

Chemically modified field-effect transistors; a sodium ion selective sensor based on calix[4]arene receptor molecules

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Abstract

The development of an ion-sensitive field-effect transistor for sodium ions is described. Calix[4]arene derivatives incorporated in a poly(vinyl chloride)-based membrane provide the selectivity. A poly(2-hydroxyethyl methacrylate) interlayer between the silicon dioxide gate and the sensing membrane is necessary to obtain a Na⁺-sensitive ISFET with Nernstian behaviour. The potentiometric selectivity coefficients ($\log K_{i,j}^{pot}$) for Na⁺ over K⁺ and Li⁺ are -1.9 and -2.5 , respectively.

Keywords: Potentiometry; Ion-sensitive field-effect transistor; Sodium

An ion-sensitive field-effect transistor (ISFET) combines the ion-selective electrode (ISE) and solid-state integrated circuit (IC) technologies. ISFETs have a number of potential advantages over conventional electrodes because of their rapid response, small size, low output impedance, suitability for temperature and noise compensation, and the possibility of manufacturing small combined multisensors including a reference electrode [1]. In 1970, the ISFET was introduced by Bergveld [2] who removed the gate metal of a metal oxide semiconductor field-effect transistor (MOSFET) and exposed the silicon dioxide gate insulator to a saline solution. An important further development was the physical attachment of a plasticized poly(vinyl chloride) (PVC) membrane containing

a K⁺-selective ionophore (valinomycin) to the gate surface of an ISFET by Moss et al. [3].

Plasticized PVC is the commonly used matrix for permselective polymeric membranes on ISFETs, but it has some serious drawbacks. The fact that ISFETs modified with a PVC-based membrane (MEMFET) have not been commercialized is due to several problems. First, the membrane components (plasticizer, anionic sites, and ionophore) are leached from the relatively thin polymer layer by the contacting solution. Secondly, the membrane tends to become detached from the ISFET surface by water seepage between the polymeric membrane and the encapsulant, as reported by Oesch et al. [4], and subsequently the solution penetrates the mem-

brane-insulator layer interface. Thirdly, the membrane-insulator layer interface is thermodynamically ill-defined and potential changes at this interface will occur due to interference by permeated carbon dioxide [5]. Fourthly, the combination of ISFETs with commonly used reference electrodes (Ag/AgCl or saturated calomel electrode) is unattractive because of the size of these latter electrodes, the necessity for a liquid junction, and the different temperature-dependences of the reference electrodes and the ISFETs.

Part of our current research is focussed on the synthesis and application of macrocyclic receptor molecules that are able to form complexes with cations or neutral molecules selectively. For the selective complexation of potassium, benzo- and dibenzo-crown ethers and hemispherand-type ionophores have been synthesized [6]. In contrast to valinomycin, the molecular cavity of synthetic ionophores can be tuned to the desired ion selectivity. Moreover, it is easy to attach functional groups and this offers the possibility of covalent chemical anchoring of the ionophore to the membrane matrix [7,8]. It has been shown [9–12] that detachment of the membrane can be prevented by covalent chemical anchoring of the membrane to the ISFET. In combination with a chemically attached poly(2-hydroxyethyl methacrylate) (poly-HEMA) hydrogel interlayer, a thermodynamically well-defined interface is obtained between the membrane and the insulator layer. When adequately buffered, this interlayer also suppresses interference from carbon dioxide. A reference electrode based on ISFETs (REFET) modified with chemically anchored acrylates has also been developed. Such a REFET can be used in differential measurements [13]. Because most of the basic problems in CHEMFET technology have now been solved and lifetimes exceeding 200 days have been demonstrated for K^+ - and Ca^{2+} -sensitive sensors after continuous exposure to an aqueous solution, it seems worthwhile to extend the range of ions that can be detected selectively. In this paper the development of a sodium-sensitive ISFET is described.

Despite the many potential applications of a Na^+ -sensitive ISFET (e.g., in medicine, biology, process control, and environmental protection) the

development of a Na^+ -ISFET has received little attention. The first study was reported by Oesch et al. [4], who used the oxamide ETH 227 to introduce Na^+ -selectivity to a MEMFET. This ionophore was also used more recently by Sibbald et al. [14] in an integrated multiple-ISFET for the analysis of blood, and by Wakida et al. [15–17] who incorporated the compound in a MEMFET based on Urushi lacquer. The only other Na^+ -selective ionophore studied so far on a MEMFET is bis(12-crown-4) [18].

Several ionophores can potentially introduce Na^+ -selectivity in a CHEMFET e.g., derivatives of bis(12-crown-4) [18–21], 15-crown-4 [22], amides [4,14–17], and monensin [23,25]. However most have serious drawbacks which make them unattractive for use in CHEMFETs. First, inadequate lipophilicity will limit the lifetime of the MEMFET because of leaching out of the ionophore. Secondly, there are only limited possibilities for improving the Na^+ -selectivity by tuning the cavity or by varying the number and the donating character of the coordinating atoms in the cavity.

Calixarene-based molecular receptors are a new class of ionophores and several calixarene esters and ketones seem to have the potential to overcome the drawbacks of other Na^+ -selective ionophores [26,27]. Some calix[4]arene derivatives have already proved to be versatile neutral carriers in sodium-selective electrodes [28–30]. Therefore, it

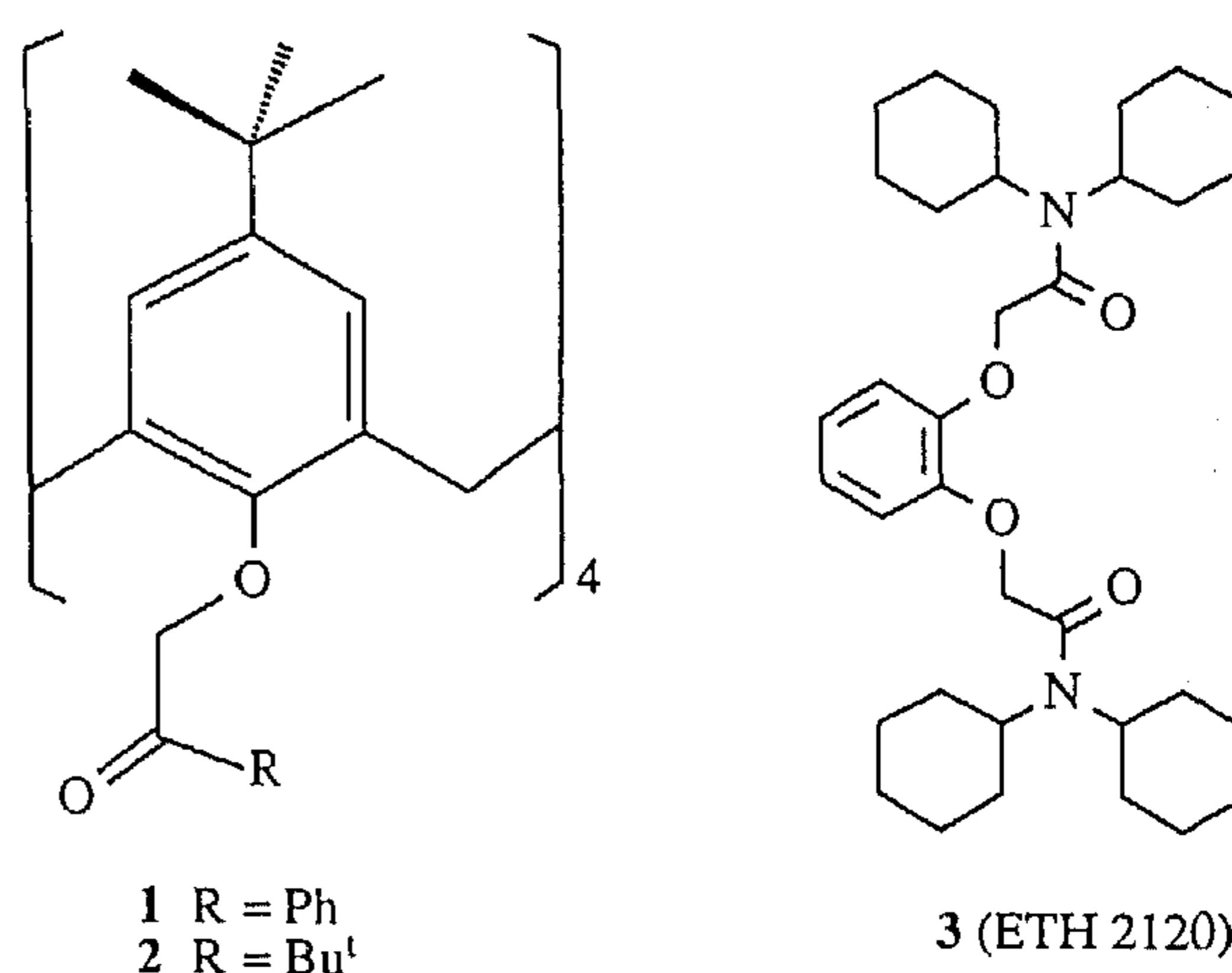


Fig. 1. Structures of the investigated ionophores.

was decided to develop a series of Na⁺-sensitive CHEMFETs based on calix[4]arene derivatives. Here, some calix[4]arenes derivatives are incorporated in a plasticized PVC matrix. Although this will not be the ultimate system for a Na⁺-CHEMFET, it offers a simple and fast method to assess the sensing properties of a variety of calixarenes. For comparison, the oxamide ETH 2120 is included. The structures of the ionophores used are shown in Fig. 1.

EXPERIMENTAL

Chemicals

High-molecular-weight PVC was obtained from Janssen Chimica; ETH 2120, bis(2-ethylhexyl) sebacate (DOS), bis(1-butylpentyl) adipate (BBPA) and potassium tetrakis(4-chlorophenyl)borate (KTCPB) were obtained from Fluka. The pH 4 buffer was purchased from Yokogawa. The synthesis of calix[4]arene ketones **1** and **2** has been described previously [27]. Tetrahydrofuran (THF) was freshly distilled from benzophenone/sodium before use. The alkali and alkaline earth metal salts used were of analytical-reagent grade (Merck-Schuchardt), except for sodium chloride (Suprapur). All solutions were made with doubly distilled and deionized water.

ISFETs

The ISFETs were fabricated as described previously [10]. The ISFETs that were used in this study can be divided into two types: (a) MEMFETs on which the sensing membrane was directly attached to the gate oxide; (b) CHEMFETs which contained an intermediate hydrogel layer of polyHEMA between the gate oxide and the sensing membrane. The polyHEMA layer was anchored chemically to the gate oxide as described before [8,12]. The membranes were made by solvent-casting of a mixture of 100 mg of PVC, 200 mg of DOS or BBPA, 7 mg of ionophore, and 2 to 4 mg of KTCPB (50–60 mol% with respect to the ionophore) in 3 ml of THF, on mounted ISFETs that were encapsulated with epoxy resin (Hysol). The THF was allowed to evaporate overnight. In the case of polyHEMA-modified ISFETs, the hydrogel layer was conditioned by immersion in buffered

(pH 4) 0.1 M sodium chloride for 3–6 h prior to solvent casting. Before measurements were started, the membranes were conditioned in 0.1 M sodium chloride for one night.

ISFET measurements

The output of the ISFETs was measured in a constant drain-current mode ($I_d = 100 \mu\text{A}$), with a constant drain-source potential ($V_{ds} = 0.5 \text{ V}$) [31]. This was achieved by using an ISFET amplifier of the source-drain follower type. The developed membrane potential was compensated by an equal and opposite potential (ΔV_{gs}) via the reference electrode. A saturated calomel electrode (SCE) was used as reference with a double junction containing 3.0 M KCl. Ten ISFETs were monitored simultaneously and the data were collected and analyzed by using an Apple IIe microcomputer. The equipment was placed in a dark, grounded metal box to eliminate any effects from static electricity and the photosensitivity of the ISFETs. The potentiometric selectivity coefficients $K_{i,j}^{pot}$, were determined by the fixed interference method (FIM) [32]. The constant background concentration of all the interfering ions was 0.1 M for measurements made with the ion-sensitive FETs incorporating the calix[4]arene ketones **1** and **2**, except for potassium for which a 0.01 M solution was used. When ETH 2120 was incorporated in the sensing membrane, the constant background concentration of all the interfering ions was 0.01 M, except for Ca²⁺ for which a 10⁻⁵ M solution was used. All concentrations were converted to activities by using the extended Debye–Hückel equation [33]. The obtained response characteristics were analyzed according to the Nicolsky–Eisenman equation [34]:

$$E = E^0 + S \log(a_i + \sum K_{i,j}^{pot} a_j^{z_i/z_j})$$

where $S = 2.303RT/z_iF$ and all symbols have their conventional meanings.

RESULTS AND DISCUSSION

In the first experiments, MEMFETs were used, i.e., the sensing membrane was physically, not covalently, attached to the gate oxide. Membranes

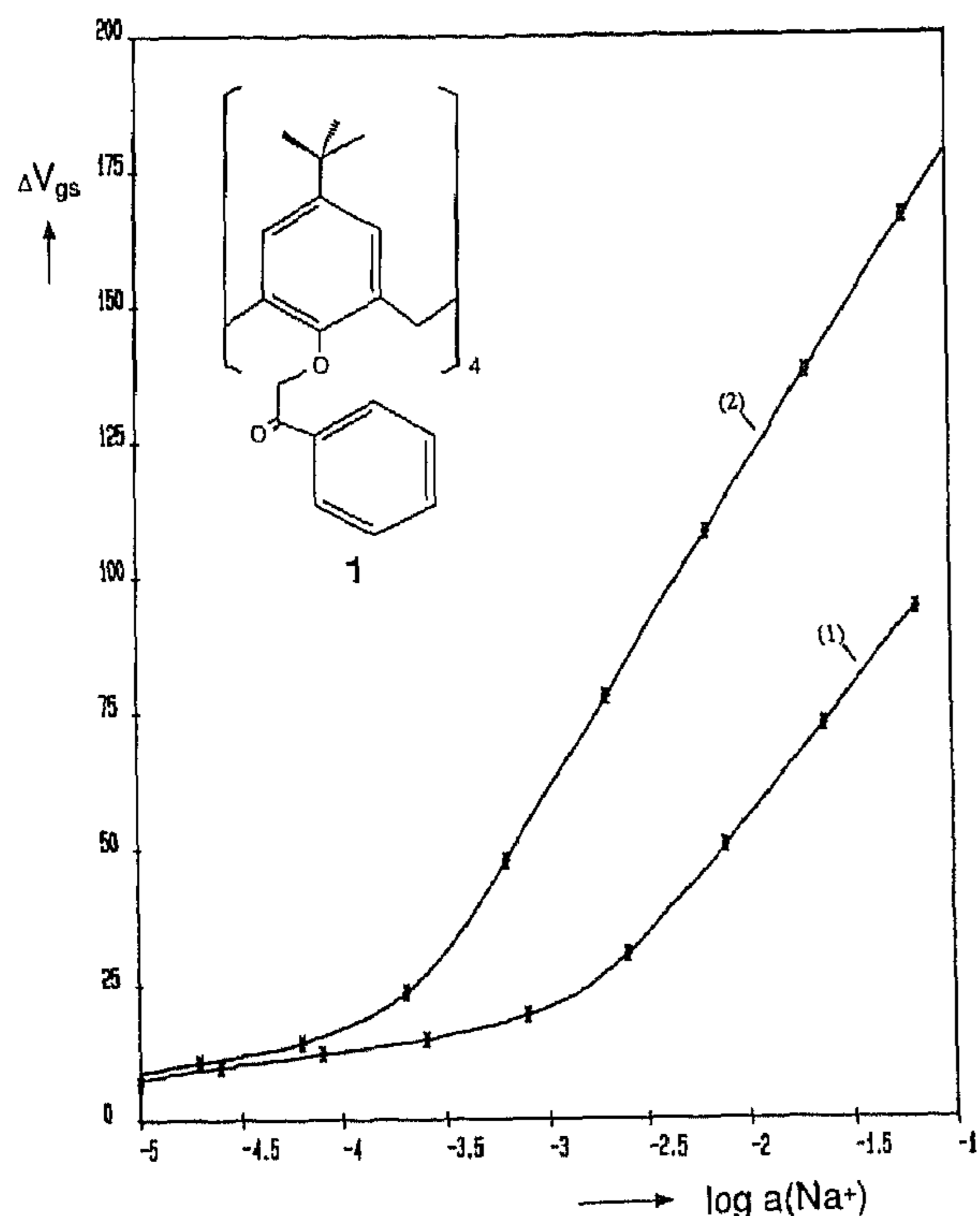


Fig. 2. Response curves measured in 0.01 M KCl for a MEMFET (1) and a CHEMFET (2), containing calix[4]arene ketone 1 in a plasticized PVC membrane.

containing some calix[4]arene derivatives, including calix[4]arene ketones 1 and 2, were examined. From the response characteristics, it became obvious that no Nernstian response was obtained in solutions containing interfering cations such as K^+ or Li^+ (Fig. 2).

The series of experiments was repeated with CHEMFETs, i.e., a polyHEMA interlayer, conditioned in buffered (pH 4) 0.1 M NaCl, was placed between the gate oxide and the sensing membrane. Satisfactory Nernstian behaviour was observed for solutions containing alkali metal ions, as well for solutions containing alkaline earth cations (Table 1, Fig. 2).

When the values of the slopes of the response curves of these CHEMFETs are compared with the values previously found for MEMFETs based on ETH 227 (57 [4] and 53 [15–17] mV/decade change in Na^+ activity) and the value of 52 mV/decade for MEMFETs based on bis(12-crown-4) [18], it is obvious that the response behaviour is improved by the introduction of the polyHEMA layer. In addition to the need for the polyHEMA layer in order to obtain a Na^+ -sensitive FET with Nernstian behaviour, there is the opportunity of chemically anchoring the sensing membrane to the hydrogel interlayer, because of the presence of hydroxyethyl functional groups at the hydrogel surface.

The CHEMFETs based on the calix[4]arene ketones 1 and 2 show good selectivity coefficients, not only compared to CHEMFETs based on ETH 2120, but also in comparison with the selectivities found for MEMFETs based on ETH 227 and bis(12-crown-4) [4,14–18]. Especially noteworthy are the selectivities shown by calix[4]arene ketone 1 in the presence of K^+ and Ca^{2+} , which usually interfere strongly. This interference is caused generally by the favourable partition of the interfering

TABLE 1

Response characteristics for CHEMFETs containing the calix[4]arene ketones 1 and 2, and ETH 2120

Interfering ion, j	Ligand 1		Ligand 2		ETH 2120	
	Slope ^a	$K_{Na,j}^{pot}$ ^b	Slope ^a	$K_{Na,j}^{pot}$ ^b	Slope ^a	$K_{Na,j}^{pot}$ ^b
Cs^+	58.8 ± 0.2	-3.30 ± 0.02	59.1 ± 1.5	-2.68 ± 0.04	58.8 ± 1.1	-1.98 ± 0.04
Rb^+	58.7 ± 0.3	-3.05 ± 0.05	58.1 ± 1.4	-2.56 ± 0.07	57.5 ± 1.0	-1.75 ± 0.05
K^+	58.3 ± 0.9	-1.85 ± 0.10	54.5 ± 1.9	-1.38 ± 0.06	56.9 ± 1.0	-1.48 ± 0.21
Li^+	57.6 ± 1.0	-2.50 ± 0.11	56.7 ± 1.5	-2.31 ± 0.03	55.9 ± 0.9	-1.30 ± 0.02
Ca^{2+}	59.1 ± 1.0	-3.54 ± 0.08	60.4 ± 2.1	-2.90 ± 0.32	56.5 ± 1.4 ^c	-1.38 ± 0.16 ^c
Mg^{2+}	58.3 ± 0.3	-3.61 ± 0.03	58.1 ± 1.1	-3.52 ± 0.19	56.4 ± 0.9	-3.34 ± 0.16

^a mV/decade. ^b Logarithmic value: mean and standard deviation ($n=10$). ^c Measurements made with a membrane matrix composed of PVC and BBPA as mediator.

cation into the membrane phase compared to Na^+ and/or by the association constants between different cations and the ionophore having about the same order of magnitude. It is evident that calix[4]arene **1** introduces Na^+ -selectivity to a CHEMFET, by ignoring these interfering cations to a greater extent. The selectivities found for ETH 2120 agree well with the selectivities found for Na^+ -selective electrodes by Maruizumi et al. [35] and Gehrig et al. [36], apart from the selectivity for the calcium ion. In order to observe response curves with Nernstian behaviour, the constant background concentration of Ca^{2+} had to be lowered to 10^{-5} M and BBPA had to be used as solvent mediator. A possible explanation is that the bis(2-ethylhexyl) sebacate used as plasticizer reacts with calcium ions. Apparently, the Na^+ ion is only weakly complexed by ETH 2120, because no interfering effects were noticed for the calix[4]arene derivatives **1** and **2** when this solvent mediator was used. It has been noticed before that for oxamides the $\text{Na}^+/\text{Ca}^{2+}$ selectivity can vary over a wide range. For ETH 227, Maruizumi et al. [35] reported a selectivity coefficient, $\log K_{\text{Na},\text{Ca}}^{\text{pot}}$, of -1.6 with a Na^+ -ISE based on a membrane composed of PVC and BBPA, whereas Steiner et al. [37] found a value of $+0.2$ with a microelectrode filled with a solution of ETH 227 in *o*-nitrophenyl octyl ether.

The selectivities reported for the calix[4]arene ketones **1** and **2** correlate well with data obtained from extraction experiments [27]. The reduced selectivity of ionophore **2** compared with **1** is probably a consequence of the larger steric hindrance induced by the bulky *tert*-butyl groups. This produces a less favourable fit of the Na^+ ion in the cavity.

Current research is focussed on investigation of a series of calix[4]arene esters, ketones and amides to elucidate the relationship between structure and selectivity, taking into account the varying donating ability of the carbonyl oxygen in the ester, ketone and amide functions.

Conclusions

A Na^+ -sensitive FET based on calix[4]arene ketones with satisfactory Nernstian response characteristics can be fabricated by introduction of a

polyHEMA layer, equilibrated with buffered 0.1 M sodium chloride, between the silicon dioxide gate and the PVC membrane. The Na^+ -CHEMFET based on *p*-*tert*-butylcalix[4]arene tetraphenylketone **1** exhibits better selectivity than the commercially available ETH 2120.

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