation are practicable. Electrochemical transducers offer the advantages of simplicity and low cost: a basic working device can be constructed by immersing two electrodes in an analyte solution and connecting them to a potentiostat. Sensitivity can be high, quantitative data are readily obtained using simulation programmes, and a wide range of analyte concentrations can be employed.

This article reviews molecular recognition phenomena in thin films attached to an electrode surface by different preparative techniques, with the aim of devising voltammetric chemosensors.

2. Direct molecular recognition

We define direct molecular recognition as the process whereby an electroactive receptor (host) interacts with an analyte (guest) to form a supramolecule. The resulting change in electronic properties between the pristine receptor in the thin film and the supramolecule can be monitored electrochemically. We should emphasise that it is the electrochemical properties of the host which are recorded; the guest is often a non-electroactive species.

2.1 Conjugated polymers

Overviews of molecular recognition using various conjugated polymers have been published[5] and other reviews focus on polythiophene derivatives.[6] From a chemical point of view, all known conjugated polymers possessing molecular recognition properties can be divided into the generalised structures represented in Fig. 1. In structures **Ia** and **Ib** the receptor unit (a crown ether) is fused to the signalling conjugated polymer backbone. Structure **II** possesses a conformationally-flexible, pendant chain receptor [typically an oligo(ethylene glycol) chain], and is relatively easy to synthesise. Structures **III**–**VI** incorporate a receptor or redox substituent (or both) into the pendant chain. For structures **III**–**V** the signalling process *a priori* must involve through-space interactions as the receptor moiety of the host molecule is not conjugated to the polymer backbone. In structure **VI** the conjugated polymer backbone is not the signalling unit; it serves only to attach the film to the electrode surface, and as the electron-transporting material. The signalling unit is the substituent redox group. In structure **VII** the receptor is a counterion inserted into the polymer film with no chemical link to the polymer: this type of sensor will be discussed in Section 3.1.

Historically, the first example of molecular recognition using conjugated polymers was reported by Roncali and co-workers for oxyethylene substituted polythiophene (PT) derivative **1** (structure type **II**).[7] The underlying principle is that the interaction of metal ions with the ether chain causes a change in conformation of the PT chain from planar (conjugated) to twisted (non-conjugated) or *vice versa*. The electronic properties of these two conformations are different and metal binding can be monitored electrochemically and spectroscopically. In this early work it was noted[7] that the cyclic voltammetric (CV) properties of polymer **1** depended markedly on the type

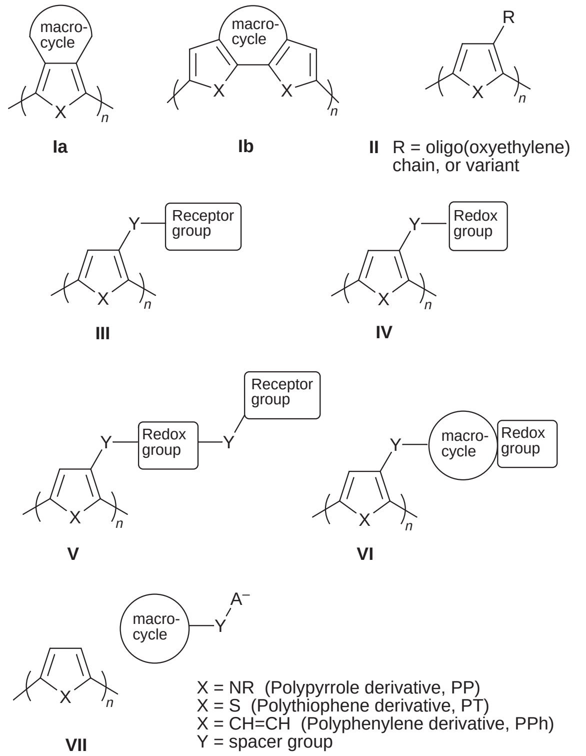


Fig. 1 Generalised structures of conjugated polymers possessing molecular recognition properties.

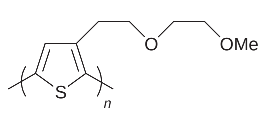
and the concentration of electrolyte employed. For instance, a ten-fold increase in the concentration of the bulky, hydrophobic Bu_4N^+cation led to a positive shift of the oxidation peak potential by *ca.* 150 mV, whereas a similar increase in the concentration of hydrophilic Li^+ cation led to a comparable negative shift, and to a sharpening of the redox peaks. Also, substitution of Bu_4N^+ electrolyte for Li^+ electrolyte, of the same concentration, led to a positive shift of *ca.* 1 V for the reduction of the polymer.[7a] The structure of the podand chain in polymer **1** may be suitable for complexation with Li^+; however, this process should make the polymer harder to oxidise. Several explanations for this unusual phenomenon have been offered.[7] In the light of subsequent results with other materials (see below) the most plausible explanation would be a change of polymer backbone conformation (to a more planar and consequently more conjugated state) after the complexation of Li^+. This was considered in the initial work and is consistent with the slight bathochromic shift of the absorption maximum in the UV–Vis spectrum.[7b]

Bauerle and Scheib electropolymerised crown-annelated PT monomers **2** (structure type **Ia**).[8] As suggested earlier,[9] these materials selectively bind Na^+ cations, and, as expected, upon complexation, the oxidation of the electropolymerised polymer films of **2** became more difficult due to the electron-withdrawing effect of the bound cation.[8] It was suggested that diffusion of ions is hindered in these films, as a stable CV response was established only after a few voltammetric cycles, and the maximum shift (*ca.* 0.8 V) was registered after *ca.* 30 cycles. In contrast, in the presence of the non-interacting cation Bu_4N^+, the CV response was stable. Experiments with mixtures of cations were not reported. Slow ion diffusion is likely to prevent applications of these films in electrochemical sensors.

A number of polyphenylenes and analogues (structure type **Ia**) derived from aromatic crown ethers were obtained by electropolymerisation of benzocrown ethers,[10] dibenzocrown ethers,[10,11] dinaphthocrown ethers[12] and binaphthylcrown ethers.[10,13] Complexation with different metal cations[14] and organic molecules, predominantly of biological importance,[14g] has been investigated. These films were used as potentiometric sensors for catechol and other neurotransmitters,[10,11i,13] for hydrogen sulfide[13a] and strontium.[11k]

We note an interesting example of electrochemical detection of binding of TCNQ and TTF into solid poly(dibenzo-18-crown-6).[14g] The CV responses of TCNQ and TTF guests in the polymer host cuttings were registered. The formation of the entrapped TTF–TCNQ charge transfer complex was suggested after successive treatment of polymer cuttings with TCNQ and TTF solutions.[14g]

A more sophisticated crown-PT system **4** (structure type **Ib**)[15a] and similar polymers[15] have been obtained by electropolymerisation of the open-chain 3,3′-bithiophene derivative **3** ($m = 4$)[15a] due to a template effect in the presence of Li^+ (this effect is characteristic of macrocyclic synthesis). The voltammetric response of most of these polymers was not affected by the addition of Li^+. Only the polymer with $m = 5$ exhibited a 50 mV positive shift of the oxidation potential. With the same idea in mind, a number of difluorenyls linked with polyether spacers were anodically electropolymerised, *e.g.* compound **5**.[16] Alkali metal cations influenced the reduction of some of the polymers, increasing the reduction current and decreasing the reversibility of the process.



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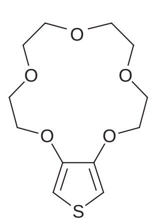

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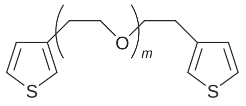
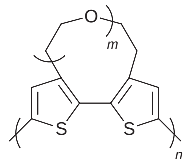
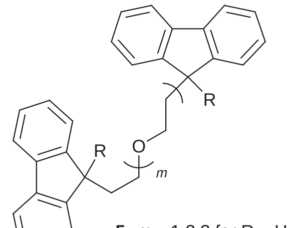


3 $m = 1,3\text{-}7$



4 $m = 1,3\text{-}7$



5 $m = 1,2,3$ for R = H
$m = 1$ for R = Me

Polymers **6–8** been prepared by chemical routes.[15b,c] The idea behind their study is based, in part, on Kaifer's demonstration that the complexation of an electron donor pseudorotaxane with a strong electron acceptor (*e.g.* paraquat **9a**) can be monitored by changes in the oxidation potential of the former species.[17] The sensor properties of polymer films of **6–8** were tested by CV and *in situ* conductivity measurements. In these experiments interdigitated electrodes were covered by the polymer film, and the drain current due to the small potential difference between the electrode fingers was monitored against the electrode potential.[18] Polymer **6** was selective for the stronger acceptor guest **9b** (the electron affinity of which is enhanced by the *para*-fluorophenyl substituent) which caused a positive shift of the oxidation potential (100 mV) and a *ca.* twofold decrease in the drain current; both sets of data are diagnostic of binding (Fig. 2).[15b] It was later found that thinner films of polymer **6** showed a small, but negative, shift of the oxidation potential and a small decrease in drain

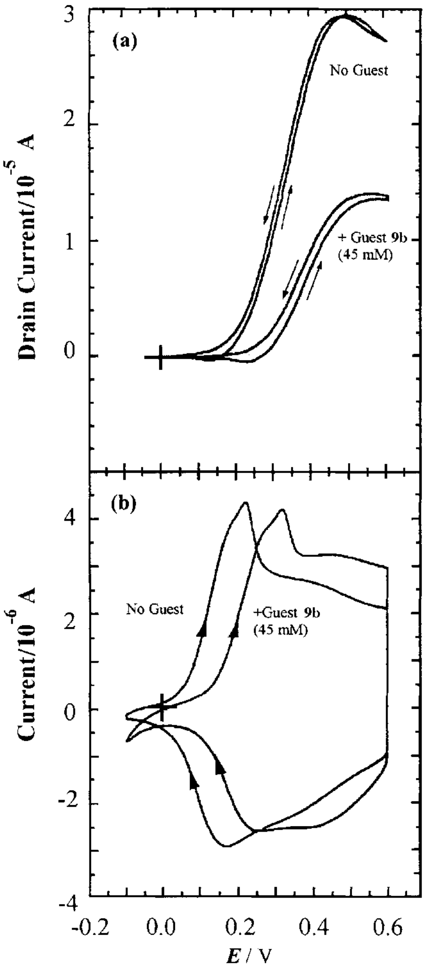
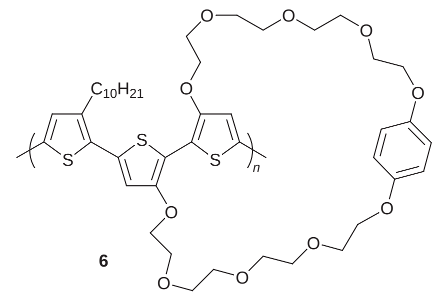


Fig. 2 (a) Drain current, and (b) CV for polymer **6** in the absence and presence of guest **9b** (0.1 M $LiClO_4$, acetonitrile–water 1 : 1, *vs.* Ag wire). Reprinted with permission from M. J. Marsella, P. J. Carroll and T. M. Swager, *J. Am. Chem. Soc.*, 1994, **116**, 9347. Copyright 1994 American Chemical Society.

current in response to paraquat **9a**.[15c] This unexpected shift of potential was explained by a conformational change in the polymer chain induced by interaction with **9a**. Polymer **7** showed a 40 mV positive shift of its oxidation potential and a 25% decrease in the drain current in response to **9a**. Treatment of the open chain polymer **8** with acceptor **9b** resulted in a 40 mV positive shift and no change in the drain current. An explanation for the varying potential shift behaviour of polymers **6–8** has not been offered.[15b,c]

PT substituted with a calix[4]arene receptor **10** demonstrated a remarkable selectivity to Na^+ over K^+ and Li^+ (positive shift of the peak potential of *ca.* 100 mV and *ca.* two orders of magnitude decrease in the drain current in response to 0.5 mM of Na^+, Fig. 3).[15d] However, this voltammetric effect was the opposite of the results of spectroelectrochemical experiments which suggested that conjugation of the PT chain increased in the presence of Na^+. Thus, the voltammetric effect was attributed to an electrostatic effect of Na^+ (or/and an electron withdrawing effect) and to reduced electron donor ability of sodium-bound oxygen atoms at the lower calixarene rim.[15d] The latter explanation would require the oxygen atoms directly attached to the PT backbone to be involved in metal binding. It was demonstrated[15d] that ionoresistivity possesses a much lower sensitivity threshold than voltammetry or spectroscopy: while Li^+ and K^+ resulted in a negligible response in voltammetry and absorption, the deviation of the *in situ* conductivity response was significant.



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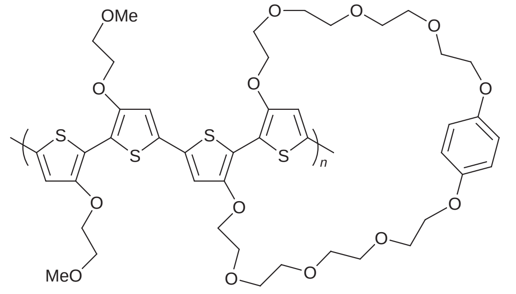

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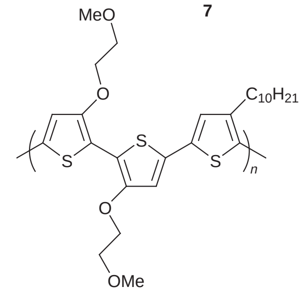

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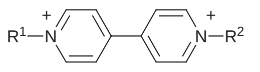
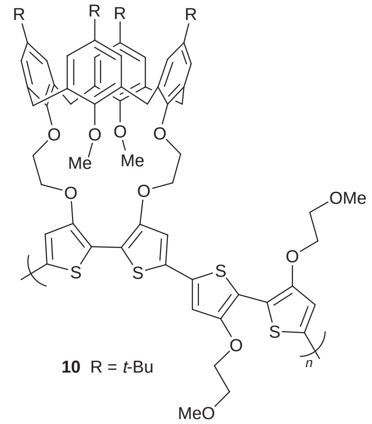
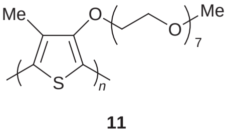


9a $R^1 = R^2 = Me$
b $R^1 = R^2 = 4\text{-}F\text{-}C_6H_4$
c $R^1 = Et$; $R^2 = C_{18}H_{37}$



10 R = *t*-Bu

Type **II** structures are the simplest from a synthetic chemistry viewpoint, and, as mentioned above, electrochemical recognition was first identified in the conjugated polymer **1** by Roncali *et al.*[7] A similar polymer structure **11**, possessing a longer polyether chain has been synthesised by a chemical route in Leclerc's group.[19] Ionochromic properties in solution[19] and thermochromic properties in thin films[20] were identified. Recently, electrochemical cation recognition was demonstrated in thin cast films of polymer **11**,[21] and in LB films prepared under special conditions.[22] Addition of alkali metal salts induced a change of conformation of the backbone of polymer **11** from conjugated to twisted, with a consequent decrease of conjugation length and increase of redox potential. Selectivity in the order $K^+ > Na^+ > Li^+$ with ability to recognise K^+ at sub mM level was demonstrated (Fig. 4).[21]



11

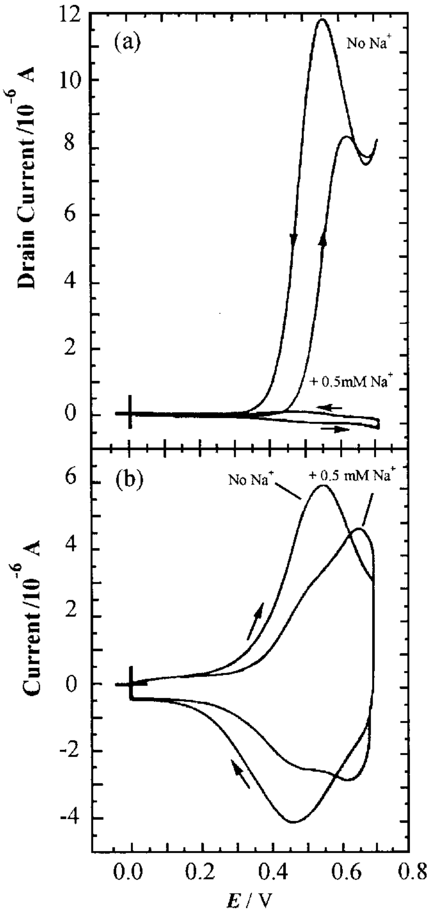


Fig. 3 (a) Drain current, and (b) CV for polymer **10** in the absence and presence of Na$^+$ (0.1 M Bu_4NPF_6, acetonitrile, *vs.* Ag wire). Reprinted with permission from M. J. Marsella, R. J. Newland, P. J. Carroll and T. M. Swager, *J. Am. Chem. Soc.*, 1995, **117**, 9842. Copyright 1995 American Chemical Society.

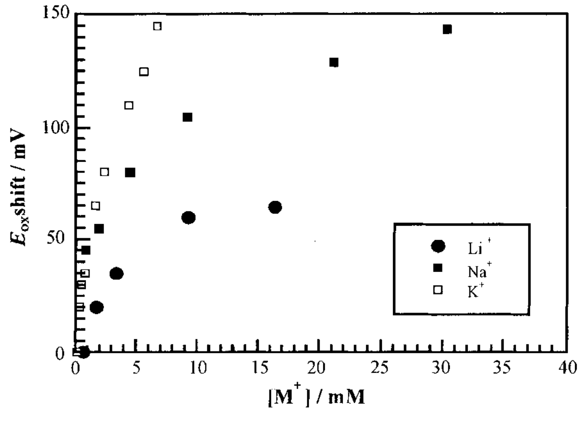


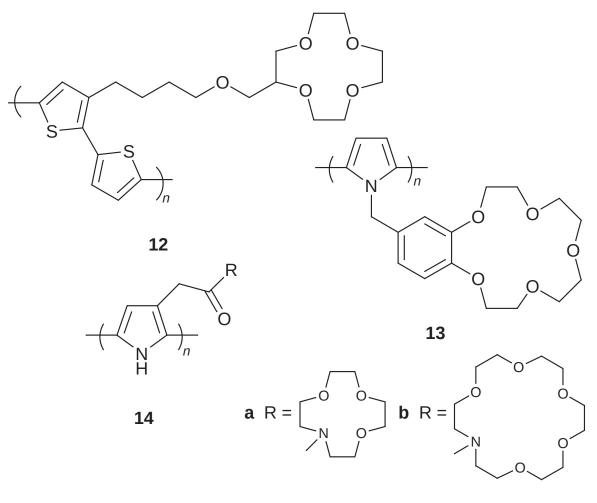
Fig. 4 Shift of the oxidation potential for polymer **11** cast onto Pt disk 1.6 mm diameter (in 0.2 M Bu_4NClO_4, acetonitrile, scan rate 0.05 V s^{-1}, *versus* concentration of metal ions as indicated. Reprinted from *J. Electroanal. Chem.*, **447**, L. M. Goldenberg, I. Levesque, M. Leclerc and M. C. Petty, 246, Copyright 1998, with permission from Elsevier Science.

Another approach is to attach a receptor unit *via* a flexible spacer, to create structural type **III**. In this case, due to the flexibility of the spacer, it is possible for the receptor to attain close proximity to the polymer backbone, and hence to perturb the electronic state of the conjugated chain. For macrocyclic receptors this idea has been pursued by several groups. Polymer **12** synthesised by Bauerle and Scheib is representative:[23] conceptually similar systems have been studied by Garnier *et al.*,[24] Bartlett *et al.*[25] and Beer *et al.*[26] Non-macrocyclic receptors have also been studied in this context.[27]

The redox behaviour of films of **12**[23] was similar to that of the oligo(oxyethylene)-substituted PT derivative **11**.[21,22] However, the order of selectivity to alkali metal cations was reversed, because the 12-crown-4 cavity in **12** is more suitable for Li$^+$, which at concentrations as low as 5×10^{-5} M visually affected the CV response.

Benzo-15-crown-5 is known to bind Na$^+$ more strongly than other monocations in acetonitrile.[28] However, polypyrrole (PP) derivative **13** containing this receptor (obtained by electropolymerisation) did not show any Na$^+$ recognition in the shape of the CV nor in the redox potentials.[25] This was explained by possible steric constraints for the complexation of the solvated cation by the crown ether.[25] Another plausible explanation is that while Na$^+$ is bound by the crown ether, due to geometric constraints of the rigid benzene ring it does not affect the PP backbone either electronically or sterically. PPs substituted with azacrown ethers **14a,b** have been obtained.[24b,29] No difference in the CV response with respect to added alkali metal cation was observed for monomer **14a** either in acetonitrile or in water, due to the small size of the crown-4 cavity. However, complexation of Na$^+$ and K$^+$ within the larger crown cavity of **14b** was observed electrochemically. While polymer **14b** was obtained using Li$^+$ containing electrolyte, a positive shift of the oxidation potential of 380 or 420 mV was gradually observed upon cycling the films in acetonitrile containing Na$^+$ and K$^+$, respectively. The replacement of Li$^+$ by Na$^+$ and K$^+$ was irreversible. While Na$^+$ was added to polymer **14b** in acetonitrile containing a 0.1 M solution of Bu_4NClO_4, the oxidation potential shifted positively (Fig. 5a) starting at 10^{-5} M Na$^+$ concentration and saturating at 10^{-2} M Na$^+$ (Fig. 5b).[29] Similar behaviour was observed with K$^+$, but no such effect was observed in aqueous electrolyte.[29] This was explained by strong competition of water for cation solvation.[24b] The advantage of polymer **14b** over polymer **13** was explained by better conjugation of the PP chain when substituted at C3 rather than at N; this is manifested in the considerably higher oxidation potential for material **13**. As **13** already lacked coplanarity, complexation with metal cations did not further decrease the conjugation. In fact, electrochemical recognition for PP-based materials, where PP serves as the signalling unit, has, to date, been observed only for 3-substituted derivatives.

A different synthetic approach was realised in the synthesis of polymer **16** where the crown ether receptor was grafted onto a polymer backbone using the preformed electropolymerised film **15**.[24a] The CV response of films of **16** was affected by the choice of electrolyte cation, with Na$^+$ and K$^+$ positively shifting the peak potential by *ca.* 200 mV. This procedure allows the attachment of other receptors in the same way. An



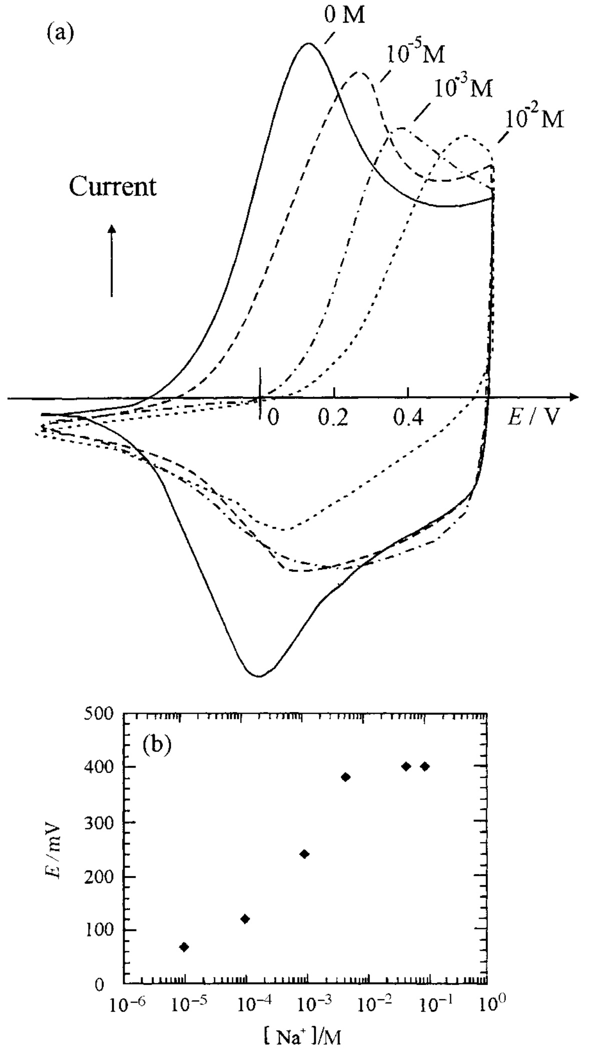
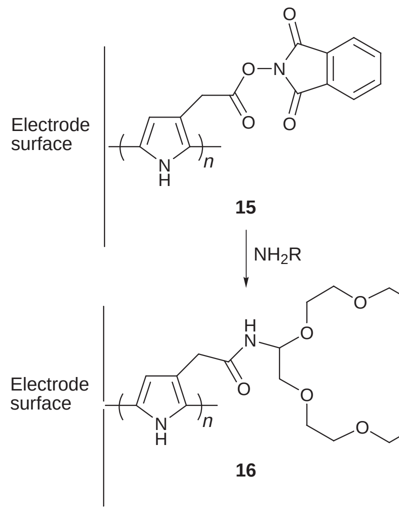


Fig. 5 (a) Voltammograms of films of polymer **14b** synthesised in acetonitrile $+0.5$ M Bu_4NClO_4 and analysed in acetonitrile $+0.7$ M Bu_4NClO_4 in the presence of increasing $NaClO_4$ concentration as shown; scan rate 20 mV s^{-1}, *vs.* SCE. (b) Shift of the oxidation peak potential with the concentration of $NaClO_4$. Reprinted from *Synth. Met.*, **67**, H. Kossi Youssoufi, A. Yassar, S. Baiteche, M. Hmyene and F. Garnier, 251, Copyright 1994, with permission from Elsevier Science.



electropolymerised copolymer of **15** and (pyrrol-3-yl)acetic acid was grafted by oligonucleotides containing 15 and 25 bases.[30] Incubation of the polymer with the attached oligonucleotide in a solution of a complementary oligonucleotide led to a positive shift of the PP oxidation potential. The detection limit using an electrode modified with a 15 base oligonucleotide was estimated on the level of 10^{-11} mol of 14 base target oligonucleotide in solution. An even larger positive shift was observed for a PP modified with a 25 base oligonucleotide whilst incubated in the solution of a complementary oligonucleotide.

This synthetic approach (structure type **III**) was used for the fabrication of conjugated polymers containing receptor moieties for other biologically important compounds. Thus, with the aim of recognition of a complementary base adenine, the polybithiophene derivative **17** functionalised with a uracil unit was synthesised.[27a] However, only a slight decrease in the electrochemical activity was observed upon addition of acetyl-9-octyladenine to the electropolymerised film of material **17**.

PP has been functionalised with various mono- and dipeptides for the voltammetric recognition of enzymes.[27b] PP modified with Gly-D-Phe **18** recognised carboxypeptidase A, which forms a stable enzyme-inhibitor complex at neutral pH: a positive shift of the oxidation potential by *ca.* 150 mV was observed on addition of the enzyme. Bound enzyme could be released into a blank solution by application of an anodic potential step.

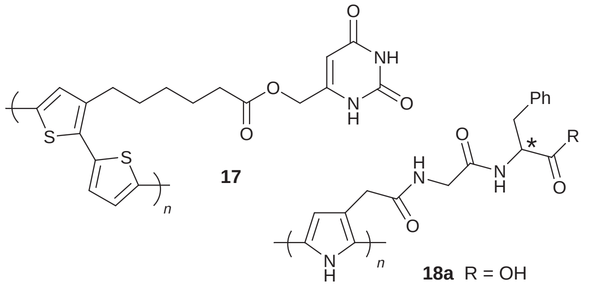
Recently, biocytin hydrazide was bound by acid–base complexation to a poly[2-(4-methyl-3-thienyloxy)ethanesulfonic acid] monolayer (attached also by acid–base complexation to an aminosilane-modified ITO). This modified electrode showed an anodic shift of 200 mV in response to the binding of biocytin with avidin from the solution.[27d] This result is explained by a planar-to-nonplanar transition of the PT backbone induced by interaction with the very large avidin molecule, in agreement with UV–vis spectroscopic data.

Chiral PT derivatives **19** and **20** were synthesised by electropolymerisation of the corresponding enantiomerically pure monomers.[27c,31] When chiral camphorsulfonic acids were used as electrolytes for CV, the doping level for the polymer **19a** with (+)-camphorsulfonic acid as electrolyte was 50% higher compared to cycling with (−)-camphorsulfonic acid. Similar results were obtained for polymer **20**.[31] The observed difference in the doping rate was assigned to enantioselective recognition.

Moutet *et al.* achieved improved enantioselective recognition of camphorsulfonic acids by using glucosyl-modified PP derivative **21**.[32] A remarkable feature of monomer **21** is that electropolymerisation occurs only in the presence of (−)-camphorsulfonic acid. Polymerisation was completely inhibited if the (+) enantiomer or a racemic mixture were used instead, suggesting that there are strong and selective interactions between monomer **21** and the (+) or (−) enantiomers of camphorsulfonic acid which may be responsible for the enantioselective recognition in the polymer.

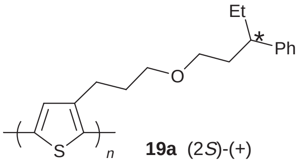
The same group[33] prepared the disubstituted ferrocene derivative **22** (structural type **IV**), polymerisation of which gave the conducting PP backbone required to form a film on the electrode surface. This idea stems from work of Beer *et al.*, who demonstrated a propensity for ferrocene bis-tertiary amides selectively to recognise Li^+ in solution.[34] An increased amount of Li^+ in the electrolyte solution during electropolymerisation of monomer **22** improved deposition efficiency, which may indicate amide complexation with Li^+. Neither Na^+ nor K^+ affected the electropolymerisation. However, addition of Li^+ to the electrolyte during potential cycling of an electropolymerised film of **22** did not affect the position of the Fc/Fc^+ peak potential.[33]

The bispyrrole derivative **23** [which contains a Ru(II) tris(bipyridine) complex as the redox centre, rather than the Fc group of **22**] was polymerised electrochemically to afford a PP derivative.[35] As observed previously by Beer *et al.* in solution studies,[36] the electrochemistry of the Ru complex in films of

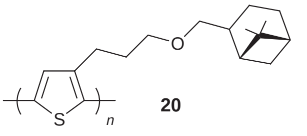


17

18a R = OH
b R = OMe



19a (2*S*)-(+)
b (2*R*)-(–)



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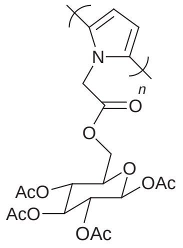
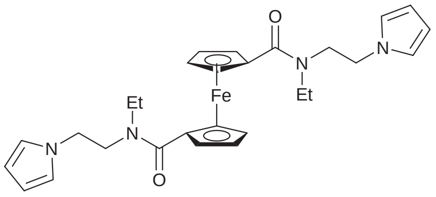


21 Ac = C(O)Me



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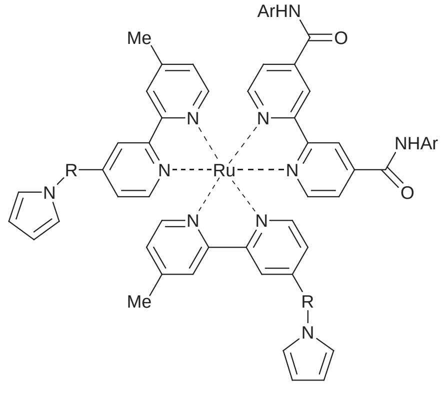


23 R = (CH$_2$)$_4$; Ar = 2,4-di-OMe-C$_6$H$_3$

polymer **23** is affected by the presence of Cl$^-$. Addition of Cl$^-$ (starting from sub mM concentration) shifted the formal potential for the first bipyridyl reduction wave in polymer **23** by up to 40 mV (Fig. 6). The binding with Cl$^-$ was completely reversible and selective (no response to Br$^-$ or I$^-$ was observed).[35] A marked change in the CV response (however, not completely reversible) was found in the presence of F$^-$; this has not yet been explained.[35]

The next development from Moutet *et al.*[37] was the realisation of the more complicated structural type **V**, where the Ru complex was attached to PP (similar to structure **23**) and then a calixarene[37a] or macrocyclic receptor[37b] was attached to one of the viologen ligands. PP ensured a communication with the electrode (overoxidation of PP led to a very poor response for the Ru couple). Four redox transitions (one oxidation and three reductions) were observed in the resulting films. Electrochemical recognition of alkali metal cations with potential shifts of up to 35 mV (for Li$^+$) was observed for compounds with N$_2$O$_4$ or NO$_5$ macrocycles.[37b]

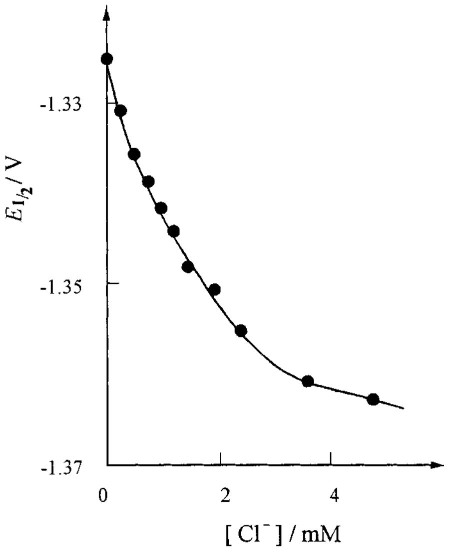


Fig. 6 Evolution of the half-wave potential, $E_{1/2}$, of the [Ru^{II}(L^1)$_2$(L^2)]$^{2+}$/[Ru^{II}(L^1)$_2$(L$^{2\bullet-}$)]$^+$ redox couple immobilized as poly(**23**) film on a Pt electrode (5 mm diameter) *vs.* Cl$^-$ concentration in acetonitrile–Bu$_4$NPF$_6$ 0.1 M; Γ_{Ru} = 1.5 × 10^{-8} mol cm^{-2}; *vs.* Ag/Ag$^+$ 10 mM in acetonitrile–Bu$_4$NPF$_6$ 0.1 M. [From ref. 35].

Ru bipyridyl complexes have also been immobilised onto an electrode surface using well-known reductive polymerisation of vinyl and alkynyl derivatives.[38] For some systems having benzo-15-crown-5 and azacrown ether substituents linked to the bipyridyl ligand, spectroscopic recognition (a shift of absorption and the fluorescence emission peak) in the presence of Na$^+$ and Mg^{2+} was observed.[38a,c] However, the results of electrochemical studies were disappointing.[38b] A variation of oxidation potentials in electrolytes with different cations was comparable with the shift of potential of the internal reference couple Fc/Fc$^+$ due to changes in the junction potential. This was explained by the large distance between the bound cation and the redox couple.[38b]

For structural type **VI** the signalling unit is the redox group (which might possess more clearly-defined electrochemical properties compared to the polymer) and this group is attached to a macrocyclic receptor unit. This type of structure was achieved recently in a synthesis of pyrrole derivative **24**.[39] A modified electrode obtained by electropolymerisation of monomer **24** demonstrated a good symmetrical surface wave response of the Fc/Fc$^+$ couple in acetonitrile. Upon the addition of Ba^{2+} cations (at a concentration as low as 10^{-6} M) a new wave positively shifted by 120 mV developed at the expense of the original wave (Fig. 7). The formation of a 1:1 complex of **24** and Ba^{2+} was confirmed by UV–vis spectroscopy and mass spectrometry for the monomer in solution. The electrode was also responsive to Ca^{2+} although the sensitivity was ten-fold lower. Micromolar concentrations of these cations can be analysed by this type of sensor. The polymer films released the cations into the blank solution upon application of an oxidation potential.

Quite recently a new type of structure, *e.g.* compound **25**, has been developed.[40] A salophen group, with a strongly-chelated metal, is adjacent to the thiophene unit, and an oligo(oxyethylene) region is present for metal binding. The materials were made by template synthesis in the presence of Ba^{2+}, with subsequent template ion removal by guanidine sulfate and electropolymerisation. Alkali and alkali earth metal ions when added to a 0.05–0.1 M solution of Bu$_4$NClO$_4$ as

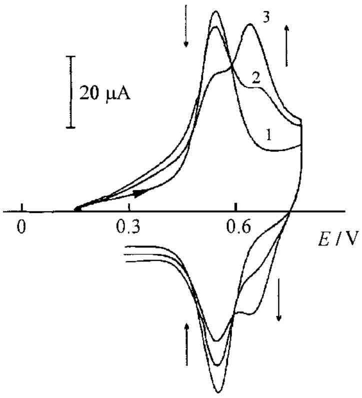
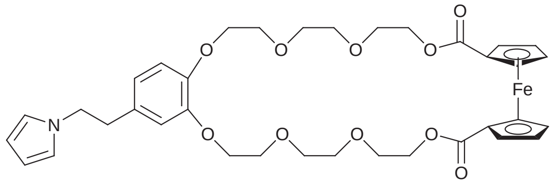


Fig. 7 Voltammograms of a Pt/poly(**24**) modified electrode (5 mm diameter) in acetonitrile +0.1 M Bu_4NPF_6; *vs.* Ag/Ag^+ 0.1 M $AgNO_3$+0.1 M Bu_4NPF_6+acetonitrile; scan rate 0.1 V s^{-1}; $[Ba^{2+}]$= 0 (1), 10^{-6} M (2), 2×10^{-6} M (3). Reprinted with permission from A. Ion, I. Ion, A. Popescu, M. Ungureanu, J.-C. Moutet and E. Saint-Aman, *Adv. Mater.*, 1997, **9**, 711. Copyright 1997 Wiley-VCH.



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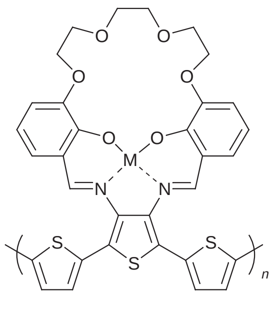


25 M = Ni, Cu

the electrolyte caused a 25–145 mV shift of the redox potential of polymer **25** in the order $Li^+ < Na^+ < Mg^{2+} < Ba^{2+}$. Also, the addition of monocations led to sharpening of the redox peaks indicating enhanced ion mobility. Alkali metals could be reversibly exchanged, while alkali earth ions complexed irreversibly and could be removed only chemically (guanidine sulfate). If electrochemical cycling was performed in the presence of a non-complexing electrolyte (Bu_4NClO_4) diffusion limited behaviour was observed. On the other hand, alkali metal cation electrolytes led to a surface electrochemical reaction. Films of **25** were also able to detect neutral electron donor molecules that were able to bind as additional ligands to the metal salophen site. Thus addition of 5 nM of pyridine to Li^+ containing electrolyte solution resulted in the complete loss of electroactivity.

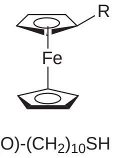
PP and its derivatives have been employed as sensors for halogenated solvents.[41] Films demonstrated a shift of the oxidation peak potential of up to 400 mV in response to dichloromethane and other small chlorinated hydrocarbons (saturated solutions of organics in aqueous electrolytes were used). This was explained by the higher partition of dichloromethane into the reduced polymers compared to the oxidised polymers. Consequently, upon oxidation extra energy was required to expel dichloromethane and provide room for the electrolyte anion. Amperometric sensors with detection of CH_2Cl_2 in a range between 10 nl ml^{-1} and 1 mg ml^{-1} in water were constructed.[41a–c] The method allows simple direct on-site detection in aqueous solutions. Wallace and co-workers have developed amperometric sensors for haloacetic acids based on PP electropolymerised onto microelectrodes with a detection limit of 1 ng ml^{-1} for chloroacetic acid.[41d]

2.2 Molecular recognition by monolayers

The combination of molecular recognition processes and the two-dimensional structural order of monomolecular layers formed by Langmuir–Blodgett (LB) or self assembly (SA) techniques offers a very powerful route to the development of nanoscale sensing devices. Thin monolayers can facilitate controlled access of an analyte species to the receptor sites, compared, for example to relatively thick cast or electropolymerised films of conjugated polymers, discussed in the previous section. SAMs offer several attractive features: they are generally straightforward to prepare; they possess good stability due to their covalent attachment to the electrode surface; and several different functional groups can be incorporated into SAM structures yielding tailor-made surfaces. Comprehensive electrochemical studies of SAMs have attracted great attention in recent years,[42] and prospects for the design of an interface for analytical chemistry by SA or LB techniques have recently been discussed.[43]

The importance of ferrocene (Fc) derivatives in supramolecular chemistry is widely recognised,[44] and their extensive use for electrochemical recognition in solution has been reviewed by Beer.[3] It is not surprising, therefore, that Fc has proved to be a popular building block for construction of redox-active monolayers by SA or LB techniques.[22,42a,45,46] For example, amphiphilic Fc thiol derivative **26a** was immobilised on the surface of a gold electrode together with a shorter chain unsubstituted thiol to create Fc sites protruding from the compact thiol monolayer.[46a] It was known from earlier work that sulfonated calix[6]arene is an excellent host for Fc in aqueous solution.[47] However, exposure of the mixed Fc SAM to a solution of the calixarene derivative did not affect the Fc redox potential.[46a] It was suggested that the calixarene is strongly solvated in aqueous media, and the water molecules prevent complexation with the relatively hydrophobic Fc. However, an amphiphilic derivative of the same sulfonated calixarene had a profound effect even in 0.4 mM concentration (90 mV positive shift, Fig. 8).

Similarly, immobilisation of the thiol **26b** and decanethiol was employed for binding of cyclodextrin in aqueous solution.[46b] Only β-cyclodextrin had some effect on the electrochemistry of the immobilised ferrocene. Addition of host to the solution led to a decrease of the peak current, a slight decrease of peak separation, and an increase of the standard electron transfer rate constant, but there was no change of the formal potential. These results were explained by only free ferrocene being redox-active and the reaction proceeding through a chemical step/electrochemical step scheme. Binding constants for the guest immobilised on the surface and the host in solution were determined using electroactive coverage values similar to the results discussed above.[46a] Figures in the range of $1.4–3.6\times10^{-4}$ and $0.9–3.2\times10^{-4}$ M^{-1} were found



26a R = $C(O)\text{-}(CH_2)_{10}SH$
b R = $C(O)\text{-}O\text{-}(CH_2)_{11}SH$
c R = $CH_2NMe_2^+(CH_2)_7C(O)NH(CH_2)_2SH$
(as the disulfide for **c**)
d R = $(CH_2)_6S(CH_2)_7CO_2H$

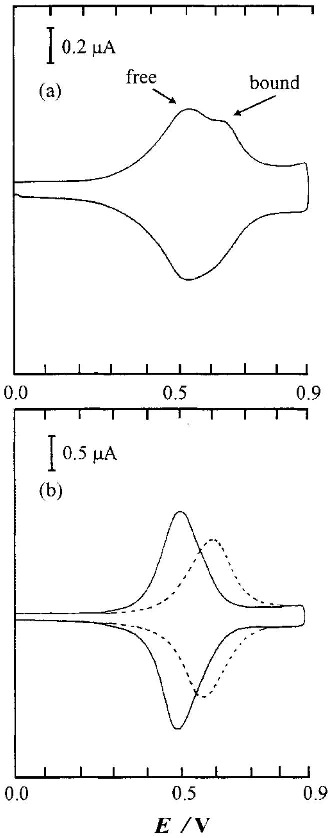


Fig. 8 (a) Voltammetric response of a mixed monolayer prepared by coassembly of **26a** and decyl thiol on a gold electrode in the presence of sulfonated calixarene (0.4 μM) in the contacting solution. (b) Comparison of the voltammograms obtained in the absence (continuous line) and in the presence (dashed line) of sulfonated calixarene (2 μM) in the contacting solution: in 0.1 M $HClO_4$, *vs.* SSCE, scan rate 0.5 V s^{-1}. Reprinted with permission from L. Zhang, L. A. Godinez, T. Lu, G. W. Gokel and A. E. Kaifer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 235. Copyright 1995 Wiley-VCH.

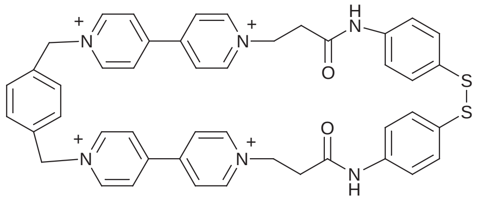
for different surface concentrations for ferrocene and ferricinium ions, respectively.

A similar strategy was recently employed for a related disulfide **26c**; this derivative contains an additional hydrophilic ammonium cation in the chain.[46c] Using shorter-chain nonanethiol for coassembly on Au enabled both the Fc head group and the ammonium cation to protrude into the solution. The coassembled monolayer bound both β- and γ-cyclodextrins to form stable host–guest complexes. The hosts are believed to interact with the SAM in two ways: by inclusion of the Fc moiety within the cyclodextrin cavity, and by interactions between the ammonium counterions (Br^-, PF_6^-, ClO_4^-) and the hydrophilic regions of the cyclodextrin. The interaction was monitored by a decrease in the voltammetric oxidation current for the surface-bound Fc centres after exposure to dilute solutions (10 μM) of the host, resulting from restricted access to the Fc of the charge-compensation anions. Only a small positive shift (15–20 mV) in the formal potential of the free (uncomplexed) Fc was observed: this was explained on the basis of a balance of the different host–guest interactions in the system.

Very recently it has been reported that the electrochemical response of monolayers of sulfide **26d** is strongly influenced by the pH of the electrolyte solution: the ferrocene unit senses the protonation and deprotonation of the carboxylate group. With increasing pH values the carboxylates stabilise the Fc^+ state of the redox couple and as a consequence a negative shift of the redox potential is observed. Preliminary studies on cation binding (Et_4N^+, Na^+, K^+) were also noted.[46d]

Viologen is another popular redox moiety, and the amphiphilic derivative **9c** forms compact monolayers on a Au surface.[48] Addition of an extremely low concentration of an amphiphilic calixarenesulfonic acid (1–5 μM) resulted in a negative shift of the first reduction potential of **9c** by 120 mV.[49]

Receptors of the paraquat type can be bound to an electrode surface by SA of the disulfide derivative, *e.g.* compound **27**.[50] Admixture with unsubstituted thiols gave monolayers with receptor sites protruding from the hydrophobic layer which can recognise practically-useful guests, such as indole and catechol, in concentrations of 10^{-5} M in aqueous solutions (discriminating other aromatics, such as benzonitrile or nitrobenzene). The paraquat reduction potential is monitored (Fig. 9).



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Electroactive tetrathiafulvalene (TTF) units have recently been incorporated by Becher *et al.* into macrocyclic structures which function as metal cation sensors in organic media.[51] Although the voltammetric response upon metal binding in these systems is usually quite small (< 100 mV), an advantage of the TTF moiety is that only the first oxidation potential (*i.e.* the $TTF^0/TTF^{\bullet +}$ wave) is affected, and the second (unchanged) oxidation potential ($TTF^{\bullet +}/TTF^{2+}$) serves as an internal reference (both TTF redox steps occur in a convenient potential window). We combined this property with the known ability of TTF derivatives possessing a terminal thiol group to form redox-active SAMs,[52] and created thin layer sensor devices based on molecular recognition using TTF-crown derivatives **28**.[53] Electrochemical recognition of Na^+, Ba^{2+} and Ag^+, with the largest response for Ag^+ (positive potential shift of 60–85 mV of the first TTF oxidation

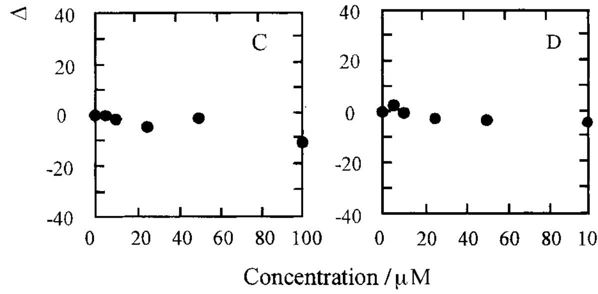


Fig. 9 Observed shifts in the formal potential for the mono-electronic reduction of the surface-confined paraquat groups of Au/**27** + decyl thiol electrodes immersed in 0.1 M phosphate buffer solutions (pH = 7), also containing variable concentrations of (A) indole, (B) catechol, (C) benzonitrile, and (D) nitrobenzene. For comparison purposes, graph A (open circles) also shows similar data obtained with a Au/(thiolated paraquat) + decyl thiol electrode. Reprinted with permission from M. T. Rojas and A. E. Kaifer, *J. Am. Chem. Soc.*, 1995, **117**, 5883. Copyright 1995 American Chemical Society.

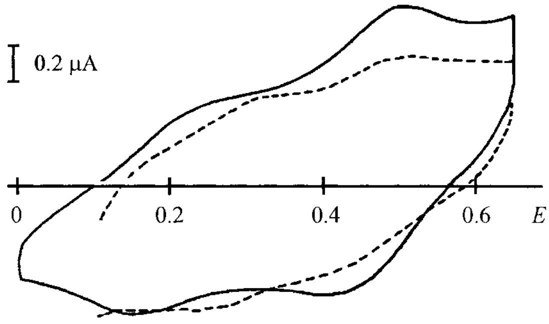
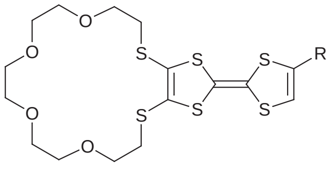


Fig. 10 Change of CV response for a SAM of compound **28b** on a 1.6 mm diameter Pt electrode, in 0.2 M $LiClO_4$–acetonitrile, potentials *vs.* Ag/Ag^+. Scan rate 200 mV s^{-1}; dashed line represents the CV on the same monolayer after addition of $AgClO_4$ give an 0.085 M solution. Reprinted with permission from A. J. Moore, L. M. Goldenberg, M. R. Bryce, M. C. Petty, A. P. Monkman, C. Morenco, J. Yarwood, M. J. Joyce and S. N. Port, *Adv. Mater.*, 1998, **10**, 395. Copyright 1998 Wiley-VCH.



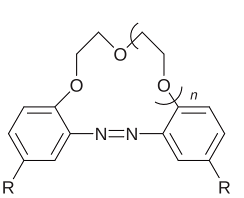
28a R = $C(O)\text{-}O\text{-}(CH_2)_6SH$
b R = $C(O)\text{-}O\text{-}(CH_2)_{12}SH$
c R = CH_2SH

potential) was observed for solutions of these compounds in acetonitrile, and for SAMs. Fig. 10 shows the electrochemical response of a SAM of **28b** to Ag^+ ions.

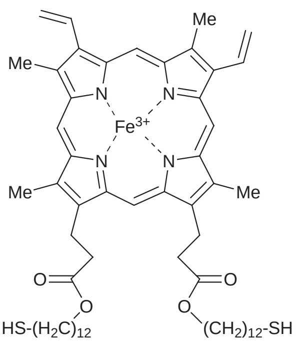
Molecular recognition properties were investigated for crown ether derivatives **29a** and **29b** bearing azo groups within the macrocycle structure.[54] Monolayers of compound **29a** were assembled on Au or thin layer Hg electrodes using the LB technique. The CV response of the LB film on a gold electrode was unstable, but the thin layer Hg electrode modified by the LB monolayer showed a very stable surface wave response. An increased peak separation was observed when Li^+ cations in the electrolyte solution (peak separation 20 mV) were substituted by Na^+ or K^+ cations (80 and 400 mV, respectively). This was attributed to molecular recognition in the LB monolayer due to complexation with the crown ether.[54a] At the same time the formal potential did not change significantly.

For LB monolayers of compound **29b**, we observed that the CV response in different electrolytes showed a linear dependence of the peak current on the scan rate.[54b] However, a deviation from linearity was observed at higher scan rates, indicating diffusion limitation. The greatest deviation was noted with Na^+ (the current saturated at lower scan rates) and the smallest with K^+: this effect was ascribed to the complexation of Na^+ with **29b**. The largest difference in reduction potential was observed between Li^+- and Na^+-containing electrolytes, which may also be related to complexation with Na^+. The dependence of the CV response in 0.1 M $LiClO_4$ upon the addition of $NaClO_4$ revealed a negative shift of the reduction peak, which is opposite to the expected response for complexation with Na^+. The shift of the reduction potential was approximately linear to Na^+ concentration in the range 0.01–0.07 M. We do not have any explanation for this behaviour.[54b]

The electrochemistry of SAMs of the Fe porphyrin derivative **30** has provided some indications of binding with apomyoglobin.[55] Incubation of a SAM of **30** in a solution of apomyoglobin resulted in an increase in peak separation in the CV response. It was also found that interaction of apomyoglobin with a SAM containing a higher proportion of the Fe porphyrin prevented intermolecular cross-linking between porphyrin moieties (manifested by an additional peak in the CV).



29a $n = 2$, R = $C_{12}H_{25}$
b $n = 1$, R = $C(Me)_2CH_2C(Me)_3$



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3. Recognition of redox active guests by redox inactive films

3.1 Organic and organometallic guests

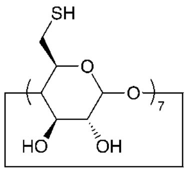
It has been demonstrated that electrodes modified by cast films of phosphatidylcholine can be irreversibly loaded with amphiphilic viologens and ferrocenes, whereas shorter chain analogues were not bound by the film.[56] In this way the electrode can clearly distinguish between methylviologen **9a** (for which the electrochemical response is almost completely suppressed) and analogue **9c**. These electrodes generally exhibit very low voltammetric currents for hydrophilic redox couples like $Fe(CN)_6^{4-}$ and $Ru(NH_3)_6^{3+}$. Reduced forms of amphiphilic viologens usually precipitate onto the electrode surface which complicates the CV response; however, binding into the phosphatidylcholine layer creates a matrix, where electrochemistry of the viologen is free from complications.

The thiolated β-cyclodextrin **31** was chemisorbed onto a Au surface.[57] Upon surface attachment, the wider opening of the cyclodextrin ring would be oriented into the solution. This material formed rather poor SA submonolayers which had to be cured with post-adsorption of pentylthiol. To avoid the sealing of the cyclodextrin cavity by pentylthiol, co-adsorption was performed in the presence of ferrocene, which was bound within the cyclodextrin cavity. After the removal of Fc, the monolayer was ready for complexation experiments. A clear surface-confined voltammetric response was observed with these electrodes at a Fc concentration in water as low as 5 mM (binding constant 3.9×10^4 M^{-1}). Fc could be replaced in the binding sites by *m*-toluic acid, which binds more strongly to the β-cyclodextrin. Porter and co-workers[58] pioneered this work by constructing SAMs of heptakis(6-dodecylthio-6-deoxy)-β-cyclodextrin which were able to discriminate the electrochemical response of Fc-carboxylic acid against ferricyanide and $Ru(NH_3)_6^{3+}$.

Another way of using the binding ability of cyclodextrins was suggested by Lepetre *et al.* who synthesised the pyrrole substituted cyclodextrin **32** (structure type **V**).[59] The functionalised PP obtained by electropolymerisation of **32** was then over-oxidised electrochemically to destroy the electroactivity of the PP backbone which can mask a response of the redox-active guest. The CV responses for binding of phenothiazine and Fc from 50 mM solutions of polymer **32** were then observed. Only Fc retained electroactivity in aqueous electrolyte after the electrode was rinsed with acetonitrile.

Assembly of the fullerene derivative **33** onto an electrode surface was achieved using another method, namely, through binding within the crown ether cavity of the guest ammonium group of a SAM formed by the adsorption of cystamine [from the disulfide $(NH_3^+CH_2CH_2S)_2$] onto gold.[60] The electrochemical response in a 0.13 M solution of compound **33** was low and could be registered only by the more sensitive technique of square wave voltammetry which showed that the binding of **33** was fully reversible and compact C_{60} monolayers were formed.[60] Only the first C_{60} reduction wave was monitored (-0.64 V *vs.* Ag/AgCl) to avoid desorption of the thiolated monolayer which occurred at more negative potentials.

SAMs of thiolated poly(ethylene glycol) on gold form inclusion complexes with α-cyclodextrin, and this rigid complex acts as a barrier prohibiting electrochemical oxidation of the protein cytochrome *c*.[61] The redox wave of cytochrome *c* was fully recovered when the modified electrode was placed in a solution of cytochrome *c* not containing α-cyclodextrin. β-Cyclodextrin, which does not form a crystalline inclusion complex with poly(ethylene glycols) caused little decrease in the redox currents.



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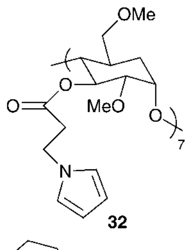

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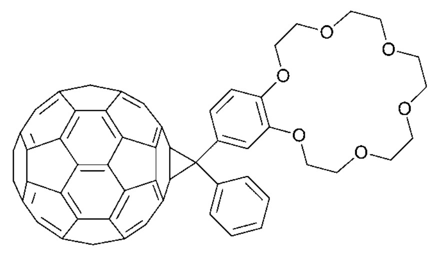

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Binding properties of SAMs have been suggested to offer practical analytical applications.[62] A separation-free sandwich-type enzyme immunoassay for protein is based on a diagram presented in Fig. 11. In this system, the analyte protein in solution, which is introduced from one side of the membrane, is bound to an antibody conjugate, and then, in turn, this complex binds to an enzyme-labelled antibody confined to a gold surface by thiol groups. When a substrate (*e.g.* 4-aminophenyl phosphate) is added from the other side of the membrane, it penetrates into the membrane, and through an enzymatic reaction on the bound complexes, a product (*e.g.* aminophenol) is generated, the formation of which is registered amperometrically by applying to the membrane a potential of 0.19 V *vs.* Ag/AgCl, which oxidises aminophenol, but not aminophenylphosphate. The device was demonstrated to function effectively in human blood with a protein detection limit of 2.5 units l^{-1}.[62]

Bidan and Niel incorporated commercially available calixarenesulfonic acid into a PP matrix during electropolymerisation (structure type **VII**).[63] The calixarene cavities in these films were able to bind $FcCH_2NMe_3^+$ cations from solution, which led to a *ca.* 100 mV negative shift for the potential of the Fc couple.[63] PP was also obtained with heptasulfonated β-cyclodextrin as the dopant anion[64] and this system bound *N*-methylphenothiazine (NMP, as a model, for drug release).[64a] Release of the encapsulated compound could be triggered by electrochemical oxidation of the system. Initially the PP backbone would be oxidised, followed by oxidation of NMP to $NMP^{\bullet+}$ which is consequently expelled due to Coulombic repulsion. This process resulted in a substantial (*ca.* 300 mV) negative shift of the PP electrochemical potential. No spectroscopic study was reported which could shed light on the conformational changes which accompany this process.

Similarly, sulfonated β-cyclodextrin was incorporated into polyaniline.[65] The complexation of the guest molecule 4-nitrophenol by this material was confirmed by spectroelectrochemistry. In the same way, different sulfonated dyes were incorporated into PP.[66] These electrodes were used for the amperometric detection of protein in a flow injection system at the potentials of PP overoxidation. A detection limit of up to 2 nM and sensitivities of up to 20 nA μM^{-1} using a pulsed potential waveform were achieved. The mechanism was ascribed to binding of proteins with dye molecules in the polymer films.

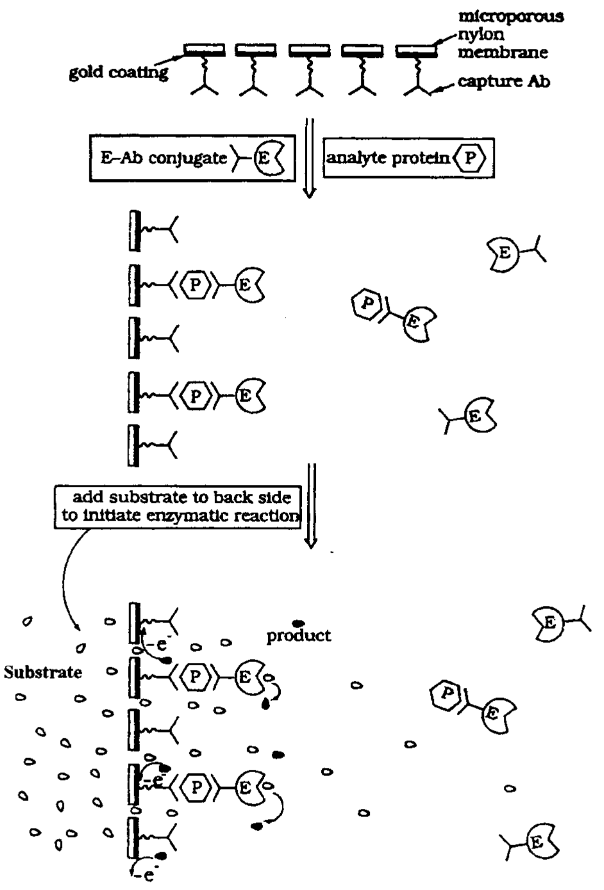


Fig. 11 Principle and sequence of steps for the proposed separation-free electrochemical sandwich enzyme immunoassay. Reprinted with permission from C. Duan and M. E. Meyerhoff, *Anal. Chem.*, 1994, **66**, 1369. Copyright 1994 American Chemical Society.

A more sophisticated mechanism was employed to fabricate a gene sensor (Fig. 12).[67] A gold electrode was modified by chemisorbed oligodeoxynucleotide, with Fc modified oligodeoxynucleotide **34** serving as a surface-confined redox marker. When the target DNA complexed with both the oligodeoxynucleotide on the electrode surface and with molecule **34**, this lead to the attachment of Fc to the electrode, and an electrochemical response of the Fc group was observed, the oxidation current reflecting the concentration of the target. In the case of mismatch between the target DNA and bound oligodeoxynucleotide, the Fc response was considerably smaller.

Using SAMs on gold of the poly(L-glutamic acid) derivative **35** in helical form (average degree of polymerisation, $n=24$) it was possible to conduct enantioselective electrochemical recognition of (D)-ferrocenylglutamic acid [Fc-Glu(D)].[68] The peak current varied linearly with scan rate indicating that Fc-Glu(D) was surface-confined to the monolayer of **35**, and not diffusing to the electrode. Only this enantiomer could be immobilised on the SAM with subsequent CV detection.

3.2 Metal ion analysis

Binding of reducible metals by redox inactive layers on an electrode surface leads to the possibility for voltammetric

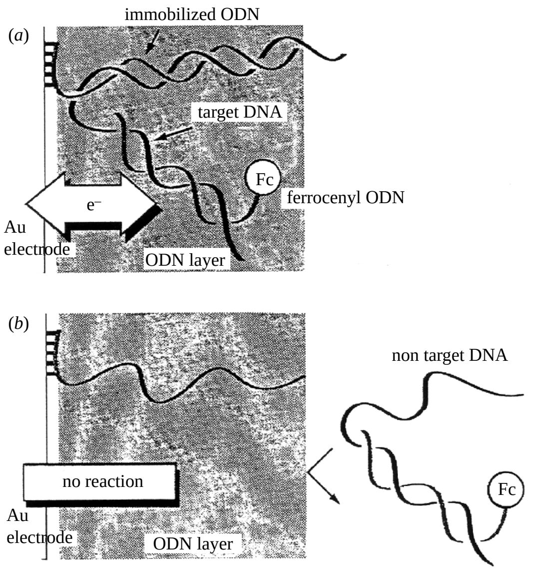
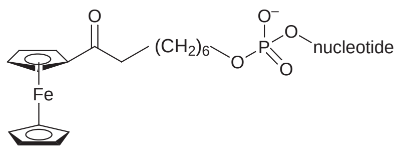


Fig. 12 Schematic representation of the electrochemical gene sensing system based on the formation of a complementary complex. (*a*) Target DNA combines the ferrocenyl oligodeoxynucleotide (ODN) with the ODN on the electrode. (*b*) Non-target DNA does not concentrate the Fc units onto the electrode. [From ref. 67].



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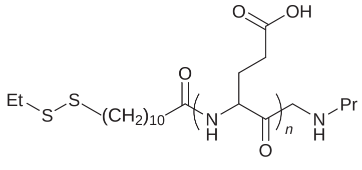

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determination of accumulated metal by reduction and then reoxidation (stripping). This forms the basis of accumulation stripping voltammetry and the preparation and use of chemically modified electrodes for this purpose has been reviewed.[69,70] SAMs are also of interest in this context.[43b] We will discuss briefly the use of these films for accumulation determination of metal ions.

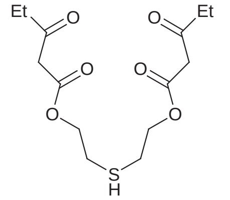
Probably the first example of an organised monolayer that selectively binds redox-active metal ions was described by Rubinstein and co-workers who used mixed monolayers consisting of SA tetradedant ligand receptor molecule **36** and passivating molecules (either SA octadecyl thiol or octadecyltrichlorosilane or electropolymerised 1-naphthol).[71] The resulting monolayer selectively formed a 1 : 1 complex with Cu^{2+}on the surface of the electrode. The selectivity of binding in the monolayer ($Zn^{2+} > Cu^{2+} \approx Cd^{2+} > Pb^{2+} >> VO^{2+}$, no binding of Fe^{3+}) was very different from the binding in solution for the same ligand ($Fe^{3+} > VO^{2+} > Cu^{2+} > Zn^{2+} > Cd^{2+} \approx Pb^{2+}$). This difference was attributed to the stereochemical constraints imposed by the monolayer matrix (geometry and size of cavity).[71e] Analytical determination of Cu^{2+}in a concentration range 10^{-7}–10^{-3} M, even in the presence of a very large excess of Fe^{3+}, was demonstrated by using CV and the Cu/Cu^{2+} stripping peak current as an analytical signal.[71d]

Turyan and Mandler demonstrated the successful application of SAMs of $HS(CH_2)_nCOOH$ ($n = 1$, 2, 5, 10) on thin film mercury or gold electrodes in the determination of Cd^{2+} with a detection limit of 4×10^{-12} M.[72] The high sensitivity was explained by the extremely high binding constants for the formation of bidendant complexes between Cd^{2+} and 2-mercaptoacetic acid in solution.[73] SAMs of pyridinium derivative **37** were used for the determination of Cr(VI) with a detection limit as low as 2×10^{-11} M.[74] In both cases, analysis was accomplished by square wave stripping voltammetry.

An example of the application of the LB technique to similar sensors was recently reported: Ag^+ accumulated by the LB film of amphiphilic crown ether copolymer **38** was analysed by stripping voltammetry in a blank solution.[75]

In this context, PP is the most widely used conjugated polymer.[76] As noted by Teasdale and Wallace,[76e] molecular recognition sites can be introduced into conducting polymers (PP is a typical example) in the following ways: (1) as a counter ion; (2) as an additive during polymerisation; (3) synthetically *via* covalent grafting onto preformed polymer; (4) by chemical modification of the monomer; and (5) by ion exchange. Thus, using approach (1) PP was modified during electropolymerisation with pyridine-2,6-dicarboxylic acid and EDTA;[76b] with a number of sulfonic and carboxylic acids;[76g] phenanthroline dye derivatives, sulfosalicylic acid and alizarin red S.[77] These electrodes were able to accumulate Ag^+ with subsequent analysis by stripping.[76b] PP microelectrodes modified with Tyron were used for amperometric flow injection analysis of Al^{3+} with the detection limit of 2 ppb for the best systems.[76g] Similar electrodes were used for the analysis of Cu^+ and Cu^{2+}, using the signal of the square-wave peak of the Cu^{2+}/Cu^+ redox step.[77]

Using approach (4), pyrrole was *N*-substituted with a dithiocarboxylate group to give monomer **39**.[76a,d] The resulting electrode, modified by electropolymerisation of this monomer, was suitable for an open circuit accumulation stripping voltammetric determination of Cu^{2+}. The same type of electrode could also accumulate Hg^{2+} through complexation with the anionic group[76c] with a detection limit of 0.2 mg l^{-1}. The dithiocarboxylate group was also introduced into PP by ion exchange (approach 5) in a solution of sodium diethyldithiocarbamate[78] and a detection limit for Cu^{2+} of 1 ppm was estimated for the resulting modified electrode.



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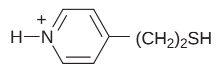

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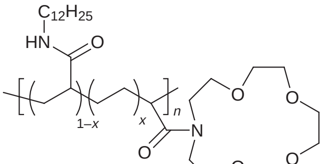

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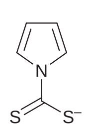

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An approach involving the incorporation of specific metal ion binding sites into entwined conjugated polymers and interlocked structures has been developed with a view to analytical applications.[79,80] A three-dimensional templating effect of the metal centre leads to entwining of the two chelating ligands (both based on the 2,9-diphenyl-1,10-phenanthroline, dpp, core) in solution to form the pre-assembled monomer **40** prior to electropolymerisation of the terminal pyrrole units to form the network system **41**. The resulting polymer can be easily demetallated, without disruption of its structure, by reaction with cyanide ion (for $M = Cu^+$) or

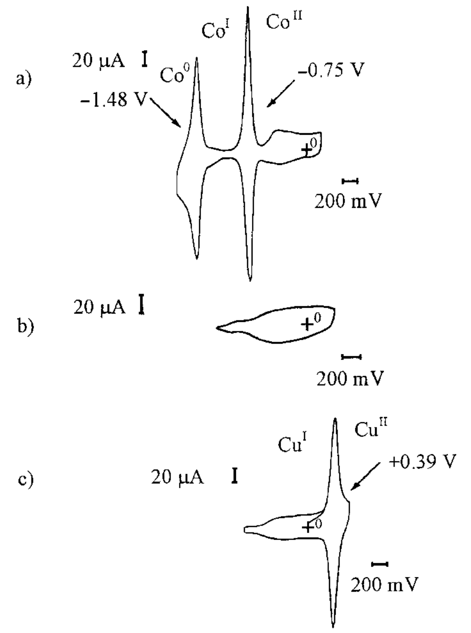
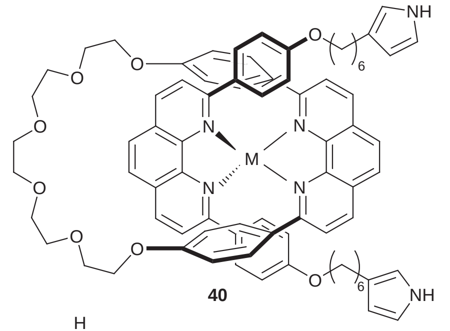


Fig. 13 (a) CV of poly-Co**40**$^{2+}$ film, *i.e.* network **41**, deposited on a carbon felt electrode, scan rate 5 mV s^{-1}. (b) CV of the film used in (a) obtained after dipping for 10 min in a 0.1 M KSCN–MeCN solution. (c) CV of the film used in (b) after dipping (2 h) in a 0.1 M Cu(MeCN)$_4$BF$_4$–MeCN solution. All potentials are *vs.* Ag/Ag$^+$. Reprinted from J. M. Kern, J. P. Sauvage, G. Bidan, M. Billon and B. Divisia-Blohorn, *Adv. Mater.*, 1996, **8**, 580. Copyright 1996 Wiley-VCH.

thiocyanide ion (for M = Zn$^+$ and Co^{2+}). The electroactivity of PP itself is retained. If these monomer units were polymerised without a metal templating effect, the resulting polymers were not able to bind metal ions from the solution.[79b] Previously, Devynck *et al.*[81] demonstrated reversible binding and release of Ni^{2+} by poly(pyrrole–2,2′-bipyridine) in DMSO solution. However, Ni^{2+} was electrochemically stable in this film for only 40 CV cycles. Metal exchange is also possible in this family of materials. Fig. 13 shows the CV response for a film of a Co^{2+} polyrotaxane of type **41** after demetallation and subsequent re-metallation by Cu$^+$. Fig. 13a shows superimposition of the two reduction steps of Co^{2+} and the PP electroactivity. After demetallation only PP activity remains (Fig. 13b). Addition of Co^{2+} to the solution regenerated Fig. 13a; addition of Cu(MeCN)$_4$BF$_4$ gave the CV shown in Fig. 13c. The reversible signal at +0.39 V is characteristic of the Cu(dpp)$_2$$^{+/2+}$ moiety, with PP redox activity also observable. Coulometric measurements showed that this incorporation of Cu$^+$ species into the coordination sites in **41** was nearly quantitative.[79c]

For polythiophene derived polyrotaxanes, Cu$^+$ remetallation was possible only if Li$^+$ ions were present during the demetallation process. In the absence of Li$^+$ the polyrotaxane scaffolding collapsed, the polythiophene peaks in the CV lost their resolution, and Cu$^+$ could not be inserted again. The molecular recognition effect was manifested by a 140 mV positive shift of the polythiophene oxidation peaks upon uptake of Cu$^+$ ions.[79e]

Swager and co-workers[80] used a similar approach with phenanthroline–2,2′-bipyridine ligands in an oligothiophene chain. Demetallation was achieved with a base (ethylenediamine), this process being accompanied by a hypsochromic shift in the UV–vis absorption spectra, and re-metallation could then be achieved. The CV of polyrotaxane **42** showed well-defined redox waves whereas for the demetallated polymer the corresponding waves were unresolved. The sharpening of the redox peaks is consistent with localisation of the redox process.



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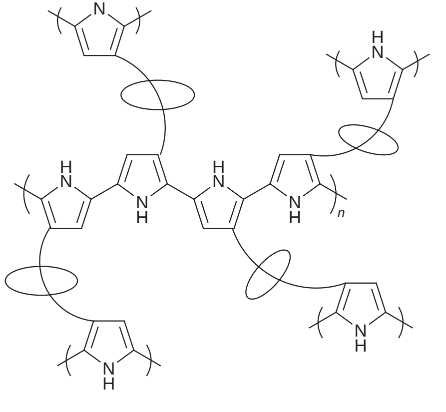
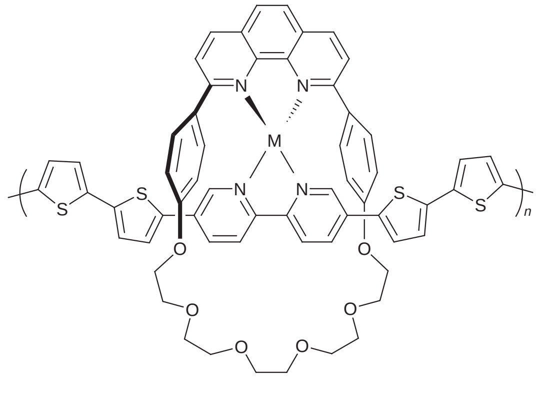


41 (The coordinating macrocycles are mechanically trapped into the PP network)



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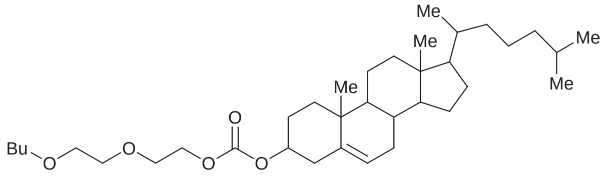
3.3 Incorporation of the recognition sites into monolayers

Another attractive approach is the deliberate creation of defects ('molecular gates') in otherwise passivating monolayers. These gates are designed to recognise solution redox species according to their size, shape and/or chemical nature. The idea, originally suggested by Sagiv,[82] involves the immobilisation of a two-component monolayer, one component of which (the template) is then removed by solvent to create molecularly sized pin-holes in the monolayer.

Thus, Yamamura and co-workers[83] reported molecular recognition by an octadecylsilyl monolayer modified by template molecules. SAMs were supported on a SnO$_2$ electrode in the presence of the following template guests: *n*-hexadecane and compounds **43** and **44**, which were removed by washing to leave defect sites in the SAM.[83a] These sites selectively bind guests whose size, space and hydrophobicity match that of the binding site. For example, the sites created by *n*-hexadecane bind hydrophobic long-chain guest molecules such as vitamin K$_1$ and K$_2$, but they do not bind short-chain vitamin K$_3$. A dependence of the cathodic peak current for the reduction of bound vitamin K$_1$ (Fig. 14) offers the possibility of analysing vitamin K$_1$ in micromolar concentrations in solution.[83a] Cholesterol was also recognised by the electrode modified with template hexadecane and compound **43**. Cholesterol inhibits the binding of vitamin K_1, but cholesterol was not recognised by the electrode made with template **44**.[83b]



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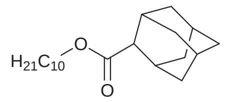

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A different approach has been employed by Crooks and co-workers,[84] who used aromatic thiols, instead of soluble template molecules, to create recognition sites in the alkyl thiol blocking monolayer, with the size, number, and chemical nature of defect sites determining the type of electrochemical response for solution redox species. The response for the same template molecule and the same solution redox probe, changes from electron tunnelling through the blocking monolayer behaviour, to radial diffusion behaviour and then to linear diffusion behaviour, depending on the concentration of defect sites. Recognition properties can also be tuned by the choice of template, *e.g.* 4-hydroxythiophenol or 4-thiocresol, with the latter creating more blocking 'molecular gates' towards $Ru(NH_3)_6^{3+}$.[84a] Solution redox guests of different physical and chemical characteristics (size, ionic charge, molecular structure and heterogeneous electron transfer rate constant) such as $Mo(CN)_8^{4-}$, $Fe(CN)_6^{4-}$, $Fe(bpy)(CN)_4^{2-}$, $Fe(bpy)_2(CN)_2^0$, $Ru(NH_3)_6^{3+}$, and cytochrome *c* were employed.[84c] The electrochemical response of different probe molecules on the same electrode containing recognition sites preformed by 4-hydroxythiophenol is shown in Fig. 15.[84c] The CV response for the fast redox couple $Ru(NH_3)_6^{3+}$ (Fig. 15a) corresponds to radial diffusion to individually addressed microelectrodes. This means that this fast redox probe is able to access only small widely-spaced defect sites. The other couples showed radial diffusion behaviour. The higher the charge, the lower the penetration through the monolayer, leading to a smaller current. Only neutral $Fe(bpy)_2(CN)_2^0$ could penetrate. At the same electrode, for the kinetically-slower redox couple $Fe(bpy)_2(CN)_2^0$ (Fig. 15e) the response characteristic of linear diffusion was observed. This means that this redox probe is able to access more closely packed defect sites with their diffussion layers overlapping. This signifies that, in spite of slower kinetics, the latter redox couple can access more defect sites or penetrate to smaller distances from the electrode surface, and that electron transfer kinetics are not a dominant factor. It was suggested[84b] that ionic charge is responsible for the discrimination between the redox species [the hydrated radius of $Fe(bpy)_2(CN)_2^0$, is smaller than $Ru(NH_3)_6^{3+}$] and, in general, the value of the Faradaic current decreases with an increase of ionic charge.

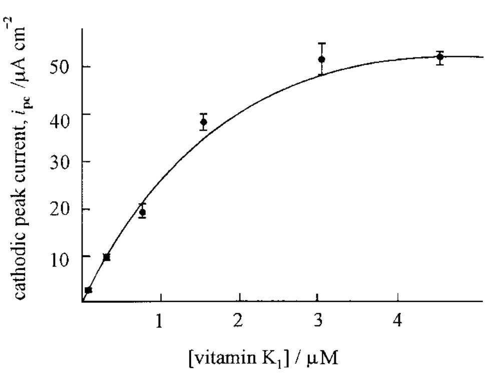


Fig. 14 Saturation behaviour of cathodic peak current, *vs.* vitamin K_1 concentration for an octadecylsilyl monolayer on ITO; template created by *n*-hexadecane. The reduction peak of the benzoquinone moiety of the vitamin at *ca.* −0.7 V *vs.* Ag/AgCl is monitored. Reprinted from *Tetrahedron Lett.*, **28**, I. Tabushi, K. Kurihara, K. Naka, K. Yamamura and H. Hatakeyama, 4299, Copyright 1987, with permission from Elsevier Science.

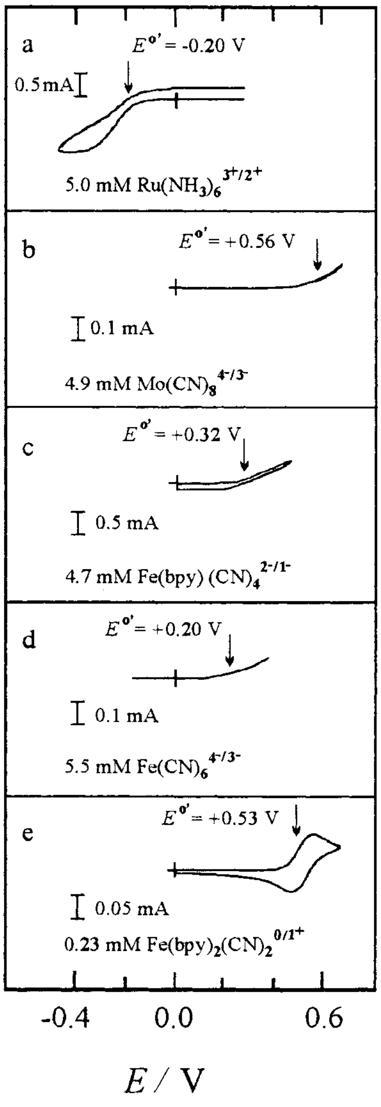


Fig. 15 CVs for nanoporous SA monolayer electrodes fabricated by immersing a Au electrode in ethanol solutions containing a ratio of 4-hydroxythiophenol/hexadecylthiol for 36 h. The probe molecules, their concentrations, and their formal potential values measured on uncoated electrodes are indicated in each frame. The aqueous electrolyte solution contained 1 M KCl for the data in frame a; 0.2 M KF for the data in frames b–d. All data were obtained using a single electrode, scan rate 0.1 V s^{-1}, *vs.* Ag/AgCl. Reprinted with permission from O. Chailapakul and R. M. Crooks, *Langmuir*, 1995, **11**, 1329. Copyright American Chemical Society.

Recently, surface-confined dendrimers have been used as molecule-sized gates.[85] Amine-terminated poly(amidoamine) (PAMAM) dendrimers were attached to the SAM of a mixture of mercaptoundecanoic acid and hexadecyl thiol. At pH 6.3, when the outer shell of the dendrimer is positively charged, negatively charged $Fe(CN)_6^{3-}$ ions can penetrate gate sites in the monolayer. Under these conditions, the electrochemical response of the kinetically-faster, but positively charged, redox probe $Ru(NH_3)_6^{3+}$ was completely blocked. At high pH, when the amine groups are in the neutral state, both redox markers can access the electrode surface. The smaller the size of the dendrimer used, the higher was the Faradaic current for the redox probe. If the dendrimer amino groups on the electrode surface were converted into bulky and hydrophobic 4-(trifluoromethyl)benzamido groups the CV response of the redox markers was blocked. These two experiments confirmed the intradendrimer mass transfer of the redox probe.

Amphiphilic quinone derivatives, coenzyme Q and vitamin K_1 have been incorporated in a low concentration in a mixed $C_{18}H_{37}SH/C_{18}H_{37}OH$ monolayer.[86] The complete electroactivity and the low capacitive background, due to the densely packed $C_{18}H_{37}SH/C_{18}H_{37}OH$ monolayer structure, enable low quinone concentrations in the monolayer to be detected. At an electrode surface concentration of coenzyme Q of $<10^{-15}$ mol cm^{-2}, the electrochemistry at single molecule 'gate sites' has been registered.[86c] These monolayers behave as an array of individually addressed 1 nm diameter disc microelectrodes. The mediated electroreduction of $Ru(NH_3)_6^{3+}$ and electron tunnelling through ubiquinone were ruled out. A plausible mechanism was suggested in which the flexible conformation of the isoprenoid chain in ubiquinone created a channel in the SAM enabling the direct approach of $Ru(NH_3)_6^{3+}$ ions to the electrode surface. Additional confirmation of this hypothesis was provided by the dependence of ubiquinone electroactivity on cation size: the electroactivity of ubiquinone was severely hindered when (exclusively) a sufficiently large cation (tetrabutylammonium) was available in solution. This may be considered as molecular recognition of electrolyte cations.

Another controllable way to create recognition defect sites in a monolayer structure was suggested by Che and Cabrera.[87] Monolayers of $HS(CH_2)_3Si(OMe)_3$ on a gold surface were created under potential scanning conditions, which leads to cyclic desorption/adsorption processes. The number of potential scans determines the size and concentration of defect sites. Subsequently, the trimethoxysilyl groups were hydrolysed and polymerised, in a manner similar to a sol–gel process, to give a passivating surface of polysiloxane. SA layers created by this technique were able to discriminate similar redox couples with different ionic charge, namely $Fe(CN)_6^{4-}$ and $Fe(CN)_6^{3-}$.

4. Ion channel sensors

As described by Umezawa and co-workers,[88] this type of recognition interface mimics biological membranes in the sense that the analyte (ions or pH) provides an extra stimulant to change the permeability of the thin film for a solution redox-active marker, the electrochemical response of which is used in a sensing device. As an example, a schematic diagram for an anionic redox marker is shown in Fig. 16.[88d] The recognition interface was created by the LB technique using the synthetic lipids **45–47** as the hosts. As redox markers, $Fe(CN)_6^{4-}$ and $Ru(bpy)_3^{2+}$ were used. Initially, the LB membrane is closed to the redox marker and no CV response is observed.

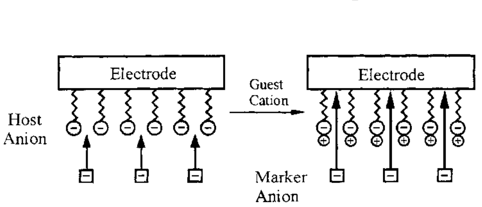


Fig. 16 Schematic representation of the mode of guest-induced permeability change for an anionic marker ion. For simplicity, the LB membrane (4–6 layers) is represented as monolayers. Reprinted with permission from K. Odashima, M. Sugawara and Y. Umezawa, *Interfacial Design and Chemical Sensing*, ACS Symposium Series, Eds. T. E. Mallouk and D. J. Harrison, American Chemical Society, Washington DC, 1994, Vol. 561, p. 123. Copyright 1994 American Chemical Society.

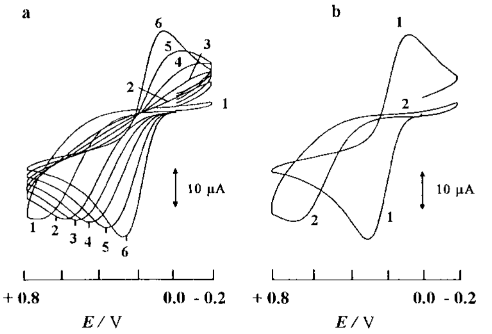


Fig. 17 Cyclic voltammetric detection of 1.0 mM $Fe(CN)_6^{4-}$ the marker ion with Ca^{2+}stimulated ion-channel sensors based on didodecyl phosphate monolayers using a supporting electrolyte of 10 mM $NaNO_3$, *vs.* SCE. (a) Response of the sensor to different concentrations of Ca^{2+}: (1) 0, (2) 0.1, (3) 0.2, (4) 0.4, (5) 1.0, (6) 3.0 mM. (b) Reversible closing of the channel by adding a Ca^{2+}quencher, EDTA: (1) 3.0 mM Ca^{2+}, (2) (1)+4.0 mM Na_2H_2(edta). Reprinted with permission from M. Sugawara, K. Kojima, H. Sazawa and Y. Umezawa, *Anal. Chem.*, 1987, **59**, 2842. Copyright 1987 American Chemical Society.

Depending on the membrane type, metal cations (Ca^{2+}, Mg^{2+}, Ba^{2+} and K^+) or anions (*e.g.* ClO_4^-) can open the membrane for marker permeation, which results in the appearance of a CV response (Fig. 17). Presumably, the mechanism involves binding of the metal cation to the membrane, thereby compensating the partially negative charge, and/or distorting the membrane arrangement to allow the negative marker ion to permeate to the electrode surface.[88b] The binding event is, therefore, transduced by the redox couple of the marker into an electrochemically detectable signal. Membrane opening by Ca^{2+} could be reversed by the addition of EDTA, which complexes with Ca^{2+}.[88a] This sensor was able to detect metal ions on the sub mM level.

Other amphiphilic derivatives **48–50** were used to detect organic anions[88b,88d] using the same markers as in previous work, and L-ascorbic acid. In this case, the anions bind to the positively charged receptors **48–50** in LB films. Selectivity was established in four different series of anions [ATP^{4-}, ADP^{3-} and AMP^{2-}; maleate and fumarate; *o*-phthalate, *m*-phthalate (isophthalate) and *p*-phthalate (terephthalate); ClO_4^-, SCN^-, I^-, NO_3^-, Br^- and Cl^-], with selectivity factors being calculated on the basis of a decrease of the CV peak current for the marker. The sensor showed only a negligible response to Cl^- and Br^-. The calibration curves for different analytes are shown in Fig. 18.[88b] The series of adenosine nucleotides (Fig. 18a) represents an influence of anion charge, while the two series of organic anions (Fig. 18b, and the phthalate isomers, Fig. 18c) show an influence of analyte geometry and the effect of intramolecular distribution of negative charge. The series of inorganic anions (Fig. 18d) shows an influence of lipophilicity.

Calixarene derivatives **51a** and **51b** were also used as hosts.[88d] Addition of Cs^+ and Na^+ induced changes in the permeability of the membranes composed of **51a** and **b**, respectively, as a result of cation binding. An increase [for $Fe(CN)_6^{4-}$] and a decrease [for $Ru(bpy)_3^{2+}$ and $Co(phen)_3^{2+}$)] of permeability was observed.[88d]

Recently, neutral nucleotide receptors **52–54** were used in a similar way, with a view to exploiting the complementary base-pairing interactions between guanosine and adenosine.[88e] Using $Fe(CN)_6^{4-}$ as a marker, the presence of guanosine induced a decrease in the permeability of membranes **52** and **54**, with a higher selectivity for the latter membrane due to multiple hydrogen-bonding of the guanine. Receptor **53** was more selective to adenosine than to guanosine. However, it should be noted that, in general, the selectivity of these

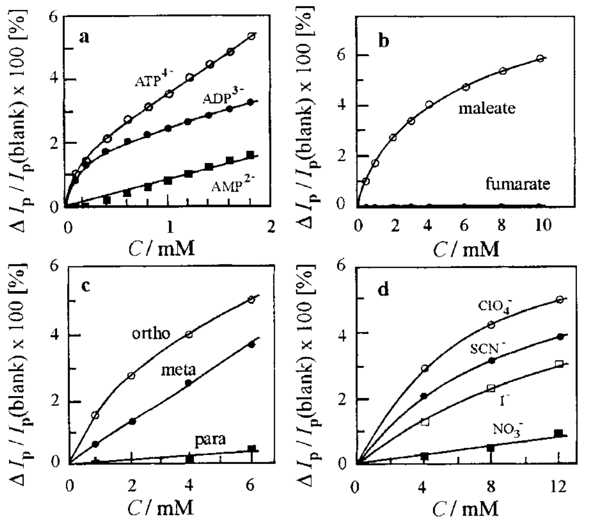
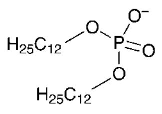


Fig. 18 Calibration curves for each series of guests showing the relationship between the decrease percentage of the CV peak current and the guest concentration for membranes composed of compound **48**. Reprinted with permission from S. Nagase, M. Kataoka, R. Naganawa, R. Komatsu, K. Odashima and Y. Umezawa, *Anal. Chem.*, 1990, **62**, 1252. Copyright 1990 American Chemical Society.



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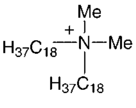

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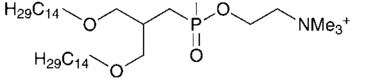

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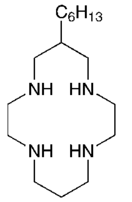

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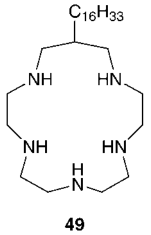

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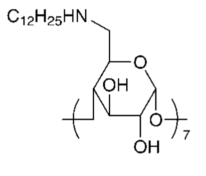

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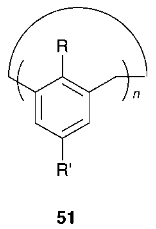

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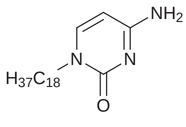
a R = OCH$_2$CO$_2$Et; R' = *t*-Bu; *n* = 6
b R = OCH$_2$CO$_2$Et; R' = C(Me)$_2$CH$_2$CMe$_3$; *n* = 4

compounds was low; a change in oxidation current was reported even for non-complementary bases.



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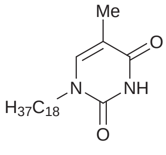

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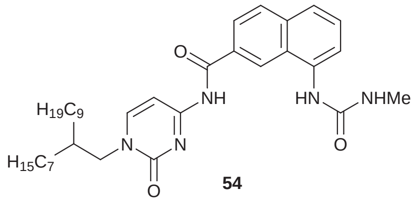
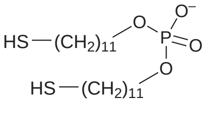


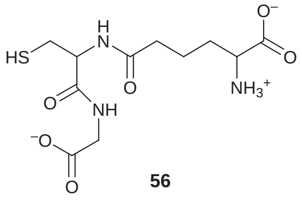
54

A SAM of lipid derivative **55** on a gold surface (short adsorption time) has been used as an ion gate membrane.[89] The electrochemical reaction of ferricyanide ion with the loosely packed monolayer of compound **55** was observed only at low pH.[89a] For the positively charged marker FcCH$_2$NMe$_3$$^+$, the opposite effect was observed and the monolayer was open for marker penetration at neutral and basic pH.[89a] Some metal cations were found to bind to the lipid monolayer, resulting in its opening to ferricyanide ions at high pH.[89b] Selectivity to different ions, especially Ba^{2+}, was expressed in an increase in the voltammetric current for ferricyanide reduction (Fig. 19). Addition of Ca^{2+} to the SAM decreased the redox peak current for FcCH$_2$NMe$_3$$^+$. Data for other metals were not given. A plausible mechanism involves the chelation of metal ions to two adjacent phosphate units, which would decrease the negative charge on the monolayer surface and thereby reduce the penetration of the positively charged marker.[89b]



55

Similar behaviour was observed for a gold electrode modified with SAMs of glutathione derivative **56**.[90] The response to ferricyanide was strongly hindered at pH 5.3 and was open at pH 2.9 when the system will be protonated. The electrochemical reaction of the marker was also significantly improved upon addition of Ca^{2+}, but not affected by the addition of K$^+$.[90a] Other alkali earth cations demonstrated a similar effect, although the influence of Mg^{2+} was comparatively very weak. The apparent heterogeneous rate constant is plotted against metal ion concentration (Fig. 20) and the order of selectivity correlated with the rate of dehydration of the inner shell (slowest for Mg^{2+}).[90b] The effect of lanthanides was three orders of magnitude larger compared to alkaline earth cations, and micromolar concentration of lanthanides can be detected, in the order La^{3+} > Eu^{3+} > Lu^{3+}.[90c]



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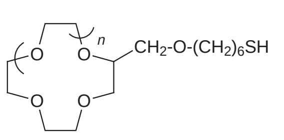

57a $n = 1$
b $n = 2$

Two new thio-functionalised crown ethers **57a** and **57b** have been used for alkali metal detection in aqueous solution.[91] Depending on the size of the crown cavity, Na$^+$ or K$^+$ complexation, to **57a** and **57b**, respectively, led to blocking by the SAM of the electrochemical marker Ru(NH$_3$)$_6$$^{3+}$. The selectivity is due to the cooperative binding (sandwich complexation) of one metal ion by two crown ether moieties. Complexation was reversible, and by using impedance spectroscopy and measurements of charge-transfer resistance, it was possible to analyse Na$^+$ in the range 10^{-5}–10^{-2} M. The electrode was able to detect Na$^+$ even in the presence of a 100-fold excess of K$^+$.

With a view to applications in food technology, SAMs of thiol-functionalised lipids have been employed to fabricate an electrochemical sensor imitating human taste receptors.[92] Using Fe(CN)$_6$$^{3-}$ as a marker, the change of the CV response was monitored under the influence of model taste compounds which were designed to mimic sour, salty, bitter and sweet foods. The change of peak current and peak potential *versus* concentration of the model taste compounds was monitored,

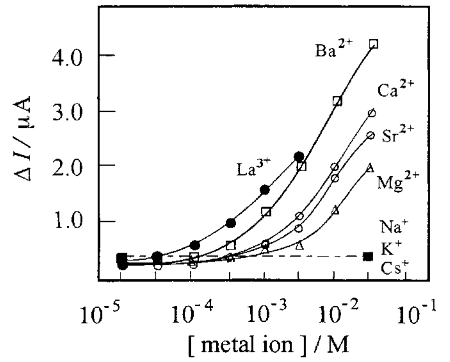

Fig. 19 Currents of voltammograms of a monolayer electrode of compound **55** as a function of added metal ion concentration, 2 mM $FeCN_6^{3-}$ 0.1 M KCl (pH 9.0), scan rate 200 mV s^{-1}. Reprinted with permission from N. Nakashima and T. Tagushi, *Interfacial Design and Chemical Sensing*, ACS Symposium Series, Eds. T. E. Mallouk and D. J. Harrison, American Chemical Society, Washington DC, 1994, Vol. 561, p. 145. Copyright 1994 American Chemical Society.

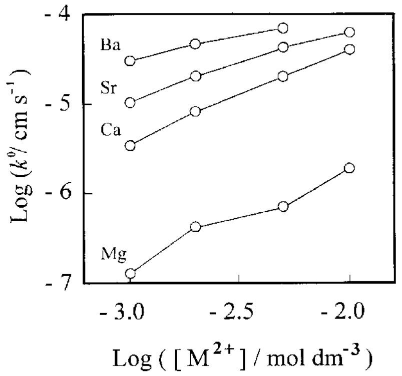

Fig. 20 Plot of log(k^0) (apparent heterogeneous rate constant) *vs.* concentration of M^{2+} for monolayer of glutathione **56** on a gold electrode. The k^0 were obtained by extrapolating log(I)–η (overpotential) plots to the mid-point potential of the 0.5 mM $Fe(CN)_6^{3-}$/$Fe(CN)_6^{4-}$ + 0.1 M KCl system (0.206 V *vs.* Ag/AgCl). Reprinted from *Bioelectrochem. Bioenerg.*, **29**, K. Takehara, Y. Ide and M. Aihara, 113, Copyright 1992, with permission from Elsevier Science.

and the sensitivity of the response was found to be similar to that in humans. Similarly, sensors for odour substances have been described.[92b] More recent work on artificial taste sensors has concentrated on lipid/polymer membranes for which the output is measured as an electrical signal.[93]

5. Conclusions and future prospects

Miniaturisation of functional devices down to the molecular and nanoscale level is set to remain at the forefront of scientific endeavour. The chemical tailoring of electrode surfaces clearly has a pivotal role to play. In this context, a diverse range of functionalised materials have been synthesised for applications in electrochemical molecular recognition in thin films. Considering direct molecular recognition, several types of transduction units have been employed to provide information transfer in the form of an electrochemical signal. From a synthetic viewpoint these materials can be divided into several groups according to the structure of their transduction unit: conjugated oligomers and polymers based on aromatic heterocycles; transition metal complexes with organic ligands; tetrathiafulvalene; viologen and azobenzene. As the receptor unit, crown ethers, laureate ethers, calixarenes, peptides *etc.* have been used. The films have been fabricated by electropolymerisation (both reductive and oxidative), casting from solution, molecular SA and LB techniques.

Using conjugated polymers, different molecular assembly strategies have been employed to combine receptor and signalling units. Some of these approaches have been successful, resulting in a prototype voltammetric sensor able to recognise metal ions with a threshold down to 10^{-6} M in the best case. The fabrication of SAMs has also provided electrodes capable of detecting indole and catechol in 10^{-5} M concentration and metal ions on a few mM level.

A number of different non-electroactive thin films have been employed for the recognition of redox-active analytes: these include lipids and different passivating SAMs (thiols and silanes). A range of interactions are used for binding: complexation with a macrocycle, protein–antibody, DNA–oligonucleotide, and inclusion by size and shape. Cyclodextrins, crown ethers and calixarenes have been used as receptors, and potentially useful enzyme immunoassays and gene sensors can be fabricated this way. Amongst redox-active analytes, metal ions are the most popular, and the most important from a practical viewpoint. These can be analysed using accumulation stripping voltammetry with a number of SAMs and conjugated polymers employed for electrode modification. The most useful mode of interaction in this case was found to be chelation of metal ions with a ligand on the electrode surface.

Recognition sites can be incorporated as defects in otherwise passivating layers. To create these defects, amphiphilic templates, aromatic thiols, natural quinonoid compounds and macrocycles are used. Electrochemical adsorption–desorption processes applied to SAMs also can be used to control the concentration and properties of defect sites.

Ion channel sensors, which utilise a solution redox marker for signal generation and opening–closing of recognition sites in the films on the electrode surface, are modulated by an analyte. To create a recognition interface in this approach, amphiphilic molecules including macrocycles, lipids, nucleotides and amino acids have been used. An electrochemical sensor imitating human taste has been constructed.

At present most of the investigations employ cyclic voltammetry and, occasionally, pulse voltammetric techniques. Amperometric detection is expected to grow in importance over the next few years. Issues relevant to the development of practical, commercially-viable sensors include long-term stability, sensitivity and selectivity (cross-sensitivity). Increases in the sensitivity might be achieved by immobilising the sensing materials onto the gate areas of thin film transistor structures, to make ion-sensitive field effect transistors (ISFETs) and related sensors. However, the problems of eliminating the pH response of the oxide and nitride gate insulators and of device encapsulation must be solved. The use of arrays of individual sensing elements may be exploited to provide an increase in sensitivity. This is the approach favoured by nature (*e.g.* the mammalian olfactory system) and has already been used successfully in the development of the 'electronic nose'.

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