Chapter 16

Molecular Materials for the Transduction of Chemical Information into Electronic Signals by Chemical Field-Effect Transistors

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Synthetic receptor molecules such as crown ethers, hemispherands and calix[4]crown ethers complex selectively with cations. These complexation reactions are kinetically fast and reversible. This offers the possibility to use these processes to store chemical information. Field effect transistors (FETs) are attractive transducing devices because they are able to register and amplify chemical changes at the gate oxide surface of the semiconductor chip. Integration of synthetic receptor molecules and FETs into a defined chemical system allows the transduction of chemical information into an electronic signal. Surface silylation of the gate oxide of the FET and subsequent chemical attachment of polymer films reduces the original pH sensitivity of the FET and incorporation of receptor molecules in these films induces a specific sensitivity to a particular cationic species. The stability of the response of the FET is greatly enhanced by application of an intermediate polyhydroxyethyl methacrylate (polyHEMA) layer.

Different materials for the hydrophobic membrane in which the receptor is incorporated, have been investigated. Polysiloxanes that have the required glass transition temperature and dielectric constant provide a stable chemical system that transduces the complexation of cationic species into electronic signals. The material properties can be optimized by copolymerization of three building blocks *viz.* dimethyl-, (3-cyanopropyl)methyl-, and methacryloxypropylmethyl siloxane. CHEMFETs made with this terpolymer have fast response times (≤ 1 sec.). With valinomycin and hemispherands (2) and (3) linear responses to changing K^+ concentrations are obtained in the range 10^{-5} - 1.0M (55-58 mV/decade) in a solution of 0.1M NaCl. Similar devices specific for Na^+ and Ca^{2+} have been obtained with other ionophores.

Almost from the beginning (1) of "host-guest" (2) or "supramolecular" (3) chemistry, this field has been associated with possible technological applications. The fact that molecular recognition can be achieved by systematic variation of the structure of the receptor molecule offers almost unlimited possibilities to design selective receptors. However, the technological application not only requires the selective receptor but also the translation of a molecular into a macroscopic property. Our work involves both the synthesis of molecular receptors (4-8) and their applications e.g. in membrane transport (9), medicine (10), optical (11) and electronic (12) sensors.

In this chapter our work is described that deals with the development of chemically modified Field Effect Transistors (CHEMFETs) that are able to transduce chemical information from an aqueous solution directly into electronic signals. The emphasis of this part of our work will be on the materials that are required for the attachment of synthetic receptor molecules to the gate oxide surface of the Field Effect Transistor. In addition the integration of all individual components into one defined chemical system will be described. Finally, several examples of cation selective sensors that have resulted from our work will be presented.

Ion Sensitive Field Effect Transistors (ISFETs)

A field effect transistor (FET) measures the conductance of a semiconductor as a function of an electrical field perpendicular to the gate oxide surface (13). When the gate oxide contacts an aqueous solution a change of pH will change the SiO_2 surface potential ψ . A site-dissociation model describes the signal transduction, a function of the state of ionization of the amphoteric surface SiOH groups (14). Typical pH responses measured with SiO_2 ISFETs are 37-40 mV/pH unit (15). Our choice for an Ion Sensitive Field Effect Transistor (ISFET) as a transducing element was based on the fact that the SiO_2 surface contains reactive SiOH groups for the covalent attachment of organic molecules and polymers. In addition the FET has fast response times and can be made very small with existing planar IC technology. **FIGURE 1**

Chemical Modification of the SiO_2 Oxide Surface

For chemical attachment of polymer films the gate SiO_2 surface was first silylated with either 3-(trimethoxysilyl)propyl methacrylate or 3-(triethoxysilyl)propylamine. The methacrylate modified surface was subsequently reacted with vinyl monomers (or prepolymers) and the amino groups, resulting from the reaction with 3-(triethoxysilyl)propylamine with isocyanato groups of polyurethanes.

The modified FETs were tested for their pH response and stability in contact with aqueous solutions. For comparison a physically attached polymer (VE) was included in these experiments (16). The results given in Figure 2 show that the pH sensitivity can be eliminated almost completely with acrylate polymers (ACE), polybutadiene (PBD) and also with the physically attached VE polymer. The latter, however, is not stable in time and a pH sensitivity similar to the untreated SiO_2 gate oxide returns after 5 days. The structures of the polymers are given in Scheme 1.

Figure 1. Schematic drawings of a MOSFET and an ISFET structure

Figure 2. pH-dependence of modified ISFETs

Scheme 1. Structures of monomers used for polymerization

In principle such a chemically modified polyACE FET can be used as a reference FET (REFET) in differential measurements. This requires not only that the pH sensitivity is eliminated but also that a REFET should be insensitive to changes in ionic strength. In principle we can distinguish between two types of REFETs, that differ in the penetration to ions into the polymer layer. In a non-ion blocking REFET there will be ion exchange between the solution and the membrane and the resulting electrical potential is a membrane potential. In an ion-blocking REFET structure, there is a negligible ion exchange and the measured potential is a surface potential which results from reversible ion complexation reactions of the interface. We have measured the electrical relaxation by means of transconductance measurement, bulk modulation and light pulse response (17). These experiments revealed that polyACE REFETs is a non-ion blocking structure with electrical relaxation times of 0.37 ± 0.03 s (18). Because of this non-ion blocking nature it was not unexpected that polyACE REFETs exhibit an undesirable cation permselectivity (see Figure 3).

This permselective behaviour, also observed for most polymeric membranes that are used in ion selective electrodes e.g. PVC (19), may have two origins. A much lower mobility of anions compared with cations may give rise to a diffusion potential. Alternatively, immobile anionic sites in the membrane may influence the concentrations of exchangeable cations in the membrane, which would give rise to a boundary potential. We have been able to eliminate the cation permselectivity for a great deal by the addition of various amounts of lipophilic cations (didodecyldimethylammonium bromide, DDMAB). The initially high permselectivity of the poly ACE membrane (curve 1, Figure 3) changes upon the addition of $2 \cdot 10^{-5}$ mol DDMAB. g^{-1} ACE) to give an almost complete insensitivity towards the K^+ concentration (curve 2). At higher DDMAB concentrations the REFET behaviour changes to that of an anion sensitive ISFET (curve 3).

Although our results show that a complete elimination of the sensitivity of such REFETs can be achieved, in a number of situations the combination of a pH sensitive ISFET and an ACE REFET can be used to measure pH values with an integrated FET device (Figure 4). An example of a differential measurement with a Ta_2O_5 ISFET/REFET combination is given in Figure 5.

Ion Sensitive FETs (CHEMFETs)

FETs that can transduce other than simple protonation/deprotonation reactions have been reported in the literature. In 1975 Moss et al (20) described an ISFET that has a PVC membrane *physically* attached to the gate oxide of an SiO_2 FET in which valinomycin was introduced to obtain a K^+ sensitive device. Although a response to variations in K^+ concentrations was observed there are some serious drawbacks that until now have prevented that such devices can compete with or even replace conventional Ion Sensitive Electrodes. Firstly, the physical

Figure 3. Permeability of an ACE modified FET

Figure 4. Differential measurement set-up

Figure 5. Differential measurement of a Ta_2O_5 ISFET/ACE REFET

attachment is not sufficiently stable in aqueous solutions and electroactive components leach out of the membrane. Secondly, the pH sensitivity is not completely eliminated, this leads among others to interference by CO₂ (21). However, the most serious fundamental problem is the fact that the interface between the gate oxide and the organic matrix is not defined in terms of common species. In the case of the pH sensitive ISFET this potential is thermodynamically defined by the (de)protonation equilibrium of the silanol surface groups.

In order to solve this problem we have introduced a chemically anchored polyhydroxyethyl methacrylate (polyHEMA) layer between the gate oxide and the polymer membrane that will contain the ion specific receptor molecules. Schematically this is depicted in Figure 6.

The polyHEMA layer can be buffered and the constant pH determines the potential at the gate oxide via the (de)protonation equilibrium *and keeps it at a constant value*. Besides it eliminates CO₂ interference as we could demonstrate experimentally.

The beneficial effect of the buffered polyHEMA layer on the stability of the response, even when the polymer membrane containing the valinomycin is only physically attached to this intermediate layer, is obvious. A comparison of the noise levels of systems with and without polyHEMA, given as peak-to-peak voltages (V_{pp}), is presented in Table 1.

New Materials for CHEMFETs

It is obvious that a PVC membrane can not fulfill the requirement of longterm stability because it can not be linked covalently to the polyHEMA layer and electroactive components or receptor molecules can not be covalently attached. From the work on Ion Selective Electrodes several general features for the design of membrane materials can be defined:

- i) The glass transition temperature must be low ($\leq 0^\circ\text{C}$); current materials use additional external solvent mediators.
- ii) For cation permselectivity anionic sites e.g. tetraphenyl borates must be present. These compounds also reduce the membrane resistance.
- iii) The membrane must be hydrophobic.

If we want to apply these materials on ISFETs in addition the membrane materials should allow covalent attachment to polyHEMA, receptor molecules, and anionic sites.

We have investigated both (meth)acrylates and polysiloxanes. The first show excellent REFET properties and the latter can be synthesized in different compositions (vide infra).

All acrylate- and methacrylate-based membranes were synthesized by photopolymerization on top of the polyHEMA interlayer. The resulting FETs showed in the absence of an ionophore a cation response of 36-54 mV/decade and therefore we concluded that residual anionic groups must be present. Titration of the ACE monomer with KOH solution indicated the presence of 7.5×10^{-5} eq. acid.g⁻¹ ACE monomer. As shown in Table 2 the ACE was chemically modified by reaction of the hydroxyl group. In this way acetyl, pentanoyl, and hydroxy

Figure 6. Schematic representation of a polyHEMA CHEMFET

Table 1. Noise level (V_{pp}) of modified CHEMFETS (0.1 M KCl)

Hydrophobic membrane	V_{pp} (mV)	
	Without polyHEMA/KCl (± 0.01)	With polyHEMA/KCl (± 0.005)
PVC ^a	0.10	0.030
ACE/Epocryl ^b	>10	0.020
Siloprene ^c	0.50	0.030
Silicone rubber ^d	0.20	0.040

^a PVC-DOS/Valinomycin
^b Polyacrylate/Valinomycin
^c Siloprene (Fluka)/Valinomycin
^d Dow Corning RTV3140/Valinomycin

hexanoyl ACE were synthesized. When valinomycin was introduced in these membranes we observed in all cases a sub-Nernstian response *and no K⁺ selectivity*. We are unable to explain this unexpected behaviour.

Polysiloxanes (Scheme 2) can be obtained from commercially available starting materials. Three different types were investigated (22) viz. the addition type Wacker RTV-ME 625 and the condensation types Dow Corning 3140 RTV and Silopren (Bayer). These siloxanes form polymeric membranes by addition or

polycondensation. In contrast to the (meth)acrylates it was not necessary to introduce a polyHEMA interlayer to obtain electrically stable CHEMFETs, although such a layer has a positive effect on the reduction of the noise level of the output signal. The Wacker RTV-ME 625 is a two-component addition-type silicone rubber which is cured via the addition of SiH groups to vinyl groups under the influence of a platinum catalyst. Dow Corning 3140 RTV undergoes polycondensation by the uptake of water from the atmosphere catalyzed by a titanium catalyst. The Bayer Silopren material undergoes polycondensation in the presence of an organotin catalyst and its use in ISEs has been described (23). The CHEMFETs with these materials all exhibited K⁺ selective responses. Optimal results were obtained with Silopren and either valinomycin (1) or hemispherands (2) and (3) as the ionophore (Figure 7).

Continuous immersion of these CHEMFETs in aqueous solution for 8 weeks showed only a minor decrease in the slope to 54 mV.(pK⁺)⁻¹. This surprising stability might be due to the bond formation of the membrane between the silanol groups and the gate oxide.

Photopolymerizable Siloxanes

The positive results with the polysiloxanes as membrane materials directly deposited on the gate oxide led us to investigate these materials for our ultimate chemical system for the transduction of complexation reactions by FETs. This work is comprised of two parts viz. the synthesis of photopolymerizable siloxanes that can be covalently attached to the polyHEMA intermediate layer and the synthesis of receptor molecules that are selective for K⁺ which can be covalently incorporated in these membrane materials. For the deposition of the membranes on wafer scale via IC compatible technology, photochemical processes are a prerequisite.

In order to meet the requirements of T_g, dielectric constant, and covalent anchoring random terpolymers have been synthesized by emulsion polymerization of octamethylcyclotetrasiloxane, a mixture of trimer and tetramer of (3-cyanopropyl)methylcyclodisiloxanes, and methacryloxypropylmethyldichlorosilane (Scheme 3). In order to optimize the properties of the resulting polysiloxane the ratio of the three reagents have been varied. An increasing amount of the cyanopropyl group will increase the dielectric constant of the membrane, and increasing the methacryl group percentage enhances the T_g. The optimal composition for a

Table 2. Effect of polymeric membrane composition on the K^+ sensitivity of CHEMFETs containing valinomycin

Polymer	Plasticizer ^a	Lipophilic salt ^b	K^+ -sensitivity (mV/dec)
ACE	-	-	44
ACE	DBP (50 wt%)	-	48
ACE/Epocryl (1:1)	DBP (67 wt%)	-	36
ACE	Oct (50 wt%)	-	54
HydroxypentanoylACE	-	-	45
AcetylACE	-	-	45
PentanoylACE	-	-	45
ACE	-	KB(PhCl) ₄	44
ACE	-	KDNNS	45

a) DBP: dibutylphthalate; Oct: Octanol

b) KB(PhCl)₄: potassium tetrakis(4-chlorophenyl)borate;

KDNNS: potassium dinonylnaphthalene sulphonate

A. Addition type cure reaction; Wacker RTV ME 625; R = methyl

B. Condensation type cure reaction

i) Dow Corning 3140 RTV: R = R' = R'' = methyl; water from the air and a titanium catalyst are needed

ii) Bayer Silopren: R = methyl, R' = H, R'' = ethyl; an organotin catalyst is used

Scheme 2. Polysiloxane synthesis

Figure 7. K^+ response of silopren modified CHEMFETs

membrane that selectively detects monovalent cations has a ratio of 10:1:2. The materials were cross-linked by irradiation in the presence of 4 wt-% of 2,2-dimethoxy-2-phenylacetophenone.

For the synthesis of a photopolymerizable receptor molecule that has a high selectivity for K^+ , we have modified the hemispherand synthesis according to Scheme 4. The final polymer membrane is represented by Figure 8. The response to a variation in K^+ concentration (10^{-5} - 10^{-1} M) in the presence of 0.1 M NaCl is given in Figure 9. The potentiometric selectivities ($\log K_{ij}$) determined by the mixed solution method are -3.0 (Na^+), -3.5 (Ca^{2+}), -4.0 (Mg^{2+}), and -0.7 (NH_4^+). This renders this CHEMFET an excellent K^+ -sensor with a longterm stability (≥ 100 days).

Impedance Spectroscopy Measurements of Silicone Rubber Membranes

For the characterization of the polysiloxane membranes we have measured the impedance spectra in the presence of different concentrations of cations. Both valinomycin (1) and the two different hemispherands (2 and 3) have been incorporated in these membranes. Buck et al (24, 25) have shown that this technique allows to separate the surface exchange rates and the rates of bulk transport. The copolymer described above containing valinomycin initially has a very high resistance but after several days conditioning in a 0.1 M KCl solution the resistance is the same as that of a similar membrane to which $KB(4-ClC_6H_4)_4$ was added.

Also the final dielectric constants of both membranes are similar. This indicates that the final amount of charge carriers hardly differs and the contributions of the lipophilic anion to the membrane conductance is of the same order as of the chloride anion. Membranes with the hemispherand, either free or covalently attached, have about the same resistance. Because at the low frequency part of the impedance spectra a slight distortion was observed with the hemispherands, kinetic measurements were carried out with the valinomycin containing membrane.

When exposed to NaCl and KCl solutions the membrane shows an interesting behaviour. The impedance spectrum of a membrane conditioned in KCl shows an ideal semicircle, but when exposed to an NaCl solution the spectrum changes to a flattened semicircle, indicating an extra resistance term. In time this second contribution increased which means that the membrane resistance grows larger when the electrolyte is changed from KCl to NaCl. It was observed that the change in the spectrum is less pronounced when the membrane is exposed to low concentrations of NaCl (10^{-3} - 10^{-4} M). Obviously the ion exchange is faster at higher concentration.

The influence of the membrane selectivity on the resistance could nicely be demonstrated in a series of experiments with mixed electrolyte solutions. The NaCl concentration was maintained at 0.1 M and the KCl concentration was varied from 0.1 M to 10^{-6} M. In the concentration range 0.1- 10^{-4} M KCl there is virtually no change in the spectra but at 10^{-5} M KCl there is a small change which becomes very prominent at 10^{-6} M KCl. Experiments starting from a low

Scheme 3. Synthesis of a photopolymerizable polysiloxane

Scheme 4. Synthesis of a photopolymerizable ionophore

Figure 8. Schematic representation of the sensing membrane after photopolymerization

Figure 9. K^+ -response of a chemically bound ionophore

Figure 10. Flow injection analysis

concentration of KCl to 0.1 M KCl show the reversal of the events. These experiments show that the potassium/sodium ion exchange starts when the concentration ratio is of the same order as the potentiometric selectivity coefficient $\log K(K^+/Na^+) \approx -4.0$.

The Application of K^+ -Selective CHEMFETs in Flow-Injection Analysis

Flow-injection analysis is a versatile technique to evaluate the performance of a detector system. CHEMFETs may have an advantage over ISEs because of their small size and fast response times. We have tested our K^+ -sensitive CHEMFETs in a wall-jet cell with a platinum (pseudo-)reference electrode. One CHEMFET was continuously exposed to 0.1 M NaCl and the other to a carrier stream of 0.1 M NaCl in which various KCl concentrations in 0.1 M NaCl were injected. The linear response of 56 mV per decade was observed for concentrations of KCl above 5×10^{-5} M (Figure 9). When we used this FIA cell (Figure 10) for determination of K^+ activities in human serum and urine samples, excellent correlations between our results and activities determined by flame photometry were obtained (Figure 11).

CHEMFETs for Ca^{2+} and Na^+

Now we have developed the technology for making CHEMFETs we can extend our synthetic work on selective molecular receptors. The first targets are CHEM-

Figure 11. Correlation of FIA measurements with flame photometry (K^+ in human serum and urine samples)

FETS for the selective detection of Ca^{2+} and Na^+ . The receptor molecules are a modified bisamide (4) and a tetra-0-alkylated calix[4]arene (5).

The Ca^{2+} CHEMFET exhibits a linear response (10^{-5} - 10^{-1} M) with potentiometric selectivities of ≤ -2.6 (Na^+), ≤ -2.6 (K^+), < -3.7 (Mg^{2+}) and < -2.6 (NH_4^+). The Na^+ CHEMFET shows selectivities of ≤ -1.9 (K^+), ≤ -2.5 (Li^+), ≤ -3.0 (Pb^+) and ≤ -3.5 (Ca^{2+}). Currently we are investigating the selective detection of anions and transition metal cations.

Summary and Conclusions

We have shown that molecular recognition by synthetic receptor molecules can be transduced into electronic signals when these receptor molecules are incorporated in a polymer membrane that is covalently attached to the gate oxide of a Field Effect Transistor.

The properties of the membrane are critical and novel terpolymer siloxanes have been developed. High ion selectivities have been found for K^+ , Na^+ , and Ca^{2+} cation responses.

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