TRANSDUCTION OF MOLECULAR INTERACTIONS INTO MACROSCOPIC PROPERTIES

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ABSTRACT. Synthetic receptor molecules derived from calix[4]arenes have been used in
different technological applications. The use of various functionalized calix[4]arenes in
selective membrane transport through supported liquid membranes, selective cation
detection with chemically modified field effect transistors, as preorganized
donor-π-acceptor systems in non-linear optics and in the development of monolayers with
receptor headgroups is discussed.

1. Introduction

The spatial organization of functional groups in hydrophobic calixarenes and their analogs
offers an excellent possibility to construct molecules with specially designed properties.
Based on these compounds we have obtained selective receptors for cations and anions,
donor-acceptor functionalized calix[4]arenes with attractive non-linear optical properties,
and adsorbates with resorcin[4]arene headgroups which are able to recognize small
organic molecules. Technological application of these molecules in materials requires the
translation of the molecular properties into macroscopic properties. In the following
sections the application of calix[4]arenes in selective membrane transport, selective ion
detection, non-linear optics materials, and monolayers of receptor adsorbates on gold will
be discussed.
2. Calix[4]arenes in selective ion transport through supported liquid membranes

Supported liquid membranes (SLMs) containing selective carriers can be used efficiently for separation of aqueous solute species. In SLMs an organic phase is immobilized in the pores of a polymeric support and receptor molecules that selectively form complexes with the solute species are dissolved in the organic layer and serve as carriers for transport. However, the relatively short life-time of SLMs has limited their large scale application. Important parameters for degradation of SLMs are the leaching of the carrier from the membrane phase to the water phases\(^1\) due to the large exchange area and volume ratio of the aqueous phases over the membrane phase, and the progressive wetting of the membrane phase\(^2\), leading to formation of water channels and expulsion of the organic phase by osmotic pressure driven water transport\(^3\). These problems can be overcome by the use of lipophilic carriers, support, and membrane solvents.

In order to prevent the partitioning of the carrier to the aqueous phase the following approaches have been investigated in our laboratory: (i) attachment of long alkyl chains\(^4,5\), (ii) attaching the carrier to a polymer\(^6,7\) and (iii) constructing carriers by using lipophilic building blocks like calixarenes\(^8,9\).

Besides transport of cations with these modified carriers, also carrier mediated transport of neutral molecules through SLMs has been studied\(^10,11\) and recently also anion\(^12\) and ditopic\(^13\) (combined anion and cation) receptors as carriers for membrane transport have been studied.

As carriers for metal cations especially the lower rim functionalized \(p\text{-}t\text{er}t\text{-}b\text{u}t\text{y}l\)calix[4]arenes have been used. The calixarenes \(1\text{a}, 1\text{b}\) with a crown-5 over two opposite aryl moieties are selective for potassium, whereas the tetraamide \(2\text{a}\), tetraketone \(2\text{b}\) and tetraester \(2\text{c}\) (Figure 1) selectively form complexes with sodium. These neutral receptors are suitable as carriers because of their high lipophilicity and complexation selectivity.

The transport of alkali cations has been studied in single cation and competitive transport. A model has been developed which describes diffusion limited transport in terms of the extraction equilibria \((K_{\text{ex}})\) and the mean diffusion constants \((D_{\text{m}})\). This model has also been used to predict the transport selectivity based on the differences in extraction ability
Figure 1. Calix[4]arene carriers in membrane transport.

of the carrier with respect to the different cations$^9$.

A more thorough investigation of the transport mechanism revealed that the potassium flux with calixcrown carriers is not always limited by diffusion of the complex through the membrane. In addition to the diffusional resistance of the membrane, a phase transfer coefficient has to be inserted into the model, which takes into account slow kinetics of release$^7,12$. It was found that the kinetics of release depend very strongly on the conformation of the calixcrowns; the calixarene 1a in the cone conformation shows pure diffusion limited transport whereas its partial cone analog 1b, which bind the potassium cation much more strongly, gives much lower transport rates because of slow release$^{12}$. This slow release of K$^+$ has a negative effect on the transport selectivity for potassium versus sodium. The selectivity can be improved by an increase of the operating temperature and membrane thickness under which condition the transport is determined by the diffusion limited regime$^7$. Furthermore, it was found that the rate limiting step of transport could be influenced by variation of the membrane solvent and the co-transported anion. A remarkable effect of the solvent polarity on the kinetics was observed; lowering of the polarity led to an increase of the flux by accelerating the release process$^{12}$.

The above calix[4]arene carriers give stable membranes, at least under laboratory conditions. In order to stabilize the SLM even further, the calixarene carriers have been covalently linked to the membrane solvent, rendering them yet more lipophilic and increasing their compatibility with the membrane solvent$^{12}$. This increased compatibility
facilitated the optimization of transport rates by using high carrier concentrations and allowed the formation of very stable membranes.

3. Calix[4]arenes in selective ion detection with chemically modified field effect transistors (CHEMFETs)

CHEMFETs are chemically modified field effect transistors designed for the selective detection of ions in aqueous solution. Basically, the CHEMFET is a special modification of the ion sensitive field effect transistor \(^{14}\) (ISFET) in which the gate oxide is covered with an ion selective membrane. Usually ion selectivity is introduced by incorporation of ion-selective receptor molecules in a hydrophobic polymer membrane. Between the sensing membrane and the gate oxide of the ISFET a buffered hydrogel layer is introduced which serves as inner electrolyte solution and eliminates pH sensitivity and CO\(_2\) interference \(^{15}\) (Figure 2). 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. A disadvantage is, however, that due to the small membrane volume plasticizer and electroactive components leach relatively fast from the sensing membrane upon prolonged exposure to the contacting solution. Much research in our group has been focused on the development of a membrane architecture on the sensor device which combines high ion selectivity with long life time. The hydrogel, poly-hydroxyethylmethacrylate (polyHEMA) was covalently attached to the gate oxide surface by photopolymerization of the monomer on the gate oxide which was pretreated with methacryloxypropyltrimethoxysilane. The methacrylated siloxane groups on the surface ensure the covalent binding of the hydrogel. The polyHEMA layer is covered with a polymeric sensing membrane, of which the nature is determined by the desired physical and chemical properties.

The selectivity of the CHEMFET is determined by the selectivity of the ion receptor in the sensing membrane, the partition coefficients of the different ions over the membrane and aqueous phase and the relative concentrations of the ions in the sample solution. An important part of our sensor research is directed to the design and synthesis of ion receptor molecules which have a high selectivity towards common interfering ions. The
membrane upon prolonged contact of the sensor with the aqueous solution. When these sensors are exposed to a continuous stream of tap water, the durability is less than a week. Therefore, a sensor with a long lifetime requires the chemical attachment of the sensing membrane to the semiconductor. Also the electroactive components in the sensing membrane must be prevented from leaching out, which can also 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 \( \leq 0 \, ^\circ C \)); (ii) The membrane must be hydrophobic, but with sufficient conductivity in order to obtain fast response times. For the permselectivity of the analyte ions, ionic sites of opposite charge must be present in the membrane. The presence of charged species in the membrane also lowers the electrical resistance of the membrane. (iii) Functionalization of the membrane should be possible to allow covalent binding of the electroactive components to the sensing membrane. (iv) In order to make sensor fabrication compatible with IC-technology, linkage of all components to the membrane matrix and attachment of the membranes to the gate oxide surface must occur by photopolymerization processes.

We have developed sensing membranes based on polysiloxanes which meet these requirements\(^7\). Good response characteristics were obtained with a copolymer composed of dimethylsiloxane, cyanopropylsiloxane (for modulation of the polarity of the membrane), and methacryloxypropylsiloxane (enabling covalent linkage of receptor and ionic sites) [2]. The synthesis of these membranes is depicted in Scheme 1.

![Scheme 1. Synthesis of a photopolymerizable polysiloxane.](image)

The receptor molecules and anionic sites containing photopolymerizable side groups were incorporated in the polysiloxane membrane. Covalent attachment of polysiloxane to the polyHEMA layer was achieved by prior methacrylation of part of the hydroxyethyl groups of polyHEMA. Subsequent photopolymerization yields a stable polymer network in which
Figure 2. Schematic representation of a CHEMFET

Use of calix[4]arenes as molecular building blocks have been proven to be particularly versatile in this respect because functionalization of the phenolic oxygens in the cone conformation offers the unique possibility to orient four ligand chains at the same side of the molecule. Moreover, these molecules have a high lipophilicity which gives them a high affinity for the membrane phase.

Using calix[4]arene as building blocks, highly selective receptors have been developed for potassium, sodium, silver, lead, and a number of other cations. For the first test of their performance in CHEMFETs, these receptor molecules were incorporated in plasticized PVC membranes. The excellent response of the CHEMFETs containing the silver and lead receptor, respectively, is given in Figure 3.

Figure 3. Response of Ag⁺-selective CHEMFET (a) and Pb²⁺-selective CHEMFET (b) in the presence of 0.1 M Ca(NO₃)₂ and 1 M KCl, respectively. Inset: Selectivity coefficients in the presence of 0.1 M of interfering ion.

Although plasticized PVC membranes with ion selective receptor molecules as sensing membranes give already quite satisfactory results¹⁶ for a limited life time, the adhesion of the membrane to the surface is not stable and plasticizer and ionophore leach out the
all membrane components are covalently anchored. A schematic representation of the architecture of the sensing layers on top of the field effect transistor for a potassium-selective CHEMFET is given in Figure 4.

Figure 4. Schematic representation of a polysiloxane sensing layer covalently attached to a polyHEMA layer, with all electroactive components covalently bound in the sensing membrane.

In this schematic representation both ionophore and anionic sites are covalently bound to the membrane matrix. The effects of covalent attachment of the electroactive components in the membrane have been investigated sequentially. In Figure 5 the time-dependent sensitivity is given for potassium-selective CHEMFETs with polysiloxane membranes with potassium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate as anionic sites and in which the ionophore is either free or covalently bound. This figure shows that due to the covalent linkage of the ionophore via the methacrylate group, leaching out from the membrane matrix is prevented and a stability of several months for the sensor in flow cells is obtained. In contrast, membranes with the same ionophore but without covalent attachment lose their activity quickly\textsuperscript{18}. The effects of covalent immobilisation of both ionophore and ionic sites in the membrane matrix is given in Figure 6. This figure shows the response of sodium-selective CHEMFETs, based on polysiloxane copolymers with methacrylated sodium ionophore covalently bound by photopolymerisation, and in which the anionic site tetraphenylborate is either free (a) or covalently bound (b) to the membrane matrix.
Figure 5. Response characteristics in time of a potassium-selective CHEMFET with the ionophore free and covalently attached to the siloxane membrane.

In the presence of 0.1 M of interfering ions good Nemstian response is obtained for activities of sodium of $8 \times 10^{-4}$ M and higher. The sensor, with all electrical active components covalently bound to the membrane, shows stable response behavior after continuous exposure to 0.1 M NaCl solution for already more than 90 days.

Figure 6. Response of sodium-selective CHEMFETs in the presence of 0.1 M potassium chloride. The ionophore is covalently bound and the tetraphenylborate anions are either free (a) or covalently bound (b) to the membrane matrix.

Non-linear optics is the basis of the strongly emerging photonics technology with important applications in, for example, data processing and data storage. Materials for non-linear optics require a high nonlinear susceptibility ($\chi^{(2)}$), by which optical properties like refractive index and absorbance vary with the intensity of light. Large nonlinear susceptibilities can only be obtained for materials that contain chromophoric units which have a large hyperpolarizability ($\beta$), and of which the orientation along their molecular axis is non-centrosymmetrically distributed in the material. Urea crystals, for example, show nonlinear optical behavior because the orientation of the polarizable dipole of the molecules in the crystal is non-centrosymmetric. However, the hyperpolarizability of the urea molecule is too small and the processability of the crystals is too low to allow widespread application. Organic molecules with both electron-donor and electron-acceptor substituents attached to a $\pi$-conjugated system (D-$\pi$-A systems) are more promising for use in nonlinear optics because of their relatively high $\beta$ values and their potential ease of processability, especially when incorporated in polymeric materials. Extension of the conjugated system in these D-$\pi$-A molecules increases the $\beta$, but unfortunately this is accompanied by a long wavelength shift of the absorbance, thereby limiting the applicability for frequency doubling in, e.g. blue laser devices.

Recently, we have successfully exploited the preorganized orientation of the aromatic moieties in calix[4]arene to develop D-$\pi$-A molecules (Figure 7) with relatively high dipole moments and $\beta$ values, without showing the undesired shift of absorption to the blue wavelength region\textsuperscript{20}. The $\beta$ values of the calix[4]arenes given in Table 1 are 2-3 times higher than the monoaromatic analogs. The $\beta$ value of the tetrakis(nitrostilbene) derivative 6 is comparable with that of $N,N$-dimethylamino-4-nitrostilbene (DANS).

![Chemical structure of calix[4]arenes](image)

**Figure 7. Donor-$\pi$-acceptor substituted calix[4]arenes.**
Table 1. Dipole moments $\mu$, hyperpolarizability $\beta$, and charge transfer band maximum $\lambda_{CT}$ of donor-acceptor substituted calix[4]arenes$^a$.

<table>
<thead>
<tr>
<th>Compd</th>
<th>$\mu$ [D]</th>
<th>$\beta$ [10$^{-30}$ esu]</th>
<th>$\lambda$ [nm]</th>
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<tr>
<td>3</td>
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</tr>
<tr>
<td>7</td>
<td>13.0</td>
<td>161</td>
<td>356</td>
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$^a$Measurements were performed in chloroform. The $\beta$ values ($\pm$ 20%) were obtained from EFISH measurements with a fundamental wavelength of 1064 nm.

Non-centrosymmetrical orientation of the chromophoric units can be achieved by applying a high electrical DC field over a thin film of the material which orients the dipoles of the molecules towards the direction of the field (poling). The electrical field orients the dipoles of the molecules towards the direction of the field. Relaxation of the poling orientation can be prevented as much as possible by poling at high temperature in a polymer of high glass transition temperature and subsequently cooling down of the material in the poling field, or by extensive crosslinking of the polymer after poling. Compounds 4, 6, and 7 have relatively high dipole moments which facilitate poling of these compounds in thin films of the material$^{21}$. In Figure 8 the frequency-doubling coefficients $d_{33}$ are given of various polymeric materials containing different weight percentages of 4, after corona poling with 200-300 V$\mu$m$^{-1}$ at 110 °C. Films with very high concentrations of 4 in PMMA could be prepared with good optical properties and high stability. Even films of pure 4 could be poled with high efficiency. In approximately ten days the $d_{33}$ values of these films decrease to two-third of the initial value measured directly after poling, but after that period no further relaxation of the orientation of the molecules is observed.
Figure 8. Frequency doubling coefficient $d_{33}$ as function of the weight% of 4 in different polymeric matrices.

The frequency doubled signal from the films is now already stable for more than two and a half years. Also for the tetrakis(nitrostilbene) derivative 6, which has even a higher dipole moment than 4, high $d_{33}$ values have been observed when this compound is poled at 110 °C in PMMA. The frequency doubling coefficient increases linearly with the amount of 6 in the polymer and at 60 weight% of 6 a $d_{33}(1064 \text{ nm})$ of 10.8 pm V$^{-1}$ is measured. This value can be further increased by poling of films of neat 6 at more elevated temperatures. Poling of 6 at 210 °C (which is still 100 °C below its decomposition temperature) gives a $d_{33}$ value of 23 pm V$^{-1}$ which, after 35% decrease in the first week, remains stable for already more than 1.5 year.


An efficient control of molecular interactions and molecular orientation in materials can be obtained by self-assembly of molecules in organized mono- and multilayers. Organosulfur compounds with long hydrocarbon chains can form stable monolayers on gold surfaces because of the strong sulfur-gold interaction and the Van der Waals interactions between the hydrocarbon chains. Several self-assembled monolayers of sulfur-adsorbates with functional endgroups (COOH, OH) have been reported. Particularly interesting for sensing purposes are monolayers with cavities protruding to the outside which are able to selective binding of neutral organic molecules. In this category, only one cyclodextrin-based adsorbate is reported, but monolayers of this adsorbate showed many defects, probably due to the imbalance of the cross-sectional area used by the alkyl chains and the cavity headgroup in the monolayer. We have designed and synthesized a number
of resorcin[4]arene receptor molecules containing four alkyl sulfide chains which self-assemble into stable, well-packed monolayers on gold substrates. The resorcin[4]arenes 8a-c have been synthesized according to the route given in Scheme 2.


The four resorcinol units form a conelike cavity which is supported by four dialkylsulfide chains connected to the methine linkages of the macrocycle. The alkyl chains at the resorcinol units are all oriented parallel to each other and perpendicular to the annulus of the cavity. In compound 8a the resorcinol oxygens are linked by a methylene bridge, providing a receptor moiety with a rigid cavitand structure. In 8b the oxygens of the resorcinol unit are methyalted, and in 8c these are acetylated, yielding flexible cavities of different polarity. Immersion of clean gold substrates in ethanol:chloroform (3:1v/v) solutions of the adsorbates at 60 °C for 13 h yielded very stable, well-packed monolayers of 8a-c. Upon binding of the sulfur atoms to the gold surface the terminal alkyl chains of the sulfide are looped back and the total lateral area of the density packed underlying alkyl chains (160 Å) is slightly larger than the area occupied by the cavity head group (140 Å). Monolayers formed by adsorption at room temperature are less well organized, probably because the alkyl chain packing is then kinetically, rather than thermodynamically, controlled.

A variety of surface analytical techniques have been used to confirm the well-organized structure of the monolayers as depicted in Figure 9.
Figure 9. Schematic representation of monolayers of 8a on gold.

X-ray photoelectron spectroscopy (XPS) indicated that the oxygen-rich cavity resides at the outer interface and that the sulfur atoms are located near the gold surface. The thickness of the monolayers, measured by surface plasmon spectroscopy is 22(±2) Å for 8a and 8c, and 24(±2) Å for 8b, which is in accordance with the expected values. Electrochemical measurements show that the heterogenous electron transfer between a gold electrode covered with a monolayer of 8a and a 1 mM K$_3$Fe(CN)$_6$, 0.1 M K$_2$SO$_4$ solution is effectively blocked, indicating the absence of defects in the monolayer structure.

Monolayers of the cavitand 8a have been successfully used for the detection of small neutral organic molecules$^{24}$. Therefore, gold electrodes of a quartz microbalance oscillator were covered with monolayers of 8a and this device was exposed to ppm concentrations of perchloroethylene and other small organic molecules (chloroform, trichloroethylene, and toluene) in synthetic air. Fast, reversible, and relatively large shifts in the fundamental oscillation frequency are observed with remarkable selectivity (> 7:25) for perchloroethylene. In contrast, monolayers of didecyl sulfide exhibit almost no detectable signal. These results indicate that perchloroethylene molecules incorporate into the molecular cavities of the cavitand monolayers. Further studies of these supramolecular assemblies with surface recognition sites are in progress.

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