

CHEMICALLY MODIFIED FIELD-EFFECT TRANSISTORS FOR MEASUREMENT OF ION ACTIVITIES IN AQUEOUS SOLUTION

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0. Abstract

Chemically modified field effect transistors for the selective detection of several cation and anion activities in aqueous solution are described. For obtaining sensors of high durability, novel polysiloxane membranes have been developed which contain different side groups to tune their intrinsic properties. These polysiloxane membranes show good performance in life time experiments. The ion selectivity has been tuned by incorporation of various novel ion receptor molecules, yielding sensors with high selectivities for sodium, potassium, lead, copper, cadmium, silver, nitrate, nitrite, fluoride, and dihydrogen phosphate.

Keywords: CHEMFET, Calixarene, Uranyl Salophene, Polysiloxane

1. Introduction

Miniaturized sensors for the (on-line) detection of low concentrations of ions in aqueous solution can find useful application in many areas, e.g. for water quality monitoring, localisation of environmental pollution and biomedical analysis. Until now such miniaturized sensor systems of sufficient stability have not been fully developed for the majority of analytes and analysis is carried out with conventional techniques like chromatography, atomic absorption and emission spectrometry and various wet analytical techniques. However, the innovative technology in semiconductor materials, micro-engineering, and molecular engineering shows great promise for the fabrication of microsensors by IC technology. Solid state pH-sensors based on ion-sensitive field effect transistors are already commercially available and it is expected that these soon will be followed by chemically modified field effect transistors capable to detect activities of other ionic species in solution.

2. Chemically modified field effect transistors

Chemically modified field effect transistors (CHEMFETs) are designed for the selective detection of ions in aqueous solution. The measurement principle of these sensors is, like for the ion selective electrode and glass electrode, based on potentiometric determination of ion activities in aqueous solution. This detection technique is particularly useful in cases where a large dynamic range of ion activities have to be measured. CHEMFETs have some important advantages compared to ion-selective membrane electrodes as fast response time, low noise level, small size and possibilities for mass production. Basically, the CHEMFET is a special modification of the ion sensitive field effect transistor (ISFET), which shows sensitivity for the activity of hydrogen ions in solution. A field effect transistor measures the

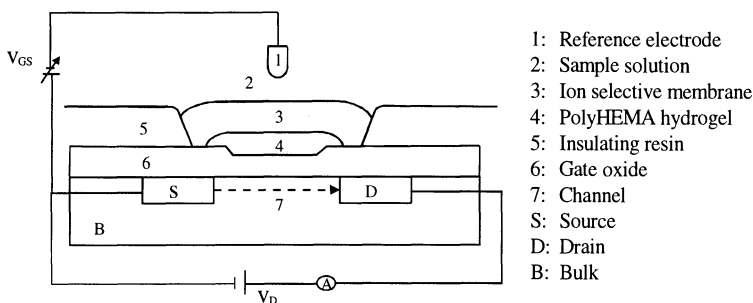
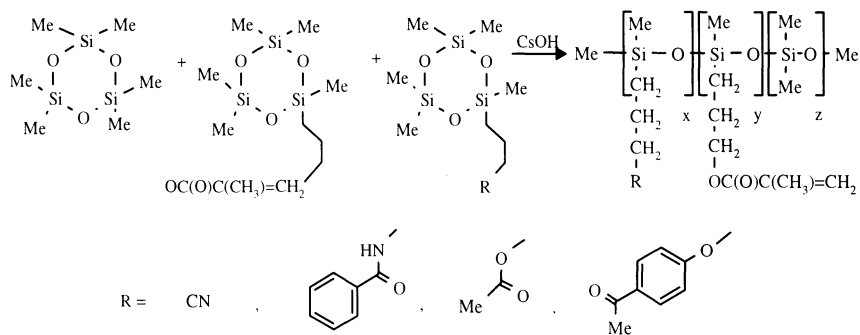


Figure 1. Schematic drawing of chemically modified field effect transistor (CHEMFET).

conductance between source and drain (the gate) of a semiconductor as a function of an electrical field perpendicular to the gate oxide surface. In contact with an aqueous solution, the state of ionisation of the surface SiOH groups of a SiO₂ gate oxide in an aqueous solution determines the surface potential and therefore the source-drain current in the transistor. A change in pH of the solution will produce a change in surface potential which can be measured by the change in conductance of the transistor. Typical pH responses thus obtained are 37-40 mV/pH unit.

For the detection of other ionic species than protons, it is necessary to introduce ion receptors which can selectively bind these species. Moreover, the intrinsic pH sensitivity caused by dissociation of the silanol groups at the gate oxide surface, has to be suppressed. Covering of the gate oxide of a silicon dioxide ISFET with a plasticized PVC membrane containing the potassium-selective natural ionophore valinomycin already gives a good potassium response upon variation of the potassium concentration. However, this construction has the severe drawback that the physical adhesion of the membrane to the semiconductor surface is not stable and that plasticizer and ionophore leach slowly from the membrane upon prolonged contact of the sensor with the aqueous solution. Moreover, such a sensor suffers from interfering pH-sensitivity (and carbon dioxide sensitivity) due to the uncontrolled ionization of the surface silanol groups of the gate oxide. The latter problem can be overcome by placing a buffered hydrogel between gate oxide and sensing membrane. We have attached a layer of polyhydroxyethylmethacrylate (polyHEMA) covalently to the gate oxide surface by photopolymerization of the monomer on the gate oxide which was pretreated with methacryloylpropyltrimethoxysilane. The methacrylated siloxane groups on the surface ensure the covalent binding of the hydrogel.

The next step in the sensor preparation was the covering of the polyHEMA layer with a sensing membrane. Although plasticized PVC membranes with ionophores as sensing membranes can give quite satisfactory results -no CO₂ and pH interference and a low noise signal- for a limited life time, a durable sensor requires the chemical attachment of the sensing membrane to the semiconductor and a membrane material which does not need a plasticizer. Also the electroactive components in the sensing membrane must be prevented from leaching out from the membrane which can be achieved by covalent attachment. To a sensing membrane suitable for these purposes a number of requirements have to be made: (i) The sensing membrane must be an elastomer (glass transition temperature below zero); (ii) The membrane must be moderately hydrophobic, i.e. it must possess a low partition of ions from the aqueous phase but must have sufficient conductivity in order to obtain fast response times. For the permselectivity of the analyte ions, ionic sites of opposite charge must be



Scheme 1 Anionic copolymerization of different cyclotrisiloxanes

present in the membrane or allowed to be added. The presence of charged species in the membrane also lowers the electrical resistance of the membrane. (iii) The electroactive components in the sensing membrane, i.e. receptor molecules and ionic sites, have to be covalently bound to the membrane matrix in order to prevent leaching out. (iv) In order to make sensor fabrication compatible with IC-technology linkage of all components in the membrane matrix and attachment of the membranes to the gate oxide surface must occur by photopolymerisable processes.

3. Polysiloxane membranes for durable sensors

We have recently developed a reproducible synthesis for well-structured siloxane terpolymers, based on anionic copolymerisation of cyclotrisiloxanes (Scheme 1) [1]. The covalent attachment of the membrane to the transducing part of the sensor can be enabled by the photopolymerization of the methacrylate groups. The crosslinking of the methacrylate groups also enhances the mechanical strength of membrane.

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

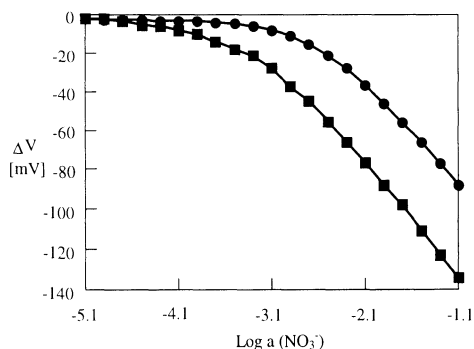
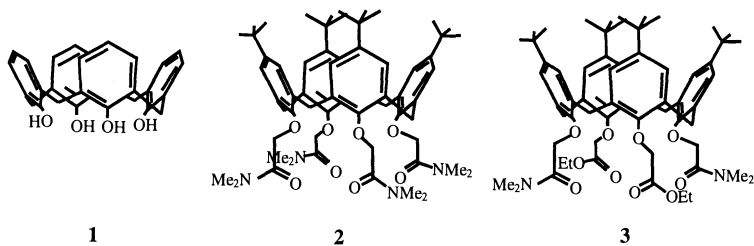


Figure 2. Effect of the polar substituent on the nitrate over chloride selectivity. Nitrate response in the presence of 0.1 M Cl⁻ for CHEMFETs with polysiloxane membranes containing cyano substituents (■) or amide substituents (●).

selective CHEMFETs based on a polysiloxane ion-exchange membrane [2]. 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 show a much lower interference of halogenide ions than sensors having membranes of polysiloxane 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 2). This difference reflects the more favorable interaction of the halogenide ions with the amide moieties, lowering the solvation energy of these ions in the membrane phase.

4. Membranes with cation selective receptor molecules

Receptors applied in sensor membranes 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.



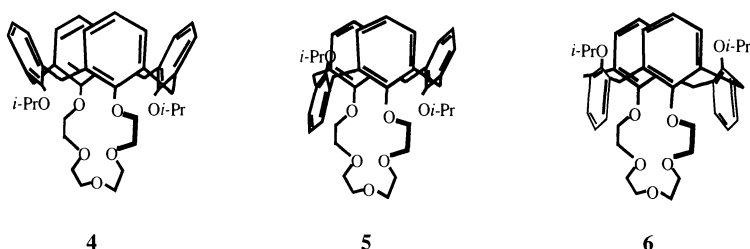
Calix[4]arene **1** is a versatile lipophilic three-dimensional building block that can be functionalized with various ligating substituents for selective ion binding and can be provided with a functional group which enables covalent anchoring to the membrane matrix.

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. 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

Table 1 Selectivity ($\log K_{\text{Na},j}$) and sensitivity (slope, $\text{mV}\cdot\text{decade}^{-1}$) of durable Na^+ selective polysiloxane CHEMFETs.^a

interfering ion	$\log K_{\text{Na},j}$ and slope ($\text{mV}\cdot\text{decade}^{-1}$) ^b		
	0 weeks	15 weeks	40 weeks
0.5 M Mg^{2+}	-3.7 [59]	-3.7 [59]	-3.0 [59]
1 M K^+	-2.6 [60]	-2.2 [59]	-1.4 [56]
0.5 M Ca^{2+}	-3.7 [59]	-3.5 [59]	-2.9 [56]

^a1Wt% ionophore and 50 mol% (with respect to the ionophore) KTFPB. ^b $\log K_{\text{Na},j} \pm 0.1$; slope $\pm 2 \text{ mV}\cdot\text{decade}^{-1} [\text{Na}^+]$.



ligands (3). For application in the sensor membranes of CHEMFETs, 1 wt% of the Na⁺ selective receptor calix[4]arene tetraethyl ester and 50 mol% (with respect to receptor) of potassium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (KTTFPB) was incorporated into cyanopropyl-functionalized siloxane terpolymers. The Na⁺ selectivities and sensitivities of the obtained CHEMFETs measured in the presence of different interfering ions are shown in columns 1 and 2 of Table 1. These polysiloxane CHEMFETs exhibit good Na⁺ selectivities ($\log K_{\text{Na},j} = -3.7, -2.6, \text{ and } -3.7$) and Nernstian responses ($59 - 69 \text{ mV.decade}^{-1}$) for Na⁺ in the presence of Mg²⁺, K⁺ and Ca²⁺ ions, respectively [3].

A crown ether moiety 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. The *cone* conformer **4** has the lowest selectivity of K⁺ over Na⁺ ($\log K_{\text{K,Na}}^{\text{Pot}} = -2.5$). The selectivity of the *partial cone* conformer **5** is much better ($\log K_{\text{K,Na}}^{\text{Pot}} = -3.9$), but the highest K⁺ selectivity was obtained for *1,3-alternate* calix[4]arene **6** ($\log K_{\text{K,Na}}^{\text{Pot}} = -4.2$). The high selectivity of the latter can be attributed to favourable cation- π interactions between K⁺ and the aromatic rings. In Figure 3 the response curve in the presence of 1 M Na⁺ of a CHEMFET with this ionophore is given. The obtained selectivity of **6** is even higher under identical conditions than that of the natural occurring ionophore valinomycin.

Changes in the nature of the donating atoms influences the selectivity. Soft heavy metal ions can be selectively bound by providing the calix[4]arene with soft thioether, thioamide, or thiocarbamate groups [4]. Again small changes in the ligand structure can alter the selectivity of the ionophore. Thioamide **7** is highly selective for Pb²⁺, thiocarbamate **8** yields well functioning Cu²⁺ selective CHEMFETs and the dimethylthiocarbamoyl-methoxyethoxy substituents of **9** introduce Cd²⁺ selectivity. With dithioether **10** Nernstian Ag⁺ response in the presence of K⁺, Ca²⁺, Cd²⁺, Hg²⁺, and Cu²⁺ has been obtained.

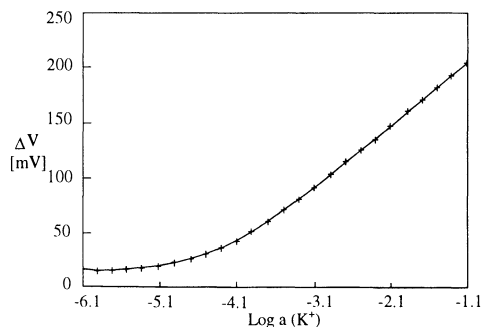
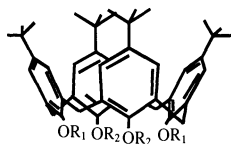


Figure 3. K⁺ response of CHEMFET containing ionophore **6** in the presence of 1 M Na⁺.



- 7 $R_1=R_2=CH_2C(S)N(CH_3)_2$
 8 $R_1=R_2=CH_2CH_2SC(S)N(CH_2CH_3)_2$
 9 $R_1=R_2=CH_2CH_2OCH_2C(S)N(CH_3)_2$
 10 $R_1=CH_2CH_2SCH_3, R_2=CH_2CH_2CH_3$

CHEMFETs with Pb^{2+} selective calix[4]arene derivative **7** in membranes of cyanopropyl or acetoxypopyl functionalized polysiloxane did not show good sensitivities (sub-Nernstian slopes). However, CHEMFETs with membranes of polysiloxanes with benzoylaminopropyl substituents 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 4, CHEMFETs with polysiloxane membranes with acetylphenoxypropyl substituents having relatively softer ester groups, show selective Pb^{2+} responses even in the presence of Ca^{2+} . Another example of the importance of the nature and polarity of the substituents present at the polysiloxane backbone is seen for CHEMFETs with Cd^{2+} selective ionophore **9**. CHEMFETs incorporating this ionophore in 3-cyanopropyl functionalized siloxane membranes are Cd^{2+} selective in the presence of Ca^{2+} and Pb^{2+} ions ($\log K_{Cd,j}^{Pot} = -2.2$ and -1.4 , respectively). These selectivities can be improved to -4.1 and -2.0 , respectively, by incorporating **9** in polysiloxane membranes with acetoxypopyl substituents. Compared with **9** in 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.

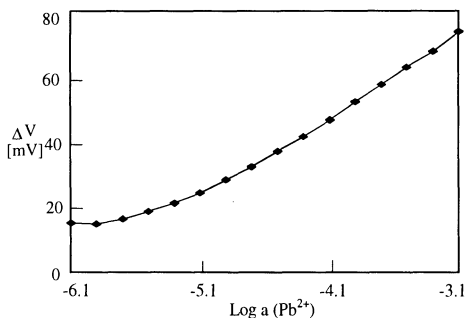


Figure 4. Pb^{2+} response in the presence of $0.1 M Ca^{2+}$ of CHEMFET with acetylphenoxypropyl functionalized polysiloxane membrane containing calix[4]arene ionophore **7**.

5. Durability of Na^+ selective CHEMFETs

The durability of the sensors have been tested by the exposure of these sensors to a continuously refreshed stream of tap water ($25 mL \cdot min^{-1}$). The CHEMFETs were conditioned in a $0.1 M NaCl$ solution for one night before measuring their characteristics (*i.e.* selectivity and sensitivity). The polysiloxane based CHEMFETs retained their Na^+ selectivity in the presence

of different alkali and alkaline earth metal ions for a period of more than 40 weeks (Table 1, columns 3 and 4). Despite of the decrease in Na^+/K^+ selectivity from -2.6 to -1.4 after 40 weeks, the CHEMFETs still have (near) Nernstian responses. Even after 40 weeks of continuously exposure to streaming tap water the CHEMFETs are still very selective ($\log K_{\text{Na},j} = -3.0$ and -2.9) for Na^+ in the presence of Mg^{2+} and Ca^{2+} ions, respectively. Similar results have been obtained with nitrate- selective CHEMFETs, incorporating a quaternary ammonium groups covalently bound polysiloxane membranes, and with potassium-selective CHEMFETs, incorporating covalently bound crown ether analogs.

6. Anion selective CHEMFETs

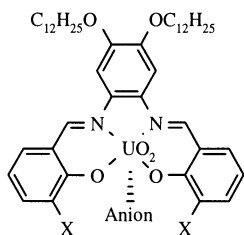
The number of anion receptors known in literature that are applied in ion selective sensors is very limited. The receptors for selective anion binding in the membrane of sensors have to meet high requirements because of the relatively large differences found in the energies of transfer from water to an organic medium like the (sensor)membrane between hydrophilic anions (e.g. phosphate or fluoride) and more lipophilic anions (e.g. nitrate and perchlorate). These differences strongly favor the partition of lipophilic ions like nitrate into the membrane even in the presence of hundred to thousand-fold excess of more hydrophilic phosphate or fluoride ions giving rise to sensor sensitivity for these lipophilic ions (*i.e.* the well-known Hofmeister selectivity). In the reversed case, when a hydrophilic ion has to be measured in the presence of lipophilic ions, the natural partition of the lipophilic ion in the membrane phase has to be overcompensated by strong and highly selective binding of the hydrophilic ion to (preferentially neutral) receptor molecules incorporated in the membrane. One of the best described receptors is a cobalt porphyrin which yields nitrite selectivity when applied in membranes of ion selective electrodes. Also applied in PVC and polysiloxane membranes on CHEMFETs good nitrite sensitivities and selectivities are obtained (table 2) [5]. Common ions like halides or nitrate do not interfere the nitrite response even when the activity of these ions is hundred to thousand fold in excess.

Recently we have developed a novel class of uranyl salophene based anion receptors which introduce selectivity for certain hydrophilic anions. In the salophene unit the Lewis acidic UO_2 cation is bound via four of its equatorial coordination sites. The fifth site in the same plane is available for anion binding (Chart 1). Lipophilic substituents are introduced to make the receptor well soluble in the membrane matrix of the ion selective membrane. Receptor **11** was used as ionophore in plasticized PVC membranes cast on top of CHEMFETs [6]. This uranyl salophene receptor introduces a high sensitivity for dihydrogen phosphate with almost Nernstian slope of the response curve, and the activity of this ion can be determined in the sub-millimolar level. The high selectivity of this receptor is reflected by the low interference of lipophilic ions in fixed interference measurements (Table 2). Phosphate can be measured with a twenty-fold selectivity over nitrate. This is a more than 10^5 fold increase in phosphate selectivity compared with the Hofmeister selectivity of ion exchange membranes in which nitrate is favored 10^4 times over phosphate.

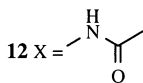
Table 2. Sensor characteristics of anion selective CHEMFETs with nitrite, phosphate or fluoride selectivity and PVC/NPOE or polysiloxane (PS) polymer membranes.

Receptor	Polymer	Primary ion (i)	Log $K_{1,j}^{\text{Pot}}$			
			NO_3^-	Br^-	Cl^-	SO_4^{2-}
Co-Porph.	PVC	NO_2^- ^a	-2.6	-2.6	-2.6	-2.9
Co-Porph.	Ketone PS	NO_2^- ^a	-2.0	-2.2	-2.4	-2.7
11	PVC	H_2PO_4^- ^b	-1.3	-1.7	-1.8	-2.3
12	PVC	F^- ^a	-2.1	-2.1	-2.0	-2.5
12	Sulfone PS	F^- ^a	-2.6	-2.5	-2.6	-3.0
13	PVC	OAc^-	-0.3	-1.2	-1.2	-2.5

^a [j] = 0.1 M in 0.01 M MES pH = 6.0; ^b [j] = 0.1 M in 0.01 M MES pH = 4.5



11 X = H



13 X = phenyl

Chart 1

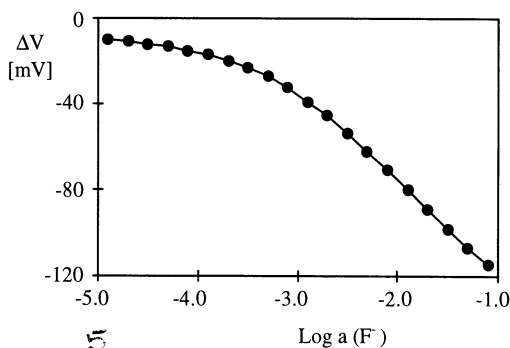


Figure 5 Fluoride response of CHEMFET with novel lipophilic uranylsalophene with amide substituents, in the presence of 0.1 M NaClO_4 .

The selectivity of the anion binding of uranyl salophenes can be influenced by introduction of additional binding sites in close proximity to the anion coordination site of the uranyl cation. The amide substituents of salophene **12** can donate hydrogen bonds to the bound anion and reduce the size of the binding cleft. This introduces very high binding selectivity for the small, strongly hydrogen bond accepting, fluoride anion. Well functioning fluoride selective CHEMFETs were obtained that show excellent selectivity over more lipophilic ions, like other halides and nitrate (Table 2). As presented in Figure 5, also in the presence of high concentrations of the highly lipophilic perchlorate ion (0.1 M), detection of fluoride is possible at millimolar level. The phenyl substituents of uranyl salophene derivative **13** result in a apolar anion binding cleft and selectivity for the organic acetate anion is obtained. CHEMFETs with **13** as anion receptor respond to acetate at concentrations $\geq 3 \times 10^{-4}$ M with an almost Nernstian slope of -56 mV/decade. The CHEMFETs are acetate selective over more lipophilic anions like Cl^- , Br^- , and NO_3^- (Log $K_{\text{OAc},j}^{\text{Pot}}$ = -1.2, -1.2, and -0.3, respectively). Furthermore, over H_2PO_4^- a 250 fold selectivity is obtained. The presence of the phenyl substituents reduces the binding strength between the H_2PO_4^- anion and the uranyl

salophene and consequently the selectivity of acetate and H_2PO_4^- is reversed compared with the H_2PO_4^- selective CHEMFETS based on salophene **11**.

7. Conclusions

In summary, we have successfully developed potentiometric cation and anion sensors based on CHEMFETS. High durability is obtained with ion-selective membranes based on modified siloxane polymers. The incorporation of calixarene cation receptors or uranyl salophene anion receptors results in a high selectivity of the detection of several analytes.

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References

- 1 R.J.W. Lugtenberg, M.M.G. Antonisse, R.J.M. Egberink, J.F.J. Engbersen, D.N. Reinhoudt *Polysiloxane based CHEMFETs for the detection of heavy metal ions*, J. Chem. Soc., Perkin Trans. 2, (1996), 1937-1941.
- 2 M.M.G. Antonisse, R.J.W. Lugtenberg, R.J.M. Egberink, J.F.J. Engbersen, D.N. Reinhoudt *Durable nitrate-selective CHEMFETs based on new polysiloxane membranes*, Anal. Chim. Acta, 332 (1996), 123-129.
- 3 H. Gankema, R.J.W. Lugtenberg, J.F.J. Engbersen, D.N. Reinhoudt, M. Möller *Crosslinkable polar siloxane copolymers for ion detection devices*, Adv. Mater., 6 (1994), 944-947.
- 4 R.J.W. Lugtenberg, R.J.M. Egberink, J.F.J. Engbersen, D.N. Reinhoudt *Pb^{2+} and Cd^{2+} selective chemically modified field effect transistors based on thioamide functionalized 1,3-alternate calix[4]arenes*, J. Chem. Soc., Perkin Trans. 2, (1997), 1353-1357.
- 5 M.M.G. Antonisse, B.H.M. Snellink-Ruël, J.F.J. Engbersen, D.N. Reinhoudt *Chemically modified field effect transistors with nitrite or fluoride selectivity*, submitted for publication.
- 6 M.M.G. Antonisse, B.H.M. Snellink-Ruël, I. Yigit, J.F.J. Engbersen, D.N. Reinhoudt *Neutral anion receptors; synthesis and evaluation as sensing molecules in chemically modified field effect transistors (CHEMFETs)*, J. Org. Chem., 62 (1997), in press.