MOLECULAR SYSTEMS FOR THE TRANSDUCTION OF HOST-GUEST COMPLEXATION REACTIONS INTO ELECTRONIC SIGNALS

D.N. Reinhoudt

University of Twente, Laboratory of Organic Chemistry,
The Netherlands

Synthetic receptor molecules that selectively bind charged guests can store chemical information. The transduction of this information into electronic signals connects the chemical and electronic domains. Field effect transistors (FETs) are attractive because they are able to register and amplify chemical changes at the gate oxide surface of the semi-conductor chip.

We have studied the integration of the covalently attached thin membranes and the ISFET.

The problem of the thermodynamically ill-defined oxide-membrane interface has been solved by applying a covalently linked hydrophilic polyHEMA gel between the sensing membrane and the silylated gate oxide.

The subsequent attachment of a polysiloxane membrane containing the receptor molecule, provides a stable chemical system that transduces the selective complexation of the cationic species K^+ , Na^+ and Ca^{2+} into electronic signals (CHEMFET).

1. Introduction

The discovery by Pedersen [1] that synthetic macrocyclic polyethers form complexes with cationic guest species has tremendously stimulated the molecular design and organic synthesis of receptor molecules that selectively recognize charged, or even neutral molecules. Almost from the beginning, this "host-guest" [2a] or "supramolecular" [2b] chemistry has been associated with possible technological applications. Solid-liquid [3], and liquid-liquid [4] extraction by these macrocyclic receptors as well as facilitated transport through (liquid) membranes [5] were reported soon after the early synthesis and complexation studies. In these applications the receptor molecule (selectively) recognizes the ionic guest and renders the solution properties of the complex different from the guest.

In this paper we describe our work aimed at the development of this approach to molecular systems that are able to transduce specific host-guest interactions into "macroscopic" electronic signals. One of the "first generation" practical applications of our fundamental studies is an accurate, functioning microsensors for the selective quantitative detection of cationic species in aqueous solutions.

As the transducing element we have chosen a field effect transistor, and for the sensing element we have used a variety of synthetic macrocyclic polyether receptor molecules and the natural ionophore valinomycin. The research described is focused on the integration of both elements in one molecular system ("molecular material") than can be regarded as a chemical entity with a designed function.

2. Ion Sensitive Field Effect Transistors (ISFETs)

The field effect transistor (FET) is able to measure the conductance of a semiconductor as a function of an electrical field perpendicular to the gate oxide surface. In the most simple form the device is a capacitive structure with an oxide layer as the insulator. A positive charge on the metal (gate) induces a negative charge on the SiO_2 -Si semiconductor interface which results in a change of its lateral conductance that can be measured between two contacts. In 1970 Bergveld placed the SiO_2 gate oxide directly in an aqueous electrolyte solution [6]. He found that the source-drain current I_D is influenced by the interface potential at the oxide/aqueous solution. Since SiO_2 was used as the insulator, the chemical nature of the interface oxide is reflected in the measured source-drain current. Consequently this microchip transduces chemical information into an electronic signal and connects directly the chemical and the electronic domains.

2.1. Modification of the Oxide Surface of ISFETs

One of the crucial problems for the development of such micro sensors was the problem of a reference based on the same field effect principle, the so-called REFET, which should be insensitive to chemical changes in the electrolyte solution. Our work was concentrated on five major problems in the area of chemically modified ISFETs: 1. Covalent coupling of organic matrices, with designed properties, to the ISFET surface gate oxide. 2. Development of a chemically inert reference based on FET technology. 3. Definition of thermodynamic equilibria at the interfaces. 4. Molecular design and organic synthesis of receptor molecules with high chemical selectivity. 5. Model description of the functioning of the chemically modified ISFET structure.

We found that silylation of the ISFET SiO_2 surface changes the pH dependency of the surface potential but does not completely eliminate the pH sensitivity [7], which is confirmed by theoretical models. Consequently our work has focused on the covalent attachment of different thin polymeric layers to the surface.

The difference between covalent chemical, and physical attachment was clearly demonstrated when the surfaces were continuously exposed to an aqueous electrolyte solution and evaluated in terms of their pH response at different time intervals. The physically attached layer of Vernis pour l'Electronique (VE) is already pH sensitive after one day, but the ISFETs with the chemically attached polybutadiene still show complete pH insensitivity after 90 days exposure. Such chemically modified ISFETs can in principle serve as a REFET.

Permselectivity of polymeric membranes originates from the mobility differences of cations and anions. The presence of lipophilic anions in the membrane therefore makes the

membrane cation selective and vice versa. In order to suppress the observed cation permselectivity we have added lipophilic cations viz didodecylmethylammonium bromide (DDMAB) to polyacrylate (ACE) prior to the in situ polymerization in the ISFET device [8]. The resulting K^+ selectivity of the various materials reveals that the initial permselectivity can be eliminated by the addition of $2 \cdot 10^{-5}$ mol DDMAB per gram of ACE. Higher concentrations of DDMAB render these ISFETs anion selective because the material acts as an anionic ion exchanger.

With this result we had achieved our first major objective, a REFET.

3. Chemically sensitive ISFETs (CHEMFETs)

Our work to develop molecular systems that transduce other than simple protonation/deprotonation reactions has taken advantage of ISFETs with *physically attached membranes* reported in the past decade. In 1975 Moss et al. [9] reported a K^+ -responsive ISFET. This device was obtained by attaching valinomycin-containing plasticized PVC membranes to the SiO_2 gate. This system has some serious disadvantages. Firstly, there is no thermodynamically well-defined membrane-ISFET interface. Secondly, ionophore and other essential membrane components leach out of the membrane. Thirdly, a physically attached membrane has a limited life time. All systems that were reported when we started our work in this area suffered from one or more of these drawbacks.

We have synthesized hydrophobic receptors that have both a sufficient K^+/Na^+ selectivity and can be *chemically* linked, which is not simply done with valinomycin. We found that the hemispherands [10] and the dimethylcalixcrown ether [10], satisfy these conditions ($K_a(Na^+)/K_a(K^+) \leq 10^{-3}$). The measured potentiometric selectivities, also recorded in plasticized PVC, and the picrate extraction constants of the complexes in solution correlate well [11]. This means that host-guest interactions at the molecular level can be selectively transduced to macroscopic signals.

4. New materials for CHEMFETs

Although the buffered intermediate polyHEMA layer solves the problem of the ill-defined thermodynamics of the ISFET-PVC membrane interface there are other problems remaining, e.g. the high amount of external solvent mediator, and the chemical inertness for covalent attachment of essential membrane components like ionophore and lipophilic anionic sites. Some general features for the design of the membrane materials can be defined:

- The membrane must be an elastomer (glass transition temperature $\leq 0^\circ C$).
- The membrane must be hydrophobic.
- For cation permselectivity anionic sites e.g. tetraphenyl borate or surfactants must be present. These also lower the electrical resistance of the membrane.

For membranes applicable to ISFETs three additional conditions have to be met.

- Covalent linkage of the membrane to the ISFET gate oxide.
- Compatibility with IC-technology which means that materials must be photopolymerizable.
- Covalent linkage of (all) membrane components e.g. plasticizing groups, anionic sites, and ionophore to the matrix.

On the basis of these conditions we have investigated acrylate and siloxane based materials. The (meth)acrylate based membrane materials were studied profoundly [12] in order to achieve ion selective FETs, since they showed excellent properties in their application to the preparation of

REFETs.

In the presence of valinomycin or hemispherand ionophores, potassium-selective chemical sensors have been prepared showing excellent performance. For instance, using diphenylhemispherand-21 in silopren, a slope of 55 mV/pK⁺ was observed and a potentiometric selectivity constant of $\log K(K^+, Na^+) \approx -3.3$ was determined.

5. Conclusions

Covalent attachment of a multi-layer membrane system in which receptor molecules are incorporated to the gate oxide of a field effect transistor gives a molecular system (CHEMFET) that transduces chemical (complexation) reactions into electronic signals. A reference field effect transistor that is insensitive to the ionic strength of a solution is obtained when a specific amount of lipophilic cation is incorporated in the sensing layer of the membrane.

The combination of the two devices, that can be integrated on one chip, allows the differential measurement of concentrations of cationic guest species in the aqueous solution.

- [1] C.J. Pedersen, *Angew. Chem. Int. Ed. Engl.* Vol 27, p. 1021: 1988.
- [2] a) D.J. Cram, *Angew. Chem. Int. Ed. Engl.* Vol 27, p. 1009: 1988. b) J.-M. Lehn, *Angew. Chem. Int. Ed. Engl.* Vol. 27, p. 89: 1988.
- [3] a) A. van Zon, F. de Jong, D.N. Reinhoudt, G.J. Torny, "Chemicals in the Oil Industry", 2nd Int. Symp. on Chemicals in the Oil Industry, University of Manchester, p. 241: 1985. b) F. de Jong, A. van Zon, D.N. Reinhoudt, G.J. Torny, H.P.M. Thomassen, *Recl. Trav. Chim. Pays-Bas* Vol. 102, p. 164: 1983.
- [4] Y. Takeda, *Top. Curr. Chem.* Vol. 121, p. 1: 1984
- [5] a) T.B. Stolkwijk, P.D.J. Grootenhuis, P.D. van der Wal, E.J.R. Sudhölter, D.N. Reinhoudt, S. Harkema, J.W.H.M. Uiterwijk, L. Kruise, *J. Org. Chem.* Vol. 51, p. 489: 1986. b) T.B. Stolkwijk, E.J.R. Sudhölter, D.N. Reinhoudt, J. van Eerden, S. Harkema, *J. Org. Chem.* Vol. 54, p. 1000: 1989. c) T.B. Stolkwijk, E.J.R. Sudhölter, *J. Am. Chem. Soc.* Vol. 109, p. 7042: 1987.
- [6] P. Bergveld, *IEEE Trans. Biomed. Eng.* BME-17, p. 70: 1970.
- [7] A. van den Berg, P. Bergveld, E.J.R. Sudhölter, D.N. Reinhoudt, *Sens. Actuators* Vol. 8, p. 129: 1985.
- [8] a) P. Bergveld, A. van den Berg, P.D. van der Wal, M. Skowronska-Ptasinska, E.J.R. Sudhölter, D.N. Reinhoudt, *Sens. Actuators* Vol. 18, p. 309: 1989. b) M. Skowronska-Ptasinska, P.D. van der Wal, A. van den Berg, P. Bergveld, E.J.R. Sudhölter, D.N. Reinhoudt, *Anal. Chim. Acta* Vol. 230, p. 67: 1990.
- [9] S.D. Moss, J. Janata, C.C. Johnson, *Anal. Chem.* Vol. 47, p. 2238: 1975.
- [10] E.J.R. Sudhölter, P.D. van der Wal, M. Skowronska-Ptasinska, A. van den Berg, P. Bergveld, D.N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas* Vol. 109, p. 222: 1990.
- [11] a) P.J. Dijkstra, H.J. den Hertog Jr., B.J. van Steen, S. Zijlstra, M. Skowronska-Ptasinska, D.N. Reinhoudt, J. van Eerden, S. Harkema, *J. Org. Chem.* Vol. 52, p. 2433: 1987. b) P.J. Dijkstra, unpublished results.
- [12] P.D. van der Wal, M. Skowronska-Ptasinska, A. van den Berg, P. Bergveld, E.J.R. Sudhölter, D.N. Reinhoudt, *Anal. Chim. Acta* Vol 231, p. 41: 1990.

Prof. D.N. Reinhoudt
Department of Chemistry, University of Twente
P.O. Box 217, 7500 AE Enschede (The Netherlands)