

A novel architecture for CHEMFETs; the integration of sensing molecules and membranes

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Summary

In supramolecular chemistry receptor molecules are designed and synthesized for the selective recognition of cations. These complexation reactions are the first step in chemical sensing. Field effect transistors (FETs) are attractive transducing elements because they are able to translate this selective recognition process into an electronic signal. A new architecture for CHEMFETs is developed in which a hydrophilic poly HEMA hydrogel is covalently attached between the gate oxide surface of the FET and the hydrophobic sensing membrane that contains the receptor molecules. Each of these layers can be covalently linked to the underlying layer by UV-polymerizable groups. Therefore different materials for the hydrophobic sensing membrane have been investigated. The optimized material for the sensing membrane is a terpolymer of different siloxanes. A potassium selective hemispherand which is covalently attached to this polymer shows a fast and prolonged CHEMFET response (>200 days). The sensing molecules can also be present as mobile hydrophobic species, in which case also a durable sensor can be obtained. Typical examples of such receptors are calix[4]arene crown ethers for K^+ and tetra-O-alkylated calix[4]arenes in the cone conformation for Na^+ , Ag^+ , or Pb^{2+} . A fast and dynamic measurement technique of these CHEMFETs is flow injection analysis. In the flow cells described, two identical CHEMFETs are used in a differential measurement set-up. The concentrations of potassium in human serum and urine samples measured by the FIA-CHEMFET combination agree well with the values obtained by flame photometry.

Zusammenfassung

In der Supramolekularchemie werden Rezeptormoleküle für die selektive Erkennung von Kationen entwickelt und synthetisiert. Diese Komplexbildungsreaktionen sind der erste Schritt in der chemischen Abföhlung. Feldeffekttransistoren (FET) sind attraktive Umformungselemente, weil sie in der Lage sind, diesen selektiven Erkennungsprozeß in ein elektronisches Signal zu übersetzen. Für CHEMFET wird eine neue Architektur entwickelt, bei der hydrophiles Poly-HEMA-Hydrogel kovalent zwischen der Gate-Oxidfläche des FET und der hydrophoben Abföhlmembran gebunden ist, die die Rezeptormoleküle enthält. Jede dieser Schichten kann durch UV-polymerisierbare Gruppen kovalent mit der darunter liegenden Schicht verbunden werden. Deshalb wurden verschiedene Materialien für die hydrophobe Abföhlmembran untersucht. Das optimierte Material für die Abföhlmembran ist ein Terpolymer verschiedener Siloxane. Eine kaliumselektive Halbkugel, die kovalent mit diesem Polymer verbunden ist, zeigt eine schnelle und verlängerte CHEMFET-Reaktion (> 200 Tage). Die Abföhlmoleküle können ebenfalls als mobile hydrophobe Arten vorhanden sein. In diesem Fall kann ebenfalls ein dauerhafter Sensor erzielt werden. Typische Beispiele für solche Rezeptoren sind Calix(4) Aren-Kronenether für K^+ und Tetra-O-Alkyl-Calix(4) Arene in Kegelkonformation für Na^+ , Ag^+ oder Pb^{2+} . Eine schnelle und dynamische Meßmethode dieser CHEMFET ist die Fließinjektionsanalyse. In den beschriebenen Fließzellen werden zwei identische CHEMFET in einem Differentialmeßaufbau verwendet. Die Kaliumkonzentrationen in menschlichen Serum- und Urinproben, die durch die FIA-CHEMFET-Kombination gemessen werden, stimmen genau mit den durch Flammenphotometrie erzielten Werten überein.

Résumé

En chimie supramoléculaire, les molécules des récepteurs sont développées et synthétisées pour la détection sélective des cations. Ces réactions de complexation sont le premier pas accompli dans le palpage chimique. Les transistors à effet de champ (FET) sont des éléments de transduction intéressants parce qu'ils sont en mesure de convertir ce processus de détection sélectif en un signal électronique. Une nouvelle architecture est développée pour CHEMFET pour laquelle l'hydrogel poly-HEMA hydrophile est lié de manière covalente entre la surface d'oxyde Gate du FET et la membrane de palpage hydrophobe qui contient les molécules des récepteurs. Chacune de ces couches peut être liée de manière covalente avec la couche sous-jacente par des groupes à polymérisation UV. C'est la raison pour laquelle différents matériaux ont été analysés pour la membrane de palpage hydrophobe. Le matériau optimal de la membrane de palpage est un terpolymère de différents siloxanes. Une demisphère à sélectivité de potassium liée de manière covalente avec ce polymère présente une réaction CHEMFET rapide et prolongée (200 jours). Les molécules de palpage peuvent également être disponibles sous forme de genres hydrophobes mobiles. Dans ce cas, un capteur durable peut également être obtenu. Le calix(4) arène-crownéther pour K^+ et la tétra-O-alkyl-calix(4) arène en conformation conique pour Na^+ , Ag^+ ou Pb^{2+} sont des exemples typiques de ce genre de récepteurs. L'analyse d'injection de flux est une méthode de mesure rapide et dynamique de ces CHEMFET. Dans les cellules de flux décrites, deux CHEMFET identiques sont utilisés dans un dispositif de mesure différentielle. Les concentrations de potassium des échantillons de sérum et d'urine humains qui ont été mesurés par la combinaison FIA-CHEMFET correspondent exactement aux valeurs déterminées par photométrie de flamme.

1 Introduction

Chemical sensors require the integration of a sensing molecule and a transducing element. Our work

in the field of supramolecular chemistry is directed towards the design and synthesis of receptor molecules that will selectively recognize either ionic or neutral guests. Possible applications of these molecules are elaborated by us in the fields of membrane transport /1/, diagnostics /2/, optical /3/, and chemical /4/ sensing. As the transducing element in chemical sensors field effect transistors (FETs) are very interesting because of their fast response time and in situ impedance transformation. Since the introduction of an ion-sensitive field effect transistor (ISFET) chemically modified with a PVC membrane containing the natural antibiotic valinomycin (CHEMFET) /5/, some serious problems have been recognized. First of all the lack of mechanical stability of the membrane and the interference of CO₂ on the potentiometric response. Furthermore a stable micro reference electrode is not available. Thirdly, 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. Another problem is the relatively high drift rate of an ISFET. The first objectives of our work were to solve these problems and to design chemically modified field effect transistors (CHEMFETs) that are selective, exhibit a fast response, low noise level, and have prolonged lifetimes. In this paper the emphasis will be placed on the integration of the design and synthesis of sensing molecules and membranes into a novel architecture for CHEMFETs.

2 Chemically sensitive field effect transistor (CHEMFET)

The novel architecture for CHEMFETs is designed to solve the problems mentioned before. The CHEMFET we use in our research consists of a hydrophobic sensing membrane on top of an ISFET.

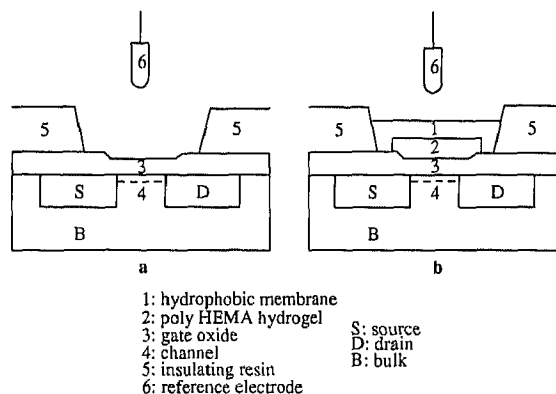


Figure 1: The architecture of the ISFET (a) and the CHEMFET (b)

The electronic operation of an ISFET resembles a metal oxide semiconductor field effect transistor (MOSFET). In case of an ISFET the metal is replaced by an aqueous solution and a reference electrode (figure 1 (a)). The ISFET /6/ consists of two n-type diffusion regions (source and drain) embedded in a p-type silicon substrate (bulk). The conductance between source and drain in the semiconductor is a function of the electrical field perpendicular to the gate oxide surface. When the gate oxide contacts an aqueous solution a change of pH will change the electronic signal /7/ as a function of the state of ionization of the amphoteric surface SiOH groups. Typical pH responses of SiO₂ ISFETs (37-40 mV/ pH unit) can be described by a site-dissociation model /8,9/.

When the ISFET is covered with an ion-selective membrane (figure 1 (b)) the developed membrane potential determines the ISFET response /4/. The extraction ability of the ionophore/membrane combination determines which ion governs the membrane potential (figure 2). This potential is related to the quotient of the free cation in the membrane and the aqueous solution. The introduction of a lipophilic anionic group and an ionophore in the membrane ensures the activity of the free cation in the membrane to be fixed. In this way there is a direct relation between the measured membrane potential and the activity of the cation in the aqueous solution.

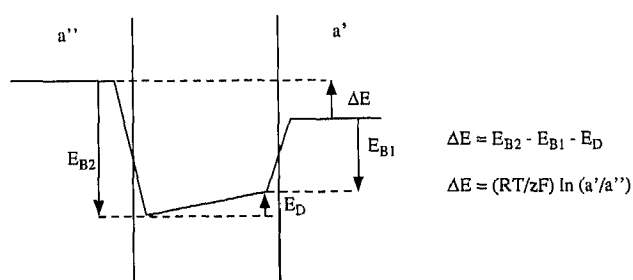


Figure 2: The principle of the membrane potential.

The contribution of interfering ions to the overall potentiometric response is given by the semi-empirical Nikolsky-Eisenmann /10/ equation:

$$E = E^{\circ} + 2.3 \times \frac{R \cdot T}{z_i \cdot F} \log \left[a_i + \sum_{j \neq i} K_{ij}^{pot} \cdot (a_j)^{z_i/z_j} \right]$$

in which E is the overall electrochemical potential, E^o is the electrochemical standard potential, RT/F are constants (x 2.3 = 59.16 mV (T=298 K)), a_i and a_j are the activities of the primary and interfering ion respectively, z_i and z_j are the charges of these ions, and K_{ij} is the potentiometric selectivity coefficient.

The attachment of such a membrane can be improved by mechanical /11/ or chemical /12,13/ anchoring to the surface of the gate oxide. For chemical attachment of polymer films the gate oxide surface is first silylated with 3-(trimethoxysilyl)propyl methacrylate (figure 3).

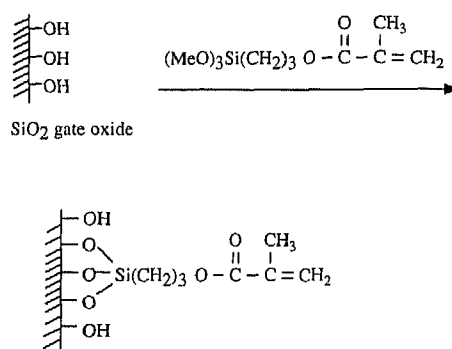


Figure 3: Surface silylation of silicon dioxide ISFETs.

The methacrylate modified surface can subsequently react with vinyl or methacryl monomers or prepolymers. The use of uv-photopolymerizable monomers is advantageous in view of the ultimately desired mass production of the CHEMFETs. The hydrophilic hydroxy ethyl methacrylate can be applied at wafer scale only on top of the gate oxide (figure 4) by use of a so-called mask-aligner /14/.

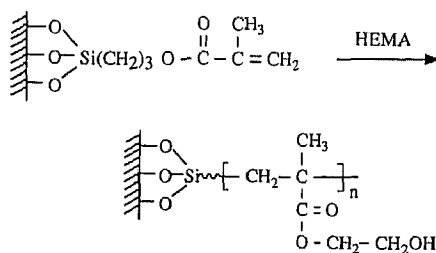


Figure 4: Covalent linking of p-HEMA on methacryl-modified ISFETs by photopolymerization.

The introduction of such a buffered hydrogel layer /14,15/ inbetween the gate oxide and the sensing membrane eliminates the interference of CO_2 on the CHEMFET response and stabilizes the potential developed in the sensing membrane. Plasticized PVC membranes that contain the ionophore are widely used as a sensing membrane. Leakage of plasticizer to the contacting aqueous solution and bad adhesion of the membrane to the ISFET prompted the search for other polymer membranes /12,15,16/ like polyurethane, silicone rubber, polystyrene, polyamide, and several polyacrylates. From this work several general features for the design of membrane materials can be defined:

- 1 The glass transition temperature (T_g) must be low ($\leq 0^\circ\text{C}$); current materials like PVC use an additional external solvent mediator (plasticizer).
- 2 For cation permselectivity anionic sites e.g. tetraphenyl borates must be present. These compounds also reduce the membrane resistance.
- 3 The membrane must be hydrophobic.

In the development of a durable potassium selective sensor /17/ good results are obtained with copolymers of differently substituted siloxanes which meet the above requirements. Random terpolymers have been synthesized by emulsion polymerization of octamethylcyclotetrasiloxane, a mixture of trimer and tetramer of (3-cyanopropyl)methylcyclotrisiloxanes, and methacryloxypropyl-methyldichlorosilane (figure 5).

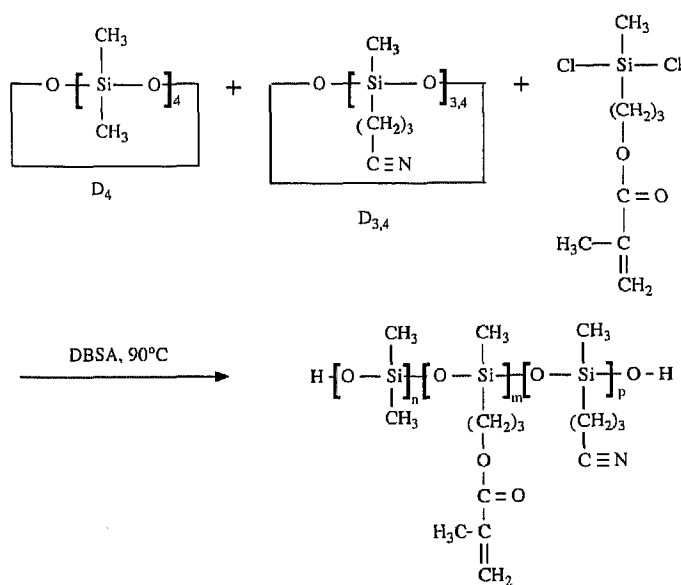


Figure 5: Synthesis of siloxane terpolymer.

The ratio between the three reagents can be varied in order to optimize the properties of the resulting polysiloxane. With the amount of cyanopropyl groups present it is possible to tune the polarity of the hydrophobic membrane to the primary ion to be detected.

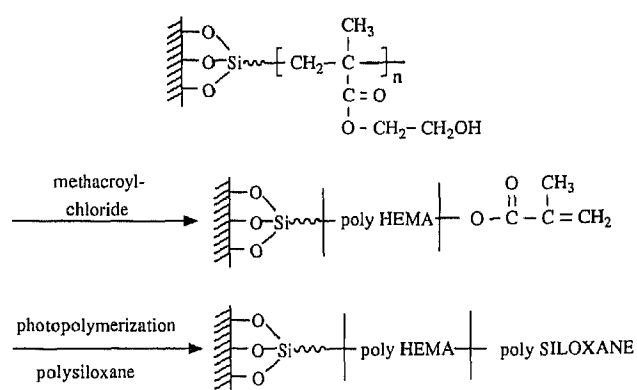


Figure 6: Methacrylation of the p-HEMA surface and covalent attachment of the polysiloxane sensing membrane.

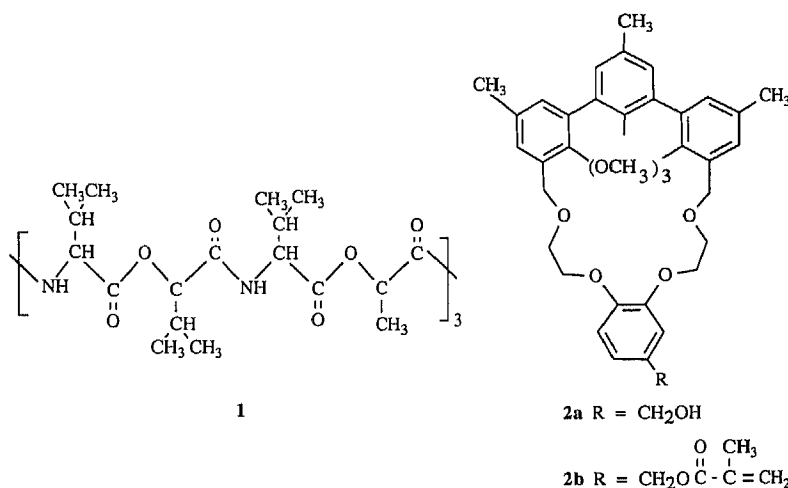
The methacryl group enables, after methacrylation of the hydrophilic poly-HEMA surface, covalent attachment of the hydrophobic sensing membrane to the hydrophilic poly-HEMA hydrogel. In this way a sensor concept is developed in which each membrane can be covalently linked onto the underlying layer.

Another improvement is to circumvent the lack of a stable micro reference electrode by combining a reference FET (REFET) and a CHEMFET (or two CHEMFETs) in a differential measurement with respect to a (pseudo-)reference electrode /18-21/. One of the remaining problems, the relatively high drift rate of ISFETs, is less important when CHEMFETs are used in flow systems, which is the subject of the last section in this paper.

3 Integration of sensing molecules and membranes

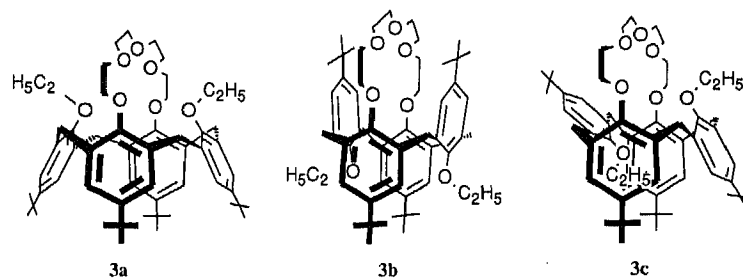
Although the natural antibiotic valinomycin (scheme 1) exhibits a very high selectivity for K^+

relative to Na^+ , it has limited possibilities for chemical modification. The work on selective receptors for potassium is based on the concept of preorganization of the ligating oxygen atoms. When this conformational freedom is restricted by the incorporation of rigid terphenyl units /22/ the K^+ / Na^+ selectivity increases /23/. The degree of preorganization and the ringsize of these hemispherands is reflected in their selectivities (K^+/Na^+) with the highest selectivity of nearly 1000. One of these hemispherands (scheme 1) has an additional functional group suitable for chemical modification or covalent binding to a hydrophobic membrane /24/.



Scheme 1: Chemical structure of valinomycin 1 and a hemispherand 2.

After covalent attachment of this hemispherand **2b** in the polysiloxane membrane the performance of the CHEMFET was evaluated. The CHEMFET showed a Nernstian response (52-56 mV) towards potassium ions. The selectivity coefficients ($\log K_{ij}$) were for Na^+ -3.0, for Mg^{2+} -4.0, and for Ca^{2+} -3.5. Only towards NH_4^+ the selectivity is modest ($\log K_{ij} \sim -0.8$). The longterm response of the CHEMFETs without the chemically linked ionophore deteriorated after four weeks under practical conditions in a flow cell. However, the CHEMFETs with the covalently bound receptor had a more or less constant response over a period of 1-20 weeks. Although it is hard to prove that all the ionophore is chemically bound to the polymeric membrane the longterm stability of these CHEMFETs indicates the covalent attachment of the receptor molecule.



Scheme 2: Chemical structure of the three possible conformations of the calix[4]arene crown ether: cone (3a), 1,3-alternate (3b), and partial cone (3c).

Another approach is the use of receptors which are not covalently attached to the membrane but which have an increased hydrophobicity like the potassium selective calix[4]arene crown ethers. The calix[4]arene building block is easily accessible /25/ and increases the hydrophobicity of the receptor.

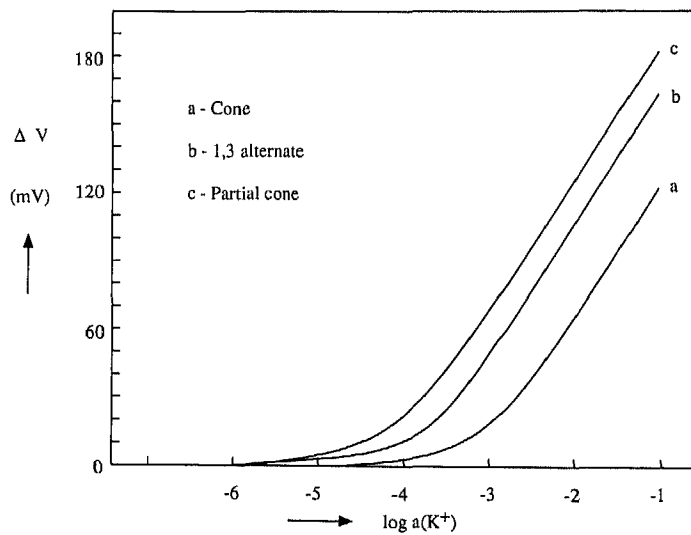
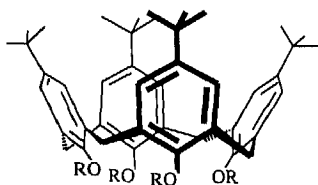


Figure 7: CHEMFET response of the three conformations of the potassium selective calix[4]arene crown ether

Different selective chemical modification of the four oxygen atoms present forms a disubstituted calix[4]arene crown ether (scheme 2: 3) which has a molecular cavity that is complementary with the size of a potassium cation /26/. The diametrical ethoxy substituents of this calix[4]arene crown ether cannot rotate through the annulus of the calix[4]arene moiety because of steric hindrance. Therefore we obtained in the synthesis three different conformers, the cone (3a), 1,3-alternate (3b), and partial cone (3c), as stable isomers. This systematic synthetic study revealed that a further improvement of the K^+/Na^+ selectivity was obtained by increasing the preorganization of the ionophore in the optimal complexing conformation. The experimentally determined K^+/Na^+ selectivity of the plasticized PVC membrane based CHEMFETs in which this ionophore is used depends therefore on its structure (figure 7). The most preorganized calix[4]arene crown ether (partial cone 3c) exhibits the largest K^+ / Na^+ selectivity ($\log K = -2.9$). Membrane transport experiments /27/ revealed that these calixcrown ethers indeed are highly lipophilic ($K_p \geq 10^5$).

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. Recently tetra-O-alkylated calix[4]arene derivatives (e.g. 4) have been reported which show selective complexation of Na^+ over K^+ ($\pm 10^2$).



- 4 R = $CH_2C(O)Ph$
 5 R = $CH_2CH_2SCH_3$
 6 R = $CH_2C(S)N(CH_3)_2$

Scheme 3: Tetra substituted calix[4]arene in the cone conformation for the selective recognition of sodium (4), silver (5), and lead (6).

For the required selective complexation it is extremely important to couple the four substituents at one face of the calix[4]arene moiety. The Na^+/K^+ selectivity of CHEMFETs in which such a calix[4]arene derivative is present ($\log K_{ij} = -1.9$) is among the highest reported for ion selective electrodes (figure 8). The selectivity coefficients ($\log K_{ij}$) were for Li^+ -2.5 and for cations like Cs^+ , Rb^+ , Ca^{2+} , and Mg^{2+} below -3.0. Again the intermediate poly-HEMA hydrogel was essential for the stability of the sensor /28/.

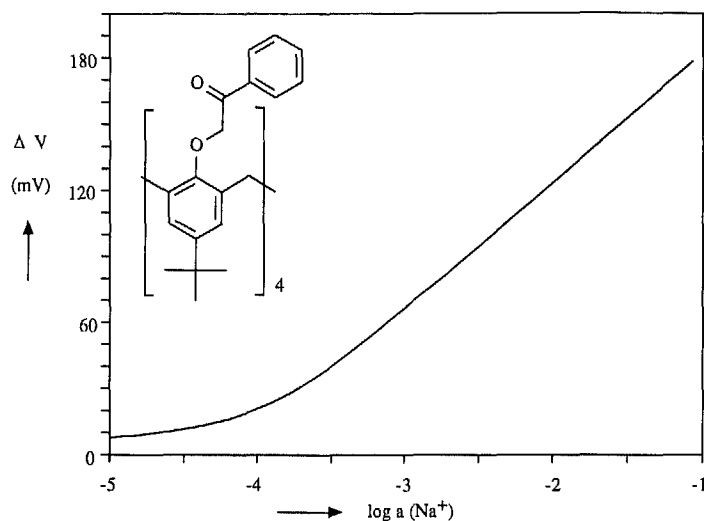


Figure 8: Response of a sodium selective CHEMFET.

Our recent investigations in the selective recognition of heavy metal ions are based on the same approach. For this purpose a number of the oxygen donor atoms are replaced by sulfur atoms for which heavy metal ions show higher affinity. So far this has led to selective complexation of silver 5 and lead 6 with tetra-O-alkylated calix[4]arenes with substituents that have thioether or thioamide groups, respectively.

The selectivity obtained with the CHEMFETs for silver ions are at least 1000 for the interfering ions like K^+ , Ca^{2+} , Cu^{2+} , Cd^{2+} . Mercury (Hg^{2+}) showed the highest interference ($\log K = -2.3$), which is of the same order of magnitude as the best ISE known so far.

The CHEMFET in which the tetrathioamide calix[4]arene 6 is incorporated, showed a response of 30 mV per decade to Pb^{2+} ions. A different CHEMFET has been reported which detects PbX^+ ($\text{X} = \text{Cl}^-$, OH^-) with a slope of 60 mV/decade /29/. The calix[4]arene CHEMFET was highly selective towards Pb^{2+} ions with respect to other mono- and divalent cations. Copper interfered most severely ($\log K_{ij} = -3.4$), towards other ions like K^+ , Ca^{2+} , and Cd^{2+} the selectivity obtained was at least 10000.

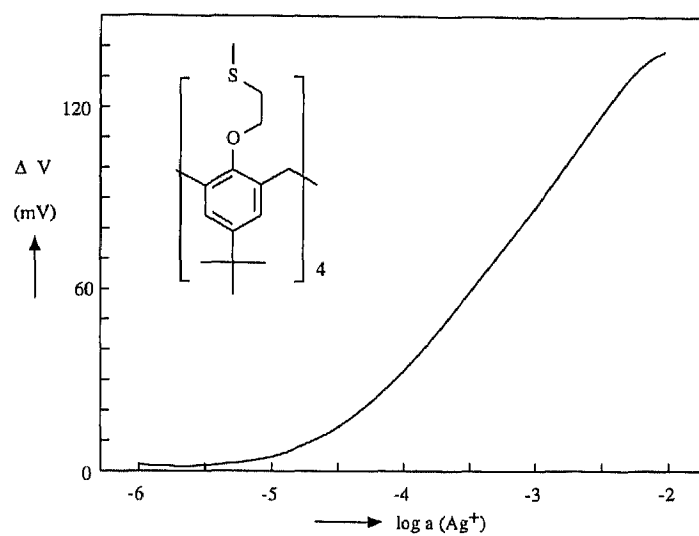


Figure 9: Response of a silver selective CHEMFET.

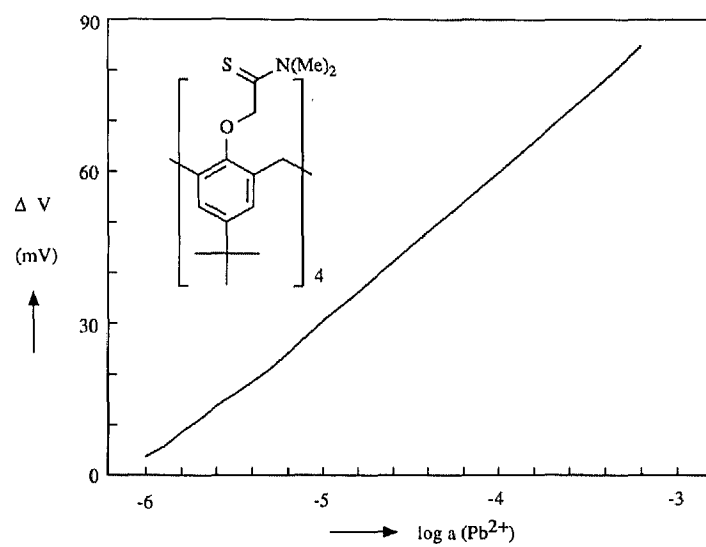


Figure 10: Response of a lead selective CHEMFET.

4 Flow injection analysis

One of the remaining problems, the relatively high drift rate of ISFETs, is less important when CHEMFETs are used in flow systems. In flow injection analysis (FIA) the sample is injected into the carrier solution which is detected by the sensor. Since its first introduction /30/ flow injection analysis has proved to be a versatile measuring technique that can enhance the performance of several detector systems. CHEMFETs are pre-eminently useful in this fast and dynamic measuring technique. We have developed a wall-jet cell /31/ in which two identical potassium selective CHEMFETs are used in a differential measurement setup. The CHEMFETs have siliconerubber membranes, chemically bound to the gate oxide with valinomycin as the ionophore.

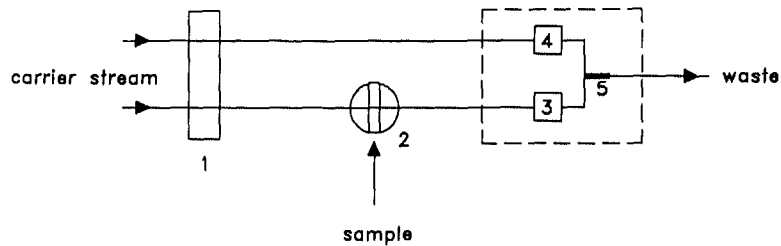


Figure 11: Schematic diagram of the flow injection system. 1, Peristaltic pump; 2, injection valve; 3 and 4, CHEMFETs; 5, (pseudo-)reference electrode.

The flow injection system is shown schematically in figure 11. A peristaltic pump (1) was used to propel the carrier stream. The sample was injected with a rotary valve (2) into one of the carrier streams. A more detailed drawing of the wall-jet cell is shown in figure 12.

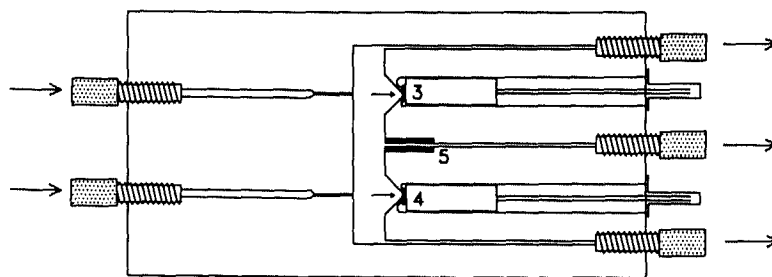


Figure 12: Detailed structure of the measuring cell.

The ISFETs (3 and 4) are positioned in the measuring cell in such a way that the gate covered with the ion-sensing membrane is placed perpendicular to the nozzle through which the carrier stream flows. The output signal of the two CHEMFETs was measured in a differential measurement set-up using a platinum tube as a pseudo reference electrode (5). The platinum tube was positioned in the central of three outlet channels. In figure 13 a calibration graph of the FIA system is shown. In a carrier stream of 0.1 M NaCl different solutions with various potassium concentrations (in 0.1 M NaCl) were injected.

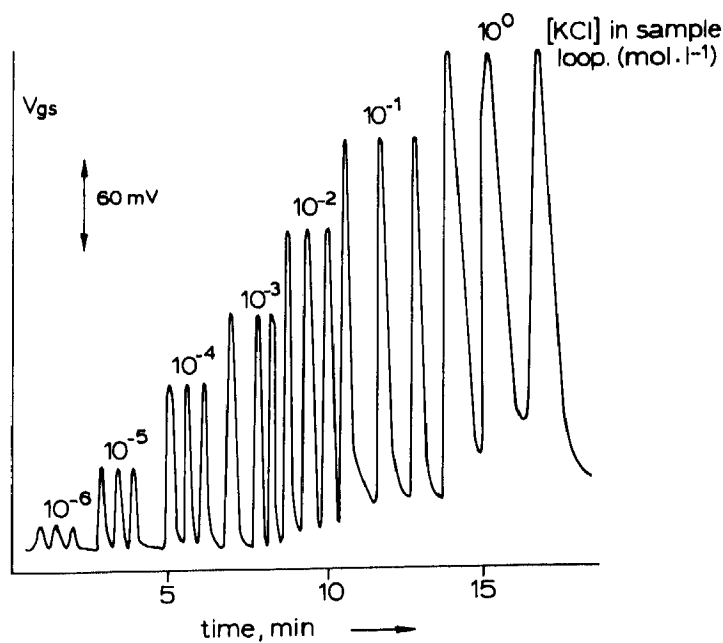


Figure 13: Strip chart recording of a calibration run. Calibrant: 10^{-6} - 10^0 M KCl in 0.1 M NaCl.

A linear response of 56 mV per decade was observed for concentrations of KCl above 5×10^{-5} M. This wall-jet cell has also been used to determine the potassium content of human serum and urine samples. The results show that the potassium concentrations measured with this FIA-CHEMFET combination are in good agreement with the values obtained by flame photometry (figure 14).

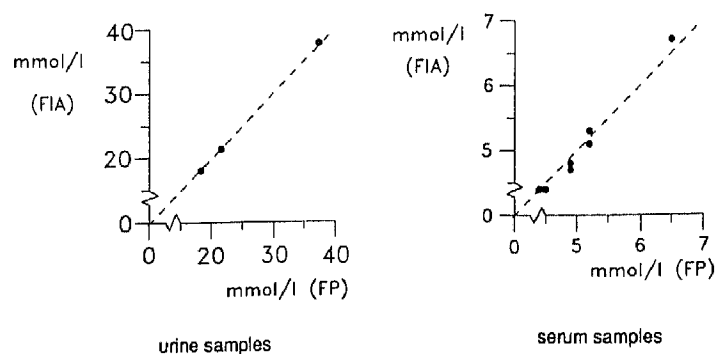


Figure 14: Correlation between K⁺ determinations with the FIA system and with flame photometry (FP) in serum samples and in urine samples.

Application of CHEMFETs in flow injection detectors brings about the difficulty of wire bonding and polymeric encapsulation. Recently we have developed flow cells in which traditional bonding and encapsulation with epoxy resin have become superfluous [32]. Valinomycin based CHEMFETs show results comparable to our earlier design.

5 conclusions

In this paper we have presented data that confirm that the new architecture of the CHEMFET is necessary to obtain a chemically stable sensor system. A novel polysiloxane material was developed to meet the requirements of the sensing membrane. In a systematic synthetic study of differently substituted calix[4]arenes new receptor molecules are obtained which are selective for K⁺, Na⁺, Ag⁺, and Pb²⁺. Flow injection analysis proved to be a fast and reliable measuring technique of these CHEMFETs.

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