Application of supramolecular chemistry in the development of ion-selective CHEMFETs*

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Abstract

The construction of chemical sensors requires the integration of a sensing molecule and a transducing element. We have developed an integrated CHEMFET on the basis of an SiO₂ ISFET by covalently linking a hydrophilic polyHEMA layer to the SiO₂ gate oxide and a hydrophobic sensing membrane that contains the sensing molecule to this polyHEMA layer. The optimized material for the sensing membrane is a terpolymer of different siloxanes. The sensing molecules that we have studied were designed for a high K⁺, Na⁺, Ca²⁺ and Ag⁺ selectivity. Typical examples of such molecules are hemispherands or calix[4]arene crown ethers for K⁺ and tetra-O-alkylated calix[4]arenes in the cone conformation for Na⁺ or Ag⁺. The sensing molecules can be present as mobile hydrophobic species or they can be covalently attached to the sensing membrane. We have compared both possibilities and in both cases a durable sensor can be obtained. The sensors that have covalently attached receptors exhibit fast response times and are chemically stable for prolonged periods (≥ 200 days).

Introduction

A chemical sensor connects the chemical and the electrical or optical domains. The response on changing concentrations of chemical species should be fast and selective for one species and the device should have a lifetime in the order of months. Such chemical sensors require the integration of a sensing molecule and a transducing system. Our work in the area of supramolecular chemistry is directed towards the design and synthesis of receptor molecules that will selectively recognize a guest species either ionic or neutral [1]. In addition we are actively investigating possible applications of these molecules, e.g. in the fields of membrane transport [2] and diagnostics [3]. An important area for the application of molecular recognition concepts is chemical sensing, because selective recognition is the first step in the sensing process. As the transducing element field effect transistors (FETs) [4] are very interesting because the gate oxide contains reactive groups that can be used for the covalent attachment of membranes and/or sensing molecules.

Moreover, the field effect transistors have the advantages of a fast response time and *in situ* impedance transformation. From a technological point of view they are interesting because they can be made very small with the available planar IC technology. Despite these obvious advantages and the fact that their use as pH sensors was reported 20 years ago, FET-based sensors have not reached widespread practical application as chemical sensors. There are two basic problems when membranes containing specific receptor molecules are attached to the gate oxide of the ISFET. First, the boundary potential at the interface between membrane and gate oxide is not thermodynamically defined and the physically attached membranes are not permanently linked to the gate oxide. Secondly, most receptor molecules for ionic species are not sufficiently hydrophobic to give chemically stable systems because they leach out of the membrane to the contacting aqueous solution. The first objectives of our work were to solve these problems and to design chemically sensitive field effect transistors (CHEMFETs) that are selective, exhibit a fast response, low noise level, and have lifetimes in the order of months. In a series of papers we have reported our strategy to achieve these objectives [5–10].

*Invited paper.

In this paper the emphasis will be placed on the design and synthesis of the selective receptor molecules in relation to both the selectivity and the lifetime of the sensors.

The architecture of the CHEMFET sensor

The architecture of the sensor we are using in our research is an improved membrane modified FET (MEMFET) device. The problem of the thermodynamically ill-defined membrane-gate oxide interface of the MEMFET has been solved by introducing a hydrophilic membrane (polyHEMA) layer between the oxide and the sensing membrane. This hydrogel is conditioned with buffered electrolyte solutions and this eliminates the CO_2 interference and the residual pH sensitivity. This also reduces the noise level [8]. Covalently attached to the hydrophilic membrane is the hydrophobic sensing membrane that contains the sensing molecule (ionophore/receptor molecule). The chemical composition of the hydrophobic membrane is tuned to the primary ion to be detected by variation of the polarity. The best results have been obtained with copolymers of differently substituted siloxanes. Details of the resulting CHEMFETs are given in a recent review article from our laboratory [11]. A schematic representation is depicted in Fig. 1.

Fig. 1. Thermodynamic equilibrium (a) and architecture of the CHEMFET (b).

Design and synthesis of receptor molecules

Receptors selective for K^+

As early as 1975 Moss *et al.* [12] reported a K^+ -responsive MEMFET in which valinomycin (**1**) was incorporated in a PVC membrane that was physically attached to the membrane. This natural antibiotic exhibits a very high selectivity for K^+ relative to Na^+ ($\geq 10^4$) but it has limited possibilities for chemical modifications or covalent attachment to a membrane. Our work on selective receptors is based on the concept of preorganization [13] of the ligating atoms, in the case of K^+ mainly oxygen atoms. Simple macrocyclic polyethers, e.g. benzocrownethers (**2**), exhibit (too) low K^+/Na^+ selectivities for practical applications [1], because they are flexible molecules that can undergo extensive conformational reorganization upon complexation.

When this conformational freedom is restricted by the incorporation of rigid terphenyl moieties the K^+/Na^+ selectivity increases. These hemispherands (**3** and **4**) were synthesized by the cyclization of a bis(bromomethyl)terphenyl derivative and the corresponding diol in the presence of NaH [14, 15]. All compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy, high resolution mass spectrometry and in the case of **3b** by single crystal X-ray analysis [14]. The ring size and the degree of preorganization is reflected in the selectivities (K^+/Na^+) with the highest selectivity $\log K_{\text{R}}(\text{Na}^+/\text{K}^+) = 2.8$ for **4**. In a similar way we have synthesized a hemispherand in which one aromatic moiety is incorporated in the polyether chain (**5a**) and that has in addition a functional group suitable for chemical modification or covalent binding to a hydrophobic membrane [10]. A second type of receptor with an increased hydrophobicity that is selective for K^+ are the calix[4]arene crown ethers (**6**). The hydrophobicity in these compounds is introduced by the calix[4]arene moiety that is a cyclotetramer of *p*-tert-butylphenol and formaldehyde. This building block plays a very important role in supramolecular chemistry because it is easily accessible and has four oxygen atoms for further chemical modification [16]. In our work on selective receptors we have first reduced the four to two free hydroxyl functions either by selective dialkylation or diametrical bridging with a flexible or rigid bridge [17]. The 1,3-dimethylcalix[4]arene crown-5

Scheme 1.

(**6a**), formed by bridging with a flexible tetraethylene glycol chain, has a molecular cavity that is complementary with the size of a potassium cation. ^1H NMR studies revealed that the 1,3-dimethylcalix[4]arene crown-5 undergoes a conformational change to coordinate K^+ . The solid state X-ray structures (Fig. 2) confirm the two

different conformations of the receptor and the corresponding alkali cation complexes. Extraction [17] and membrane transport experiments [18] were used to evaluate the complexation (or extraction) constants with the various cations. From these experiments a large K^+/Na^+ selectivity was concluded ($\log K_R(\text{Na}^+/\text{K}^+) \geq -3$). Moreover,

Fig. 2. X-ray structures of **6a** and **6a** - Rb^+ .

the membrane transport experiments revealed that the calix[4]arene moiety gives these calixcrown ethers an extremely high lipophilicity ($K_p \geq 10^5$).

A further improvement of the K^+/Na^+ selectivity was obtained by increasing the rigidity of the receptors in the optimal complexing conformation. This was achieved by replacing the small methoxy groups, which can rotate through the annulus of the calixarene moiety, by ethoxy substituents.

In the synthesis we obtained three different conformers, the cone (**6b**), partial cone (**6c**), and 1,3-alternate (**6d**) conformations, as stable isomers (Fig. 3). In the complexation with alkali cations these conformers (**6b–d**) behave very differently with an increased K^+/Na^+ selectivity of the partial cone conformer **6c**. These experiments reveal that by systematic synthetic studies both the selectivity towards a specific cation and the lipophilicity can be optimized.

Receptors selective for Na^+

Compared with the selective receptors for K^+ molecular receptors for Na^+ are less selective because of the higher hydration energy of the smaller sodium cation. Potentiometric selectivities $\leq 10^2$ have been reported for different oxamides but these receptors also complex Ca^{2+} strongly. Recently tetra-*O*-alkylated calix[4]arene derivatives have been reported that complex Na^+ selectively (e.g. **7a**: $K_{Na^+/K^+} \approx 10^2$).

We have incorporated such receptors in our CHEMFET device and have demonstrated that they have sufficient lipophilicity. Again the intermediate polyHEMA layer turned out to be crucial [19] for a stable sensor. For the design of these receptors it is extremely important to control the conformation of the calix[4]arene moiety. Only the cone conformation in which the four substituents converge at one face of the molecule give the required selective complexation. The same is observed for a tetra-*O*-alkylated calix[4]arene with

Fig. 3. Three different conformations of the 1,3-diethoxycalix[4]arene crown-5 (**6b**, **6c**, **6d**).

substituents that have sulfur atoms in addition to the four calix[4]arene oxygen atoms. In the cone conformation **7b** complexes Ag^+ selectively.

Chemically sensitive field effect transistors (CHEMFET)

There are two principally different ways to incorporate the sensing molecules in the hydrophobic membrane. First, the sensing molecules can be made very hydrophobic by chemical modification of that part of the molecule that is not actively involved in the complexation reaction. Secondly, we can introduce a functional group that allows the covalent attachment to the hydrophobic membrane. However, from a theoretical point of view there was no conclusive answer to the question if a covalently linked immobile receptor would give a workable and fast responding sensor [20]. Consequently we have first studied the response to changing concentrations of the primary ion in the presence of different interfering ions with CHEMFETs that have mobile receptor molecules in the hydrophobic membrane. The performance of K^+ -selective CHEMFETs with valinomycin (**1**) and the hemispherands **4** and **5a** is given in Fig. 4.

Similar responses were obtained with the calix[4]arene crown ethers (**6a–d**). The experimentally determined $\log K_{ij}^{Pot}$ values depend on the structure of **6**. The conformationally mobile 1,3-dimethoxy derivative **6a** ($\log K_{ij}^{Pot} \sim -2.7$) is more selective than the fixed cone 1,3-diethoxy conformer **6b** ($\log K_{ij}^{Pot} \sim -2.0$), and the 1,3-alternate 1,3-diethoxy conformer **6d** ($\log K_{ij}^{Pot} \sim -2.5$), but the preorganized and fixed 1,3-diethoxy

Fig. 4. K^+ responses of CHEMFETs with different receptors and a siloprene membrane (0.1 M NaCl).

Fig. 5. Na⁺ response of a calix[4]arene based CHEMFET.

partial cone conformer **6c** ($\log K_{ij}^{\text{Pot}} \sim -2.9$) exhibits the largest selectivity. These data agree well with the experimentally determined differences in the free energy of complexation in chloroform [17] (*vide supra*). The Na⁺ response of CHEMFETs in which the calix[4]arene (**7a**) is present with different interfering ions is given in Fig. 5. The $\log K_{ij}$ value K⁺/Na⁺ of -1.9 is among the highest reported for ISEs, moreover the interference of Ca²⁺ is reduced in comparison with acyclic amide ligands.

Similarly we have measured the effect of different Ag⁺ concentrations in the presence of Cd²⁺, Cu²⁺, Ca²⁺ and K⁺. The $\log K_{ij}$ values are -2.8 (K⁺) and ≤ -3.6 for the other interfering ions.

Covalently bound receptor molecules

The hemispherand **5b** was synthesized for the covalent attachment of the receptor for K⁺ to a polysiloxane membrane composed of three building blocks: dimethyl-, (3-cyanopropyl)methyl- and (methacryloxypropyl)methylsiloxane. The crosslinking of the polysiloxane copolymer was achieved by irradiation with UV light. A schematic representation of the ultimate copolymer is given in Fig. 6. We have used a copolymer that contains 2.8% cyanopropyl and 1.4% methacrylate groups. The CHEMFETs used contain 50 mol.% KB(4-C₆H₂Cl₄) relative to the receptor molecule. After photopolymerization we observed small crystallites inside the membrane. CHEMFETs with the methacrylate modified hemispherand showed a K⁺ response of 52–56 mV/pK. The selectivity coefficients ($\log K_{ij}$) were -3.0 for Na⁺ and -3.3 for Ca²⁺. Only relative to NH₄⁺ is the selectivity modest ($\log K_{ij}^{\text{Pot}} \sim 0.8$) (Fig. 7).

Fig. 6. Schematic representation of the sensing membrane after crosslinking with **5b**.

Under practical conditions, in a flow cell (3 ml/min), we have carried out the comparative study in which the long-term performance of CHEMFETs with **5a** and CHEMFETs with the covalently linked **5b** were evaluated. Whereas the response of the former deteriorated to ~ 10 mV/decade after 4 weeks, the CHEMFETs with the covalently linked **5b** had a more or less constant response of 50 mV/decade over a period of 1–20 weeks. Even after 200 days the CHEMFETs function well under laboratory conditions. Although it is difficult to prove that no free receptor is present in the case of **5b** it is very likely that this long-term durability

Fig. 7. K⁺ response of the chemically bound receptor **5b**.

Fig. 8. Ca^{2+} response of the chemically bound bis(amide) 8.

is due to the covalent attachment. When covalent attachment is used, the lipophilicity of the receptor is no longer important. Therefore a functionalized derivative of the commercial Ca^{2+} ionophore has been synthesized and incorporated in the polysiloxane membrane. The performance of this CHEMFET is given in Fig. 8.

Conclusions

The data presented in this paper confirm that by a systematic study of the requirements of CHEMFETs it is possible to develop a system with an architecture that gives long-term stability. The covalent attachment of the membranes, both hydrophilic and hydrophobic, improves the stability of the chemical system. The polyHEMA interlayer solves the problem of the ill-defined gate oxide-membrane interface and the polysiloxanes eliminate the necessity of solvent mediators. Our tentative conclusion is that covalent attachment of the receptor does not inhibit the fast response of the sensor. It is obvious that the durability is improved by covalent linkage of the receptor molecules.

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