

## Transduction of host-guest complexation into electronic signals: favoured complexation of potassium ions by synthetic macrocyclic polyethers using membrane-modified, ion-sensitive field-effect transistors (ISFETs)\*

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**Abstract.** The selective complexation of  $K^+$  and  $Na^+$  salts with a series of synthetic macrocyclic polyethers has been studied on the  $SiO_2$  gate surface of an Ion-Sensitive Field-Effect Transistor (ISFET). The synthetic macrocycles were incorporated in a PVC membrane directly attached to the  $SiO_2$  gate surface. The selectivities were measured either with tetraethylammonium chloride or lithium chloride as background electrolyte or by direct comparison. The slope of the response curves generally shows near-Nernstian behaviour (53–56 mV/pK<sup>+</sup>). Hemispherands **2** and **3**, which have molecular cavities composed of 21 ring atoms and 1,3-dimethyl-*p*-(*tert*-butyl)calix[4]arene crown-5 (**11**), show high selectivities of  $K^+$  over  $Na^+$  ( $\log K(K^+/Na^+) = -2.9$  to  $3.2$ ). The (substituted) benzo-27-crown-9 derivatives (**5–7**) show moderate selectivities ( $\log K(K^+/Na^+) \approx -2$ ). The 18-membered pyrido hemispherand hardly discriminates. Our results correlate well with reported data of picrate extraction experiments and with the relative-association constants in methanol.

### Introduction

As part of our research on the design, synthesis and complexation behaviour of macrocyclic polyether receptor molecules, we are currently studying the use of their ion-sensitive and ion-selective properties in thin polymeric membranes deposited on the gate oxide of an Ion-Sensitive Field-Effect Transistor (ISFET)<sup>1</sup>. Such a membrane-modified FET (MEMFET) is an integrated device (chemical system) of an ion-sensing membrane and an ISFET transducer able to function as a chemical sensor. Interaction of ionic species present in the solution with the ionophore in the membrane creates a membrane potential, which modulates the channel conductivity of the FET, if the solution is connected via a reference electrode to the bulk of the ISFET (Fig. 1).

In earlier studies<sup>2</sup>, inorganic films of sodium aluminosilicate glasses have been deposited on the gate oxide for  $Na^+$  and  $K^+$  responsive sensors. However, only a limited selectivity was achieved. A simple and fast method of modifying ISFETs was first reported by Moss<sup>3</sup>, followed by others<sup>4</sup>. By attaching valinomycin containing plasticized PVC membranes on top of the gate oxide, a  $K^+$  sensitive and selective sensor was prepared. Despite the attractiveness of an easy fabrication of such sensors, these systems contain some serious drawbacks. Firstly, they lack a thermodynamically well-defined membrane-ISFET interface. Secondly, they suffer from rapid

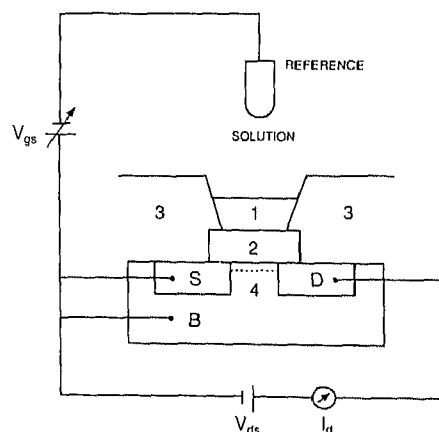


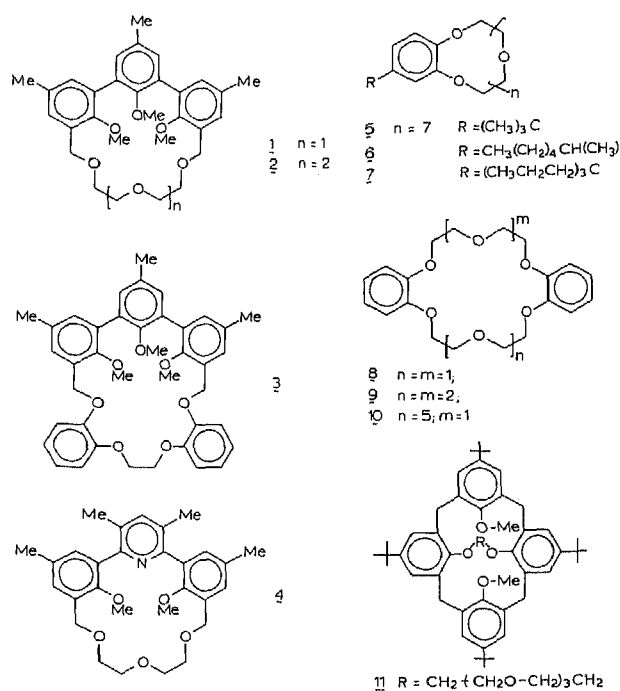
Fig. 1. Schematic representation of a MEMFET and the measuring configuration. (1) ion-sensing membrane; (2) gate oxide ( $SiO_2$ ); (3) encapsulation (epoxy resin); (4) channel; (S) source (n-Si); (D) drain (n-Si); (B) bulk (p-Si).

release of ionophore and other membrane components and, thirdly, they are sensitive to  $CO_2$  interference<sup>4e</sup> since the permeated  $CO_2$  changes the potential at the gate insulator interface. Our research efforts are directed towards solving these drawbacks<sup>5</sup> and in this paper we describe the use of synthetic ionophores for the development of chemical sensors. In contrast to valinomycin, these molecules can be easily functionalised and this opens up the possibility of anchoring the ionophore to the membrane<sup>6</sup>. In addition, the shape of the molecular cavity of the synthetic macrocycles can be tuned to the desired ion selectivity.

\* This paper is dedicated to Prof. Dr. W. Drenth on the occasion of his retirement from the Chair of Physical Organic Chemistry at the University of Utrecht.

## Results

The structural formulae of the macrocyclic ionophores studied are displayed in Scheme 1. The hemispherands type of ionophores (1-4 and 11) possess a (partly) preorganised molecular cavity, contributing to a high affinity for cations which fit the cavity. The results obtained for these compounds are compared with the properties of benzo and dibenzo crown ethers (5-10). We have determined  $K^+$ , and in some cases  $Na^+$  selectivities, using the mixed-solution method<sup>7</sup>.



Scheme 1

The results of the determined potentiometric selectivity constants,  $\log K_{ij}^{Pot}$ , and the observed detection limit of the investigated synthetic ionophores, which are shown in Table I, have been compared with the values obtained using valinomycin.

Using  $0.15 \text{ mol} \cdot \text{dm}^{-3}$  tetraethylammonium chloride

(TEACl) background electrolyte, hemispherands 1 and 2 and dibenzo-30-crown-10 (10) show a high  $K^+$ -to- $TEA^+$  selectivity. The slope of the response curves is in the range  $50\text{--}55 \text{ mV/pK}^+$ . Benzo crown ethers 8 and 9 show a similar response curve, but exhibit a lower selectivity. The  $Na^+$ -to- $TEA^+$  selectivity of hemispherand 1 is remarkable. Other determined selectivities of 1 are  $\log K(Cs^+/TEA^+) -2.25 \pm 0.25$  and  $\log K(Li^+/TEA^+) -0.75 \pm 0.25$ . For hemispherand 3, a  $K^+$  to  $NH_4^+$  selectivity of  $\log K(K^+/NH_4^+) -0.75$  was observed. Using  $0.10 \text{ mol} \cdot \text{dm}^{-3}$  LiCl background electrolyte, the  $K^+$ -to- $Li^+$  selectivities are always found to be higher than the observed  $K^+$ -to- $Na^+$  selectivities. For hemispherands 1 and 4, a poor selectivity of  $Na^+$  to  $K^+$  was observed. The slope of the response curve is found generally to be  $53\text{--}56 \text{ mV/pK}^+$ , approximating Nernst's law. The detection limit values displayed (Table I) are estimated concentrations, obtained by extrapolation of the response values to lower concentrations, since the observed electronic signal was not stable in such a dilute solution. Small  $K^+$ -to- $Na^+$  selectivities are

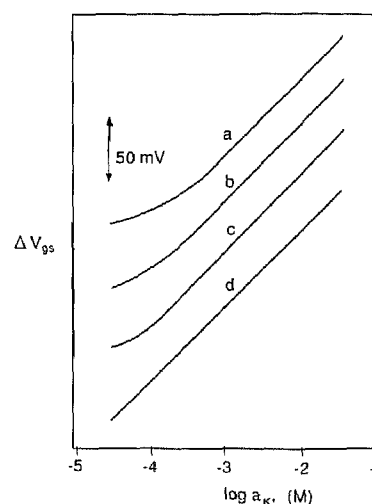


Fig. 2. Observed  $K^+$ -activity response of MEMFETs containing hemispherand 2 (a); hemispherand 3 (b); dimethylcalix[4]-arene crown-5 11 (c); or valinomycin (d). Background electrolyte:  $0.10 \text{ mol} \cdot \text{dm}^{-3}$  NaCl. Temperature:  $25^\circ\text{C}$ . The curves have been offset along the vertical axis for clarity.

Table I Ion selectivities of synthetic ionophores in plasticized PVC MEMFETs.

Ionophore	$\text{Log } K_{ij}^{Pot} (25^\circ\text{C})^a$					Detection limit <sup>b</sup>	$\text{Log } K(K^+/Na^+)$	
	$i:$ $j:$	$Na^+$ $TEA^+^e$	$K^+$ $TEA^+^e$	$K^+$ $Li^+^f$	$K^+$ $Na^+^g$		Picrate <sup>c</sup>	MeOH <sup>d</sup>
1		$< -3.5$	$< -2.5$	$-2.1$	$> 0.9$	$< 3 \cdot 10^{-6}$	0 (ref. 8)	
2			$< -2.5$	$< -3.7$	$-2.8$	$< 2 \cdot 10^{-6}$	$-2.5$ (ref. 8)	
3				$< -3.7$	$-3.1$	$< 2 \cdot 10^{-6}$	$-2.8$ (ref. 9)	
4 <sup>h</sup>				$-2.65$	$-0.4$	$10^{-3}$	$-0.5$ (ref. 8)	
5					$-2.0$	$< 5 \cdot 10^{-6}$		$-2.12$ (ref. 11)
6					$-2.6$	$< 10^{-5}$		
7					$-3.2$	$< 10^{-5}$		
8		$-0.7^i$	$-1.75^i$		$-1.6$			$-0.6$ (ref. 17)
9		$-0.5^i$	$-1.75^i$	$-1.0$				
10 <sup>h</sup>		$-0.75^i$	$< -2.5$	$-2.5$	$-2.1$	$< 3 \cdot 10^{-6}$		$-2.5$ (ref. 11)
11					$-2.8$		$-3.3$ (ref. 10)	
valinomycin			$< -3.7$	$< -3.7$	$< -3.7$	$< 2 \cdot 10^{-6}$		$-3.8$ (ref. 12)

<sup>a</sup> Mixed-solution method<sup>10</sup>, estimated error  $\pm 0.2$ . <sup>b</sup> In  $\text{mol} \cdot \text{dm}^{-3}$ , for LiCl or NaCl background electrolyte. <sup>c</sup>  $\text{Log}\{K(\text{Na picrate})/K(\text{K picrate})\}$ . <sup>d</sup> Differences in log of association constants with  $Na^+$  and  $K^+$  determined in MeOH. <sup>e</sup>  $0.15 \text{ mol} \cdot \text{dm}^{-3}$  TEACl (tetraethylammonium chloride). <sup>f</sup>  $0.10 \text{ mol} \cdot \text{dm}^{-3}$  LiCl. <sup>g</sup>  $0.10 \text{ mol} \cdot \text{dm}^{-3}$  NaCl. <sup>h</sup> 6% wt. of ionophore. <sup>i</sup> Estimated error  $\pm 0.25$ .

observed for the non-preorganised benzo crown ethers **5**, **6** and **7** and dibenzo-30-crown-10 (**10**). High  $K^+$ -to- $Na^+$  selectivities have been found using the 21-membered ring hemispherands **2** and **3** and dimethylcalix[4]arene crown-5 (**11**). The observed values come close to the selectivity of the valinomycin ionophore (Table I and Fig. 2). For instance, for the measurements of the  $K^+$  concentration in blood ( $3.5\text{--}5\text{ mmol}\cdot\text{dm}^{-3}$  and a background of ca.  $0.14\text{ mol}\cdot\text{dm}^{-3}$  NaCl), the synthetic ionophores **2**, **3** and **11** can replace the valinomycin, without any loss of  $K^+$  sensitivity. In Table I, the  $K^+$ / $Na^+$  selectivities obtained from reported picrate-extraction experiments and potentiometric-association constants determinations are also included. It is interesting to observe the similarity of these values as compared to the  $K^+$ / $Na^+$  potentiometric-selectivity coefficients determined in this study. This implies that the difference in complexation behaviour of  $K^+$  and  $Na^+$  ions with the respective macrocyclic polyether (and valinomycin) dictates the potentiometric-selectivity coefficients. Previously, Morf et al.<sup>13</sup> have shown that there is a good correlation, which can be theoretically explained, with the permeability selectivity found in ion-transport experiments.

## Conclusion

We have demonstrated that synthetic macrocyclic polyether ionophores **2**, **3** and **11** incorporated in plasticized PVC membranes, which have been solvent-casted onto  $\text{SiO}_2$  ISFETs, exhibit a high  $K^+$ / $Na^+$  potentiometric selectivity. The observed selectivities correlate well with data obtained from extraction experiments and potentiometrically determined association constants. These ionophores can undergo further chemical modification in order to render covalent chemical anchoring to the membrane possible.

## Experimental

### Ionophores

The macrocyclic polyethers **1**<sup>14</sup>, **2**<sup>8</sup>, **4**<sup>8</sup>, **5**–**10**<sup>15</sup> and **11**<sup>10</sup> were prepared according to procedures described in the literature.

**Synthesis of hemispherand 3.** 1.00 g (1.82 mmole) of 3,3'-bis(bromomethyl)-2,2',2''-trimethoxy-1,1':3',1''-terphenyl and 0.45 g (1.82 mmole) of 2,2'-[1,2-ethanediylbis(oxy)]bisphenol in 25 ml of dry THF were added over 16 h to a refluxing suspension of 0.17 g (7.28 mmole) NaH in 150 ml of dry THF. The mixture was cooled to room temperature and the excess NaH was reacted with 5 ml of water. The solvent was evaporated and the remaining residue was dissolved in  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$ . The aqueous layer was acidified to pH 2 using 4N HCl. The layers were separated and the organic layer was dried ( $\text{MgSO}_4$ ). After filtration and evaporation, the material was purified by column chromatography ( $\text{Al}_2\text{O}_3/\text{CH}_2\text{Cl}_2$ ) and subsequently by recrystallization from  $\text{EtOH}/\text{CHCl}_3$ . Yield 600 mg (52%). M.p.  $262\text{--}266^\circ\text{C}$ . Mass spectrum  $m/e$  632.270 ( $M^+$ , calcd. for  $\text{C}_{40}\text{H}_{40}\text{O}_7$ : 632.277).

### Preparation of MEMFETs

The MEMFETs were prepared by solvent casting of solutions of high-molecular-weight PVC (32% wt., Fluka), di-*n*-butyl phthalate plasticizer (65% wt., BDH) and ionophore (3% wt.) in THF. For most ionophores, this corresponds to a concentration of  $30\text{--}100 \times 10^{-3}\text{ mol}\cdot\text{dm}^{-3}$ . The solvent was allowed to evaporate for at least 30 min, resulting in polymeric membranes of 5–10  $\mu\text{m}$  thickness. The applied  $\text{SiO}_2$ -ISFET chip was mounted on a printed circuit board and encapsulated manually using an epoxy resin (Hysol H-W796/C8 W 795).

### Response measurements

The MEMFETs were measured in a constant drain-current mode ( $I_D$ , 100  $\mu\text{A}$ ), with a constant drain-source potential ( $V_{DS}$  0.5V).

This was achieved using a source-and-drain-follower type-ISFET amplifier. The developed membrane potential was compensated by an equal and opposite potential ( $\Delta V_{GS}$ ) via the reference electrode. Ten MEMFETs were simultaneously monitored and the data analysed using an Apple IIe microcomputer. Where needed, primary-ion activities were calculated using the Debye-Hückel expression for the activity coefficients, taking into account the effective diameter of the ions. This procedure is common in experiments with ion-selective electrodes, see for instance ref. 16. Most switches allowed computer-controlled elimination of ISFETs with too high a leakage current ( $> 50\text{ nA}$ ). Before measurements were started, the MEMFETs were equilibrated in the solution for 60 min. The  $K^+$ , and in some cases  $Na^+$ , selectivities were determined using the mixed-solution method<sup>7</sup>. Using a constant  $0.15\text{-mol}\cdot\text{dm}^{-3}$  TEACl (tetraethylammonium chloride) background electrolyte, the  $K^+$ ( $Na^+$ )-to- $\text{TEA}^+$  selectivity was determined by measuring the MEMFET response in solutions with a tenfold increasing  $K^+$ ( $Na^+$ ) concentration ( $10^{-4}\text{--}1\text{ mol}\cdot\text{dm}^{-3}$ ). Selectivities of  $K^+$ / $Na^+$  and  $K^+$ / $Li^+$ , as well as the slope and detection limit of the sensors, were measured by successive titration of KCl to a  $0.1\text{-mol}\cdot\text{dm}^{-3}$  solution of NaCl or LiCl, or to doubly distilled water, respectively. A potassium-ion-selective electrode (Ingold) was used to measure the  $K^+$  activity. A saturated-calomel electrode (SCE) was used as reference. The measurements were performed in a dark and electrically shielded box.

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