CHEMICAL SENSORS BASED ON FIELD EFFECT TRANSISTORS; SELECTIVE RECOGNITION OF CATIONS AND ANIONS

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Abstract. Microsensors based on chemically modified field effect transistors (CHEMFETs) for the detection of ions require a durable chemoselective membrane layer with receptor molecules of high selectivity. This contribution describes recent advances in the development of polysiloxane polymer membranes, in the design of cation and anion selective receptors, and their application in CHEMFETs to obtain sensors with improved durability.

1. Introduction

An important application in the field of supramolecular chemistry is the development of sensory systems [1, 2] and selective membrane transport systems [3] in which selective receptors function as selector element and/or as carrier molecule. In sensor systems the interaction of the receptor with the guest species has to be transduced into an optical or electrical signal. Potentiometric transducing devices have been shown particularly useful for detection of charged guest species (ions). Measurement by potentiometry offers the advantage of a large dynamic range, because the signal is proportional to the logarithm of the activity of the measured ion. In general two types of potentiometric sensing devices can be discriminated, the ion selective electrodes (ISEs) and the ion selective field effect transistor (ISFET) based sensors. Both types consist of an ion selective membrane as selector element, introducing the selectivity to the sensor, and a transducer element to convert the molecular interactions in the membrane into an electronic signal. In the case of ISEs the potential drop at the interface between membrane and sample

solution is measured directly, for ISFET sensors this membrane potential is converted into a change in current between the source and drain region of the field effect transistor. The main advantage of ISFETs over ISEs, besides the low output impedance and the use of integrated circuit microelectronic technology for fabrication, is the small size in the order of 2×2 mm. Therefore ISFETs can be used for much smaller sample volumes, for instance in micro analysis systems [4], and multi ion sensor arrays can be obtained that still have a reasonable size.

The insulating oxide layer above the gate of the ISFET (typically SiO_2 , Al_2O_3 , or Ta_2O_5) is by itself pH-sensitive due to the presence of hydroxyl groups formed by partial hydrolysis of the surface oxide. Changes in the pH of the contacting solution vary the degree of protonation/deprotonation of these hydroxyl groups and consequently the surface potential of the ISFET, which results in a change in drain current. Sensitivity of the device for ions other than the hydrogen ion is obtained by covering the gate area with the ion selective membrane. However, when the ion selective membrane is cast directly on top of the ISFET a poorly defined interface between the membrane and the SiO_2 surface is obtained. In the chemically modified field effect transistor (CHEMFET, Figure 1) an intermediate hydrogel layer, soaked with a pH buffer and containing a fixed concentration of the ionic species to be detected, is introduced between the ISFET surface and the ion selective membrane. The constant chemical composition of this hydrogel layer provides a constant surface potential at the gate oxide and a constant inner boundary potential between the ion selective membrane and the hydrogel, which improves the stability of the ISFET based sensor. Moreover, the interference by local pH changes at the ISFET surface caused by CO_2 diffusing through the membrane is eliminated [5].

The ion selective membrane is the important part of the CHEMFET as the ionophore in the membrane determines the selectivity of the sensor. The durability of the CHEMFET is mainly limited by the stability of the ion selective membrane. Poor adhesion to the surface of the sensor, and leaching of membrane components, like electroactive species (i.e. the ionophore and lipophilic counter ions) and plasticizers in PVC membranes, reduce the life-time of the sensor.

Figure 1. Schematic drawing of chemically modified field effect transistor (CHEMFET).

To obtain highly selective and durable microsensors much effort have been put in the design of ion receptors that bind the ion of interest with high selectivity and in the development of membrane materials that possess a higher durability than the commonly used plasticized PVC membranes.

2. Cation Selective Ionophores

Receptors applied in sensors should possess high selectivity, especially over interfering ions that will possibly also be present in high concentrations in the sample. Furthermore, the receptor molecule must be lipophilic in order to make it soluble in the membrane matrix and to prevent fast leaching to the contacting aqueous solution. Calix[4]arene **1** is a versatile lipophilic three-dimensional building block that can be functionalized with various ligating substituents for selective ion binding and can be provided with a functional group which enables covalent anchoring to the membrane matrix.

The selectivity of the receptor can be influenced by the type and number of substituents and the conformation of the calix[4]arene. For example, functionalization of the calixarene at the *lower* rim with amide moieties (**2**) results in the right positioning of the coordinating carbonyl and phenol oxygen atoms for complexation of Na^+ with selectivity over other alkali cations [6]. The selectivity of Na^+ over K^+ can even be improved by the use of two diametrically positioned amide ligands instead of four, in combination with two ester ligands (**3**). Applied in plasticized PVC membranes on CHEMFETs a high Na^+/K^+ selectivity ($\log K_{\text{Na,K}}^{\text{Pot}} = -3.0$) is obtained [7].

- 4 $\text{R}_1=\text{R}_2=\text{CH}_2\text{C}(\text{S})\text{N}(\text{CH}_3)_2$
- 5 $\text{R}_1=\text{R}_2=\text{CH}_2\text{CH}_2\text{SC}(\text{S})\text{N}(\text{CH}_2\text{CH}_3)_2$
- 6 $\text{R}_1=\text{R}_2=\text{CH}_2\text{CH}_2\text{OCH}_2\text{C}(\text{S})\text{N}(\text{CH}_3)_2$
- 7 $\text{R}_1=\text{CH}_2\text{CH}_2\text{SCH}_3, \text{R}_2=\text{CH}_2\text{CH}_2\text{CH}_3$

Changes in the nature of the donating atoms also influence the selectivity. Soft heavy metal ions can be selectively bound by providing the calix[4]arene with soft thioether, thioamide, or thiocarbamate groups. Again small changes in the ligand structure can alter the selectivity of the ionophore. Thioamide **4** is highly selective towards Pb^{2+} , thiocarbamate **5** yields well functioning Cu^{2+} selective CHEMFETS and the dimethylthiocarbamoylmethoxyethoxy substituents of **6** introduce Cd^{2+} selectivity. With dithioether **7** Nernstian Ag^+ response in the presence of K^+ , Ca^{2+} , Cd^{2+} , Hg^{2+} , and Cu^{2+} has been obtained [8].

In addition, one of the first synthetic host motifs used in supramolecular chemistry, the crown ether, can easily be combined with the calix[4]arene building block. The preorganization of the binding cavity of the crown ether by the calixarene skeleton enhances the binding selectivity and the molecule becomes more lipophilic. For K^+ selective sensors, a number of calix[4]arene crown ether ionophores were developed with five oxygen atoms in the crown ether bridge. These receptors clearly show the influence of the conformation of the calix[4]arene on the selectivity [9]. The *cone* conformer **8** has the lowest selectivity of K^+ over Na^+ ($\log K_{\text{K,Na}}^{\text{Pot}} = -2.5$). The selectivity of the *partial cone* conformer **9** is much better ($\log K_{\text{K,Na}}^{\text{Pot}} = -3.9$), but the highest K^+ selectivity was obtained with *1,3-alternate* calix[4]arene **10** ($\log K_{\text{K,Na}}^{\text{Pot}} = -4.2$). The high selectivity of the latter can be attributed to favourable cation- π interactions between K^+ and the aromatic rings. In Figure 2 the K^+ response curve in the presence of 1 M Na^+ of a CHEMFET with this ionophore is given. The selectivity obtained with **10** is even higher than that of the natural occurring ionophore valinomycin under identical conditions.

Figure 2. K⁺ response of CHEMFET containing ionophore **10** in the presence of 1 M Na⁺.

The effect of the size of the binding cavity on the selectivity can be illustrated with receptor **11** (the crown ether bridge is extended by one oxyethylene unit compared with **10**) which changes the selectivity in favour of the larger Cs⁺ ion over K⁺ and Na⁺ ions [10]. Again the interaction of the two aromatic rings in **11** with the cation plays a role in the binding selectivity. The Cs⁺/Na⁺ selectivity ($\log K_{\text{Cs,Na}}^{\text{Pot}} = -3.3$) is slightly better than that obtained for bis(18-crown-6) derivatives ($\log K_{\text{Cs,Na}}^{\text{Pot}} = -3.0$). Conversely, reduction of the size of the crown ether of these calix crown ionophores to a bridge with three oxyethylene units (four oxygen atoms in the ring) favours the complexation of Na⁺ [11,12].

Another possibility to obtain selectivity for larger cations is to enlarge the binding cavity and to use calix[6]arenes. In triamide derivative **12** the oxygen atoms are C₃-symmetrically positioned for binding with the guanidinium ion having the same symmetry. Selectivity ($\log K_{\text{Gu,j}}^{\text{Pot}} = -1.8$) is obtained over sodium, potassium and ammonium [13].

3. Anion Selective Ionophores

Selective sensors for anions are much less developed than sensors for cations. Most anion sensors are based on ion-exchange membranes and show a selectivity governed by the relative dehydration energy of the ions given by the well-known Hofmeister series. This will favour the detection of the more lipophilic anions, e.g. nitrate, over hydrophilic anions, like phosphate and sulfate [14,15]. To obtain sensors with selectivity deviating from the Hofmeister sequence, anion selective receptors have to be added to the membrane. Examples of such receptors are the metallo-porphyrins, e.g. cobalt tetraphenylporphyrin which introduces nitrite selectivity [16], or trifluoroacetophenone derivatives, which introduce carbonate selectivity [17].

A new group of anion receptors that we are currently investigating is based on the neutral uranyl salophene building block **13**. The uranyl cation has a bipyramidal pentagonal coordination sphere and one of the five equatorial positions is still available for anion binding. Conductometrically determined association constants with various anions show that monovalent phosphate ($K_{\text{assoc}} = 1.4 \times 10^4 \text{ M}^{-1}$, in MeCN) is bound preferentially over chloride ($K_{\text{assoc}} = 4.0 \times 10^2 \text{ M}^{-1}$). To enhance the selectivity amide substituents are introduced close to the uranyl coordination site (receptor **14**) [18]. As can be seen in the crystal structure (Figure 3), the amide protons are well positioned to form additional interactions (hydrogen bonds) with phosphate, which is reflected by the even higher phosphate over chloride selectivity ($K_{\text{assoc}} = 2.5 \times 10^6 \text{ M}^{-1}$ and $1.7 \times 10^3 \text{ M}^{-1}$, respectively).

Figure 3. Crystal structure of the complex **14**·2H₂PO₄⁻.

In nature examples can be found of phosphate and sulfate binding proteins in which the anion is bound exclusively by the formation of hydrogen bonds. Prokaryotic, periplasmatic proteins exhibit selectivities of more than 10^5 for binding phosphate over sulfate, and *vice versa* [19]. Novel neutral anion receptors that bind spheric halogenide

anions exclusively by hydrogen bonds were obtained by preorganization of urea moieties using the calixarene building block. As with cation receptors, the selectivity can be influenced by the size of the binding cavity. Lower rim substitution of calix[4]arene with (thio)urea moieties gives **15**, which binds chloride ($K_{\text{assoc}} = 7.1 \times 10^3 \text{ M}^{-1}$, in CDCl_3) preferentially over larger bromide ($K_{\text{assoc}} = 2.6 \times 10^3 \text{ M}^{-1}$) [20]. By using the enlarged cavity of calix[6]arene **16** the selectivity of binding can be reversed; binding of bromide ($K_{\text{assoc}} = 1.5 \times 10^3 \text{ M}^{-1}$) is favoured over binding of chloride ($K_{\text{assoc}} = 4.8 \times 10^2 \text{ M}^{-1}$) [21].

4. Membrane Materials for Durable Chemfets

Most potentiometric sensors are based on plasticized PVC membranes. When used with CHEMFETs the disadvantage is that these membranes are physically adhered to the ISFET surface. Upon prolonged contact of the sensor with the aqueous sample solution, the membrane can easily become detached. Moreover, both the plasticizer and electroactive species (e.g. ionophore and lipophilic ionic sites) slowly leach from the membrane into the contacting aqueous solution resulting in a deterioration of the selectivity of the sensor. In efforts to enhance the durability of the chemo-selective membrane, many polymers have been investigated, e.g. carboxylated PVC [22], copolymers of PVC, poly(vinyl alcohol), and poly(vinyl acetate) [23], Urushi latex [24], polyurethane [25], and acrylate [26]. However, these materials still need the addition of a plasticizer and it not easy to link the electroactive species covalently to the membrane and the membrane itself to the ISFET surface.

In our group we have shown that polysiloxanes having different side groups have some advantages for application as membrane material for IC based sensors. These polymers have a low glass transition temperature which makes the addition of plasticizer superfluous. Moreover, by variation of the nature and number of side groups in the

polysiloxane the polarity can be tuned. In our initial research, the polysiloxanes were synthesized by emulsion polymerization of a mixture of octamethylcyclotetrasiloxane, the trimer and tetramer of (3-cyanopropyl)methylcyclotrisiloxanes, and (3-methacryloxypropyl)methyldichlorosilane [27]. The cyano groups enhance the polarity of the otherwise apolar polysiloxane. The (methacryloxy)propyl groups can be photopolymerized after membrane casting and this crosslinking increases the mechanical strength and enables covalent attachment of the membrane to the ISFET surface. Furthermore, ionophores and lipophilic counter ions modified with methacrylate moieties can also be bound during this photo-crosslinking process, preventing leaching of these electroactive species. Significant enhancement of the lifetime was obtained with sensors having polysiloxane membranes with immobilized electroactive species. CHEMFETs with cyanopropyl and methacryloyl functionalized polysiloxane membranes with covalently bound K^+ receptor functioned well for over 230 days in continuous flowing water. PVC based CHEMFETs already failed after 25 days under similar conditions [28]. Also for Na^+ [29] and NO_3^- [15] selective CHEMFETs, the durability could be significantly improved by applying polysiloxane membranes with covalently attached electroactive components.

However, during the production of large quantities of these sensors problems were encountered with the reproducibility of the above described polysiloxane membranes. It appeared that the polymer synthesis gave batches of polysiloxanes of different composition due to the unequal reactivities of the various types of monomers (i.e. the dichlorosilane monomer has a much higher reactivity than the cyclotrisiloxane, which in turn is more reactive than the cyclotetrasiloxane). By synthesizing the polysiloxane polymers starting from only cyclotetrasiloxane monomers the reproducibility in the production of well-functioning of Na^+ selective CHEMFETs was improved significantly [30]. A further improvement of the homogeneity of the polymers was obtained by the use of only cyclotrisiloxane monomers. Cyclotrisiloxanes polymerize in a kinetically controlled reaction yielding a more narrow molecular weight distribution than obtained with the thermodynamic controlled reaction of cyclotetrasiloxanes. Furthermore, the low molecular weight of the monofunctionalized cyclotrisiloxane monomers permits purification of the starting materials by distillation. Cyclotrisiloxanes with various pendant polar substituents (**17a-d**) could be synthesized by the reaction of 1,1,3,3-tetramethyl-1,3-dihydroxydisiloxane with the dichlorosilane having the appropriate substituent (Scheme 1) [31].

The siloxane copolymers were obtained by CsOH initiated polymerization of three cyclotrisiloxane monomers; hexamethylcyclotrisiloxane **18** (which forms the bulk of the polymer), methacrylate functionalized monomer **17e** (which contains the photopolymerizable group) and one of the monomers **17a-d** (containing the polar moiety) (Scheme 2). Gel permeation chromatography of the polymer product showed a narrow molecular weight distribution (M_w/M_n) of 1.3-1.7 and from the NMR spectra it could be concluded that the stoichiometry of the substituents in the polymer was in agreement with the relative amounts of the monomers used. This indicated that all monomers have equal reactivity, resulting in a homogeneous polymer.

Scheme 1. Synthesis of monofunctionalized pentamethyl cyclotrisiloxanes.

Scheme 2. Synthesis of siloxane copolymers with photopolymerizable methacryloxypropyl substituents and various types of polar substituents.

The new polymers offer the possibility to tune the polarity and the character of the membrane by changing the amount and type of polar substituents. These changes can have a profound effect on the partition of various ions between sample and membrane phase, resulting in changes in the selectivity of the sensor. This is clearly illustrated for nitrate selective CHEMFETs based on a polysiloxane ion-exchange membrane. As these membranes contain only lipophilic cationic groups (tetraalkylammonium) and no anion selective receptor molecules, the selectivity is determined by the differences in energy of transfer from water to the polysiloxane membrane (Hofmeister selectivity). Sensors with polysiloxane membranes with cyanopropyl substituents (**19a**), show a much lower interference of halogenide ions than sensors having membranes of polysiloxane **19d** with amide substituents ($\log K_{\text{NO}_3, \text{Cl}}^{\text{Pot}} = -2.3$ for cyanopropyl, $\log K_{\text{NO}_3, \text{Cl}}^{\text{Pot}} = -1.6$ for amide respectively, Figure 4). This difference reflects the more favourable interaction of the halogenide ions with the amide moieties, lowering the solvation energy of these ions in the membrane phase [15].

Figure 4. Effect of the polar substituent on the nitrate over chloride selectivity. Nitrate response in the presence of 0.1 M Cl⁻ for CHEMFETs with polysiloxane membranes **19a** containing cyano substituents (■) or **19d** containing amide substituents (●).

Figure 5. Pb²⁺ response in the presence of 0.1 M Ca²⁺ of CHEMFET with polysiloxane membrane **19b** containing calix[4]arene ionophore **4**.

Also for membranes containing an ionophore, the relative partition of the ions between the membrane and the sample phase is important for the selectivity in addition to the relative association constants of the ionophore with various ions. Therefore the nature and polarity of the substituent of the polysiloxane can also have large effects in ion receptor containing membranes [31]. For example, CHEMFETs with Cd²⁺ selective ionophore **6** in membranes of 3-cyanopropyl functionalized siloxane **19a** are Cd²⁺ selective in the presence of Ca²⁺ and Pb²⁺ ions ($\log K_{\text{Cd},j}^{\text{Pot}} = -2.2$ and -1.4 , respectively). These selectivities can be improved to -4.1 and -2.0 , respectively, by incorporating **6** in the polysiloxane with acetoxypentyl substituents (**19c**). Compared with DOP-plasticized

PVC membranes, these results are even more striking because with the latter membranes no selectivity of Cd^{2+} over Pb^{2+} could be obtained.

CHEMFETs with Pb^{2+} selective calix[4]arene derivative **4** in membranes of cyanopropyl (**19a**) or acetoxypopyl (**19c**) functionalized polysiloxane did not have a good sensitivity (sub-Nernstian slopes). However, CHEMFETs with membranes of polysiloxanes with benzoylaminopropyl substituents (**19d**) gave linear Pb^{2+} responses, although a high interference of Ca^{2+} was observed. This can probably be attributed to the interaction between this hard ion with the hard donating carbonyl oxygen atoms of the amide substituents of the polysiloxane favouring partition of the calcium ion. As can be seen in Figure 5, CHEMFETs with polysiloxane membranes with acetylphenoxypopyl substituents (**19b**), having relatively softer ester groups, show selective Pb^{2+} responses even in the presence of Ca^{2+} .

5. Conclusions

The quantitative transduction of the recognition process between a host and a guest into a measurable signal is not a trivial process. For real application of sensor systems problems of selectivity and durability have to be overcome. High selectivity for various cations like Na^+ , K^+ , Cs^+ , Ag^+ , Cd^{2+} , Cu^{2+} , or Pb^{2+} could be obtained by use of various calix[4]arene based receptor molecules. For the detection of anions new ion receptors based on Lewis acid binding sites in uranyl salophenes and by multiple hydrogen bonding have been developed and are currently under investigation. Improvement of the durability of chemically modified field effect transistors has been obtained by the use of membranes made of homogeneous polysiloxanes. The incorporation of different types of polar substituents, like cyano, amide, ester, or ketone moieties, made it possible to tune the membrane properties in order to achieve optimal selectivity of the sensor.

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7. References

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