DOI: 10.1002/anie.200605068

Sensors

# Modern Potentiometry

*Eric Bakker* and Ernö Pretsch**

**Keywords:**
bioanalysis · host–guest systems · ion-selective electrodes · sensors · trace analysis

*For most chemists, potentiometry with ion-selective electrodes (ISEs) primarily means pH measurements with a glass electrode. Those interested in clinical analysis might know that ISEs, routinely used for the determination of blood electrolytes, have a market size comparable to that of glass electrodes. It is even less well known that potentiometry went through a silent revolution during the past decade. The lower detection limit and the discrimination of interfering ions (the selectivity coefficients) have been improved in many cases by factors up to $10^6$ and $10^{10}$, respectively, thus allowing their application in fields such as environmental trace analysis and potentiometric biosensing. The determination of complex formation constants for lipophilic hosts and ionic guests is also covered in this Minireview.*

## 1. The New Wave of Potentiometry

Potentiometric sensors based on liquid or polymer membrane materials are an established technology that spearheaded the integration of sensing devices into the clinical laboratory for the automated testing of physiological samples for key electrolytes such as potassium, sodium, calcium, and chloride, as well as for measuring the pH value.[1] This important success story in the field of electrochemical sensing took place in the 1970s and 1980s,[2–5] after which time the technology was deemed mature, and important advances were no longer thought to be possible.

One of the key turning points in the field of potentiometric sensors in the early 1990s was the introduction of the heparin-selective electrode by the groups of Meyerhoff and Yang.[6] The importance of a sensor for the widely used anticoagulant drug heparin and its antidote protamine was a driving force in its development. In the early stages of the research, the underlying sensing mechanism was not understood. The subsequent explanation of the response mechanism as a nonequilibrium ion-exchange/counterdiffusion process[7,8] helped launch the field of nonclassical potentiometry.[9]

In parallel, success with optical sensors in reaching low detection limits down to sub-nanomolar levels[10] put into question the unappealing detection limits of higher-than-micromolar levels observed with the corresponding ion-selective electrodes (ISEs) based on the very same materials.[11,12] The detection limit of potentiometric sensors, it turned out, was also dictated by nonequilibrium diffusion processes across the membrane,[13,14] which could be described by analogy to the polyion sensors mentioned above.[15,16] Understanding and eliminating the undesired zero-current ion fluxes from the membrane into the sample solution helped to lower the detection limits of ISEs to ultratrace levels.[14,17,18] Subsequently, research has continued in the direction of miniaturization and simplification of the fabrication process by incorporating suitable solid rather than aqueous inner contacts[19] to show that potentiometry is a very useful technique to assess ultralow total ion quantities in small sample volumes.[20,21] The measurement in small sample volumes is especially attractive for coupling the ion-detection step to bioanalytical assays, for example, with dissolvable nanoparticle labels.[22] Other recent trends have focused on actively controlling the ion transport by potential or current control, thus bringing the field of ISEs ever closer to that of traditional voltammetric sensors.[23]

The quest for improved lower detection limits has also reinvigorated the search for better molecular receptors and the characterization of their binding behavior in ISE membranes. New methods were proposed to determine the underlying ion-exchange selectivity of such membranes,[24,25] which yielded ion selectivities that were sometimes better by

[*] Prof. E. Bakker
Department of Chemistry
Purdue University
West Lafayette, IN 47907 (USA)
Fax: (+1) 765-494-0239
E-mail: bakkere@purdue.edu
Prof. E. Pretsch
Laboratorium für Organische Chemie
ETH Zürich
8093 Zürich (Switzerland)
Fax: (+41) 44-632-1164
E-mail: pretsche@ethz.ch

up to 10 orders of magnitude than those originally reported with traditional protocols. A number of methods were also introduced to assess the complex formation constants of lipophilic receptors directly in the organic sensing phase.[26–29] These developments, along with appropriate theoretical treatments on the ion-exchange and diffusion behavior of such membrane systems,[30,31] have provided a strong foundation for further developments in this attractive field.

## 2. Ion Selectivities

The selectivity of a polymer-membrane-based ISE may be understood from an empirical or a mechanistic perspective, and there has been significant debate of the importance of each. In the context of the design and characterization of molecular hosts, membrane materials, and sensors with optimal lower detection limits, the mechanistic perspective is far more important and useful.[25,31] In this case, the selectivity is defined as the thermodynamic ion-exchange selectivity of the membrane, and is described by the potentiometric selectivity coefficient $K_{IJ}^{pot}$ (the subscripts I and J refer to the primary (analyte) ion and the interfering ion, respectively). Smaller values of the selectivity coefficient translate into better selectivity for I. The selectivity coefficient can be directly related to the ion-exchange constant and formation constants of the relevant ion-ionophore complexes and sometimes also to membrane concentrations. For ions I and J that have the same charge $z$ and form strong complexes with an uncharged receptor L of the same stoichiometry, the selectivity coefficient is described by Equation (1).[2]

$$K_{IJ}^{pot} = K_{IJ}\frac{\beta_{JL}}{\beta_{IL}} \tag{1}$$

$K_{IJ}$ is the ion-exchange constant for the uncomplexed ions in the aqueous (aq) and membrane (m) phases [Eq. (2)], and

$$J^{z+}{}_{(aq)} + I^{z+}{}_{(m)} \rightleftharpoons J^{z+}{}_{(m)} + I^{z+}{}_{(aq)} \tag{2}$$

$\beta_{IL}$ and $\beta_{JL}$ are the overall formation constants of the indicated complexes in the membrane phase. The effect of the free energy of solvation is described by $K_{IJ}$, whereby more lipophilic primary ions $I^{z+}$ give smaller selectivity coefficients. The host molecules (ionophores) must bind much more strongly to the primary than to the interfering ions to give a selectivity pattern that deviates significantly from that of a simple ion-exchanger-based membrane, whose selectivity is dictated by $K_{IJ}$ alone.

The selectivity coefficient is accessible experimentally by recording separate calibration curves for each of the ions of interest and measuring the Nernstian calibration slopes. For the measurement of the primary ion, the relationship between electromotive force emf and ion activity $a_I$ in Equation (3) is expected.

$$\text{emf} = E_I^0 + \frac{2.303\,R\,T}{z\,F}\log a_I \tag{3}$$

$R$, $T$, and $F$ are the universal gas constant, the absolute temperature, and the Faraday constant, respectively. The intercepts, $E_I^0$ as well as $E_J^0$ obtained analogously for an interfering ion, are used to determine the selectivity coefficient [Eq. (4)].

$$\log K_{IJ}^{pot} = \frac{z\,F}{2.303\,R\,T}(E_J^0 - E_I^0) \tag{4}$$

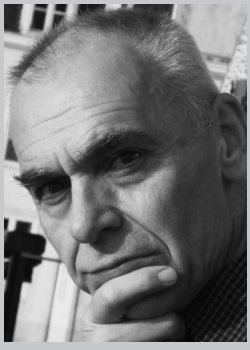
If ion fluxes are irrelevant and the two ions I and J have the same charge, one may expect the emf for a mixed solution containing both I and J to follow the Nicolsky equation [Eq. (5)].

$$\text{emf} = E_I^0 + \frac{2.303\,R\,T}{z\,F}\log(a_I + K_{IJ}^{pot}a_J) \tag{5}$$

In this case, the meaning of the selectivity coefficient is apparent as a weighting factor for the interfering ion. In cases in which the two ions have different charges or ion fluxes are relevant, the response function is described by a more complex equation.[32,33]

The historical challenge of obtaining selectivity coefficients that truly reflect the underlying ion-exchange selectivities [Eq. (1)] was the incomplete ion-exchange upon exposure of the ISE membrane to interfering ions. This situation was especially problematic with strongly discriminated interfering ions, but was overcome by working with membranes that had never been exposed to the primary ion before measurement (Figure 1),[24] by adding a complexing agent for the primary ion to the aqueous phase,[34,35] or by using

*Eric Bakker is a professor of chemistry at Purdue University in West Lafayette, Indiana. After earning his PhD from the Swiss Federal Institute of Technology (ETH) Zurich, he spent two years at the University of Michigan at Ann Arbor for a postdoctoral stay. He started his independent research career at Auburn University in Alabama, where he stayed for 10 years before moving to his current position. His research interests include the development of chemical sensors and sensing concepts based on molecular recognition and extraction principles.*



*Ernö Pretsch studied chemistry at the Technical University Budapest and the ETH Zurich, where he also received his PhD in 1968. At the ETH, he has worked as a research associate and, since 1991, as a titular professor. He is an elected external member of the Hungarian Academy of Sciences. His current research interests focus on potentiometric sensors with a view to optimizing their lower detection limit, selectivity behavior, and robust construction, as well as on the computer-aided interpretation of molecular spectra, including NMR spectra prediction.*

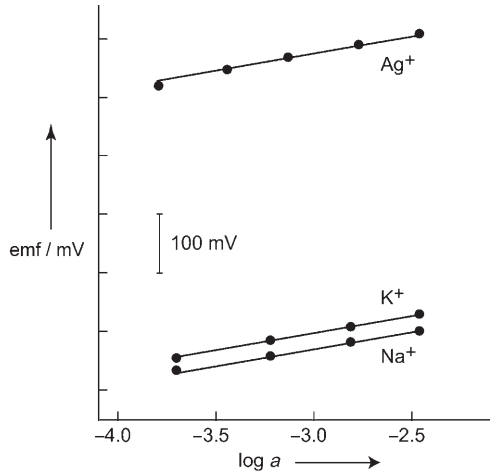



***Figure 1.*** Determination of unbiased selectivity coefficients for a $Ag^+$-selective polymer-membrane electrode.[24] According to Equation (4), the large potential difference between the $Ag^+$ and $Na^+$ calibration curves translates into a selectivity coefficient of $\log K^{pot}_{Ag\,Na} = -8.7$. The data were obtained with a membrane that was not exposed to $Ag^+$ before recording the calibration curves for $Na^+$ and $K^+$.[24]

membranes that exhibited a strong ion flux in direction of the inner solution, thus effectively preventing the leaching of primary ions from the membrane into the sample solution.[14,36]

Today, numerous ISEs have been properly characterized in terms of their underlying ion-exchange selectivity. As shown in Table 1, which summarizes a number of reevaluated

***Table 1:*** Unbiased selectivity coefficients and lower detection limits of selected ion-selective electrodes.

| Ion I | Detection limit [M] | Selectivity coefficients $\log K^{pot}_{IJ}$ | Ref. |
|---|---|---|---|
| $Na^+$ | $3\times10^{-8}$ | $H^+$: −4.8, $K^+$: −2.7, $Ca^{2+}$: −6.0 | [39] |
| $K^+$ | $5\times10^{-9}$ | $Na^+$: −4.2, $Mg^{2+}$: −7.6, $Ca^{2+}$: −6.9 | [40] |
| $NH_4^+$ | $2\times10^{-8}$ | | [40] |
| $Cs^+$ | $8\times10^{-9}$ | $Na^+$: −4.7, $Mg^{2+}$: −8.7, $Ca^{2+}$: −8.5 | [41] |
| $Ca^{2+}$ | ca. $10^{-10}$ | $H^+$: −4.9, $Na^+$: −4.8, $Mg^{2+}$: −5.3 | [42] |
| $Ag^+$ | $3\times10^{-11}$ | $H^+$: −10.2, $Na^+$: −10.3, $Ca^{2+}$: −11.3 | [43] |
| $Pb^{2+}$ | $6\times10^{-11}$ | $H^+$: −5.6, $Na^+$: −5.6, $Mg^{2+}$: −13.8 | [36, 44] |
| $Cd^{2+}$ | $1\times10^{-10}$ | $H^+$: −6.7, $Na^+$: −8.4, $Mg^{2+}$: −13.4 | [45, 46] |
| $Cu^{2+}$ | $2\times10^{-9}$ | $H^+$: −0.7, $Na^+$: $<-5.7$, $Mg^{2+}$: $<-6.9$ | [47] |
| $ClO_4^-$ | $2\times10^{-8}$ | $OH^-$: −5.0, $Cl^-$: −4.9, $NO_3^-$: −3.1 | [48] |
| $I^-$ | $2\times10^{-9}$ | $OH^-$: −1.7 | [48] |

systems, the selectivity coefficients can sometimes reach values in the order of $10^{-10}$ to $10^{-15}$, many orders of magnitude lower than those observed with traditional methods put forth by IUPAC.[37,38] These excellent selectivities have formed the chemical basis for achieving improved lower detection limits, as outlined below.

## 3. Lower Detection Limits

Ideally, the lower detection limit of an ISE results from interfering ions; hence, its value is determined by the concentration of other ions in the sample and the corresponding selectivity coefficients $K^{pot}_{IJ}$ of the membrane. For a primary ion I with charge $z_I$ and a dominating interfering ion J with charge $z_J$, the lower detection limit is defined as $a_I(DL) = K^{pot}_{IJ} a_J^{z_I/z_J}$. Note that this IUPAC definition[37,38] does not correspond to that of all other analytical methods[49] (also by IUPAC), for which the lower detection limit is expressed in terms of the signal in the absence of analyte and noise. This latter definition would result in potentiometric detection limits that would be lower by about two orders of magnitude than those according to the expression given above.[18]

Unfortunately, at sub-micromolar concentrations of the analyte ion, detection limits given by the above expression cannot be fully achieved. Although they are still related to the selectivity and the concentration of interfering ions, the relationship is much more complicated[30] because the sample is contaminated by the sensing membrane. The concentration of ions in an ISE membrane is in the order of $10^{-2}$–$10^{-3}$ mol kg$^{-1}$. Therefore, leaching of a small fraction of them into the sample as well as slow transport of primary ions from the inner solution to the sample are capable of biasing the response of ISE membranes at sub-micromolar concentrations. These processes typically uphold an approximately micromolar concentration of primary ions in the sample layer adjacent to the membrane (the sensing layer) even if the bulk of the sample does not contain any primary ions.[50] For a long time, it was, therefore, assumed that the lower detection limit of such sensors could not be better than approximately $10^{-6}$ M. For the same reason, the relevance of interfering ions had been heavily overestimated. What was presumed to be interference was in fact the result the above-mentioned micromolar concentration of primary ions. After the real cause was discovered,[13,14] a series of different methods were designed to reduce this bias.[51] Today, it is clear that the bias cannot be eliminated entirely and that the lower detection limit at sub-micromolar concentrations is always worse than expected from the interference by other ions alone.[30] As, however, many selectivity coefficients have turned out to be very low (down to as low as ca. $10^{-15}$), detection limits around $10^{-8}$–$10^{-10}$ M have already been found for more than 10 ions (see Table 1 and Figure 2).

## 4. Miniaturization

Conventional ISEs are based on polymeric membranes (in most cases, plasticized poly(vinyl chloride), PVC) with diameters of 5–10 mm, usually in contact on their inner side with a solution containing the primary ion, and equipped with an inner reference electrode (e.g., Ag/AgCl). These dimensions have mainly historical reasons and are by no means mandatory. In fact, potentiometric electrodes with diameters in the μm range have been known for more than 30 years and were used for in vivo measurements in living cells.[52] Such microelectrodes were fragile, cumbersome to prepare, and had short lifetimes of only hours or days. Although even smaller electrodes with diameters in the order of 100 nm have been prepared in the meantime,[53] most current developments focus to membrane dimensions of 0.1–1 mm, which is

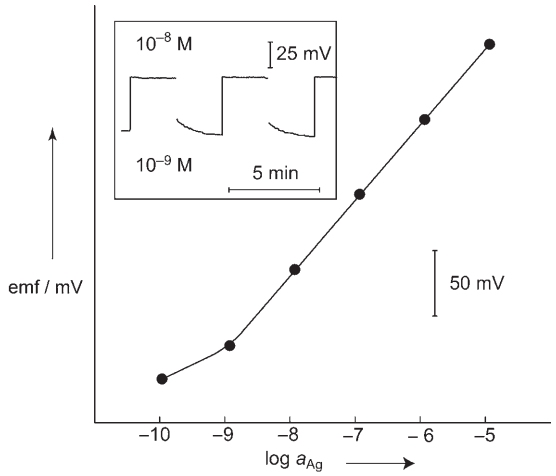



***Figure 2.*** Calibration curve of a $Ag^+$-selective polymer-membrane electrode, exhibiting a sub-nanomolar detection limit.[21] Inset: Responses upon repeated exposure to 1- and 10-nanomolar levels of silver nitrate.

the typical size of the ISE membranes used in blood electrolyte analysis, for which about 100 μL of blood, serum, or plasma is used for around 10 parallel measurements on a single sample.[1]

More-recent efforts have focused on the construction of ISEs of this size, and the lower detection limits are similar to the best ones obtained with macroscopic membranes (see Section 3). One advantage of achieving such good detection limits in samples of small volumes is the possibility to determine very low total amounts of analyte. Potentiometry has good prospects in this regard because, in contrast to most other techniques, the analyte is not consumed during measurement. Because conventional reference electrodes cannot be used in such small samples, a second miniaturized ISE membrane is utilized as a reference, which responds to an ion whose activity is kept constant. In a recent example, plasticized PVC membranes prepared in micropipette tips were used for measurements in samples of 3 μL.[20] A total of 300 attomoles of different cations generated a signal that was up to 300 times higher than the standard deviation of the background noise (Figures 3 and 4).[20] Monolithic capillaries have also been used as holders of ISE membranes (without PVC).[39] With such membranes, transmembrane ion fluxes are largely suppressed so that the ISE response is virtually independent of the composition of the inner solution.[39]

Miniaturized ISEs with a solid rather than a conventional aqueous inner contact are simpler to fabricate and currently

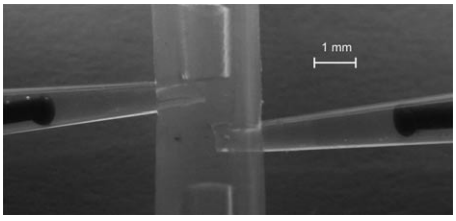



***Figure 3.*** 3-μL measuring cell. A $Ca^{2+}$ ISE indicator electrode (left) and a $Na^+$ ISE reference electrode (right) are inserted into 1-mm i.d. silicone tubing and put in contact with the aqueous sample plug.[20]

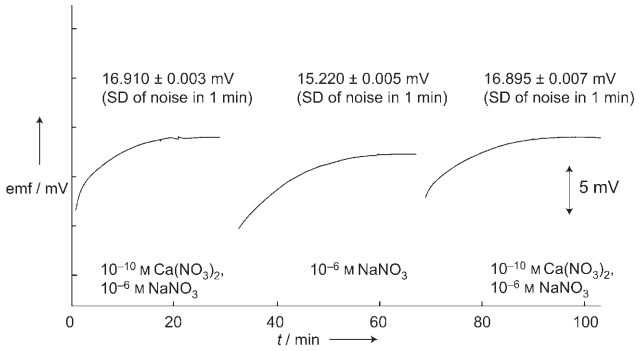



***Figure 4.*** Potentiometric detection of 300 amol of $Ca^{2+}$ ($10^{-10}$ M in 3 μL) against a constant background of $10^{-6}$ M $NaNO_3$. A miniaturized $Na^+$ ISE was used as reference electrode.[20]

represent an active field of research. Although ISEs with an internal solid contact have been known for more than 30 years,[54] until recently, they have shown insufficient potential stability as a result of the lack of a defined redox couple between the membrane and the inner electrode[55,56] as well as the formation of a thin water film between the two components.[57] Moreover, the transport of ions through the sensing membrane may significantly alter the composition of this water film of very small volume and, thus, also change the boundary potential between this layer and the contacting phases.[57] Both sources of instability can be eliminated by the use of lipophilic, redox-active self-assembled monolayers (Figure 5).[58–60] Conducting polymers are a more versatile possibility and have been extensively investigated during recent years.[61] More than 10 years ago, they were shown to be excellent ion-to-electron transducers in so-called all-solid-state electrodes.[19] However, their use in ISEs with sub-

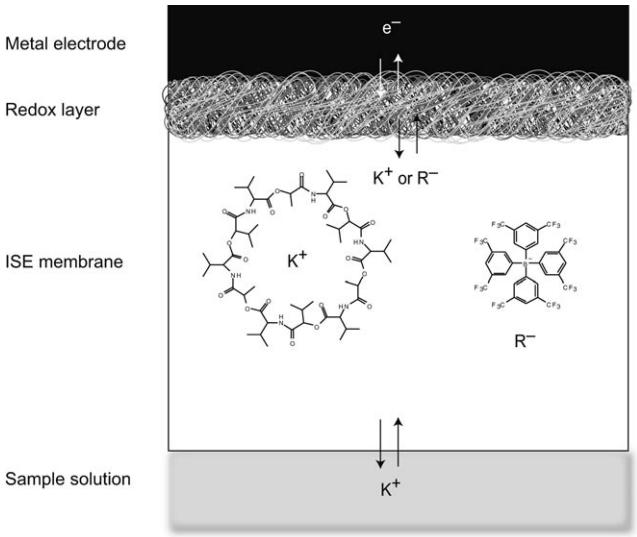



***Figure 5.*** A solid-contact ISE. The measuring current (in the order of fA) is transported by ions in the solutions and the ISE membrane and by electrons in the metal. The two processes are coupled in the redox layer (a conducting polymer or a redox-active self-assembled monolayer). If the redox layer is absent or not lipophilic enough, a water film may form at the inner surface of the membrane, which leads to potential instabilities and deteriorates the lower detection limit.

micromolar detection limits is more recent.[62,63] In particular, the formation of a water film between the ISE membrane and the conducting polymer, which is especially critical in this low concentration range, has only been investigated more recently.[64–66] If a water film is avoided, lower detection limits can be achieved with miniaturized solid-contact ISEs that are as good, or even better, than their liquid-contact analogues.[67] In most cases, the PVC matrix is replaced by acrylate or methacrylate copolymers that do not require the addition of a plasticizer.[68,69] The diffusion coefficients in such matrices are significantly lower, by orders of magnitude, than in PVC,[70] which is an advantage with respect to the response time and the possible formation of the above-mentioned water film but a disadvantage with respect to the conditioning time. Although many details and optimized preparation procedures are still to be established, it seems that miniaturized solid-contact ISEs represent the preferred method of constructing the next generation of ISEs.

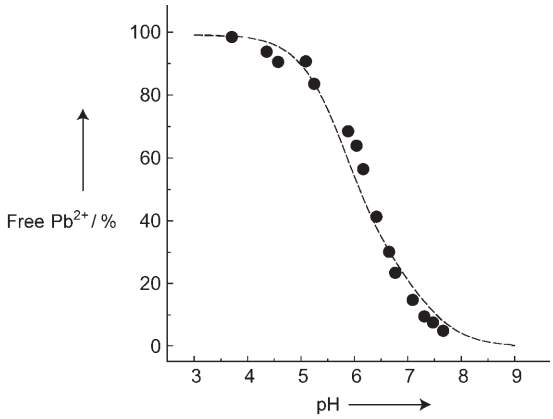



***Figure 6.*** Potentiometric determination of the fraction of uncomplexed $Pb^{2+}$ as a function of pH in a sample of drinking water spiked with 10 ppb of $Pb^{2+}$. Dashed line: calculated free $Pb^{2+}$ activity for a total carbonate concentration of 4.14 mM.[71]

## 5. Applications

For many decades, besides pH determinations, clinical analyses have been an important practical application of ISEs. As the physiological ranges of relevant ions are rather narrow, the precision and accuracy must be better than 2–3%, which is rather demanding in view of the small sample amounts and the complexity of media such as whole blood.[1] As a more recent clinical application, the determination of heparin and its antidote protamine has emerged.[8] Because of the high charges of the analytes (−70 for heparin and +30 for protamine), the sensitivity (i.e., the slope of the corresponding sensor response function, $59.2/z$ [mV dec$^{-1}$] at 25 °C) would normally be negligibly small, so nonclassical potentiometry must be used to assess these clinically important polyions (see Section 6).[7]

Various practical applications of ISEs with recently improved lower detection limits are in fact being developed. Their utility for trace-metal analysis in drinking water has been documented by the good agreement of the results with those obtained by inductively coupled plasma mass spectrometry (ICPMS).[47,71] As the ISE response depends on free-ionic activities and ICPMS does not distinguish between the different forms of the analyte, a direct comparison is only possible when the analyte is in its free form during the potentiometric measurements. The pH dependence of the response of a $Pb^{2+}$ ISE to 10 ppb of $Pb^{2+}$ illustrates this fact (Figure 6).[71] At pH > 4.0, the increasing amount of carbonate successively reduces the activity of free $Pb^{2+}$ (the dashed curve displays the calculated response). Performing the measurements at pH 4.0 resulted in an excellent correlation with the ICPMS data (Figure 7).[71] ISEs with improved lower detection limits have also been successfully applied in biouptake studies of $Pb^{2+}$ and $Cd^{2+}$.[46,72]

One emerging application of miniaturized ISEs is potentiometric biosensing with nanoparticle labels. This technique was demonstrated with a sandwich immunoassay based on the capture of gold nanoparticles and the deposition and subsequent dissolution of silver, which was detected with a $Ag^+$

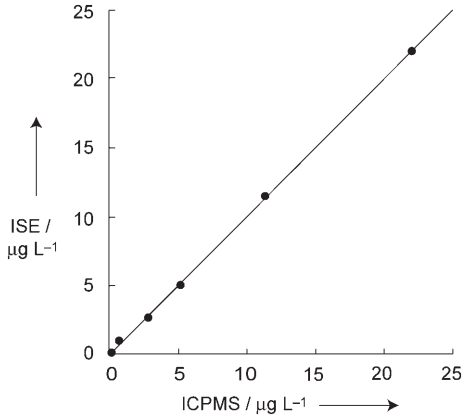



***Figure 7.*** Comparison of $Pb^{2+}$ activity values of environmental samples obtained by potentiometry at pH 4.0 with those obtained by ICPMS.[71]

ISE (Figure 8).[22] This assay showed good selectivity and a detection limit of about 12.5 pmol of IgG in a 50-µL sample (Figure 8).[22] A further possible use of such miniaturized ISEs is the detection of biorecognition-modulated ion fluxes through functionalized gold nanotubules as a novel label-free biosensing approach.[73]

The measurement of complex formation constants in lipophilic phases is another recent application of ISEs and may also be of wider interest for studying host–guest interactions. The potential difference at the membrane/solution phase boundary is a direct function of the activity of ions $a_{i(aq)}/a_{i(m)}$ in both phases. For conventional applications, the activity in the membrane is kept constant. However, ISE membranes can also be used to obtain information on free-ion activities in the membrane and, thus, complex formation constants. As complex formation also influences the phase-boundary potential on the inner side of the membrane, and the ISE response depends on the relative lipophilicity of the ions as well [Eq. (1)], a reference is required for obtaining the relevant information on free-ion activities in the membrane. One possibility is to use a second ionophore that does not interact with the ions of interest.

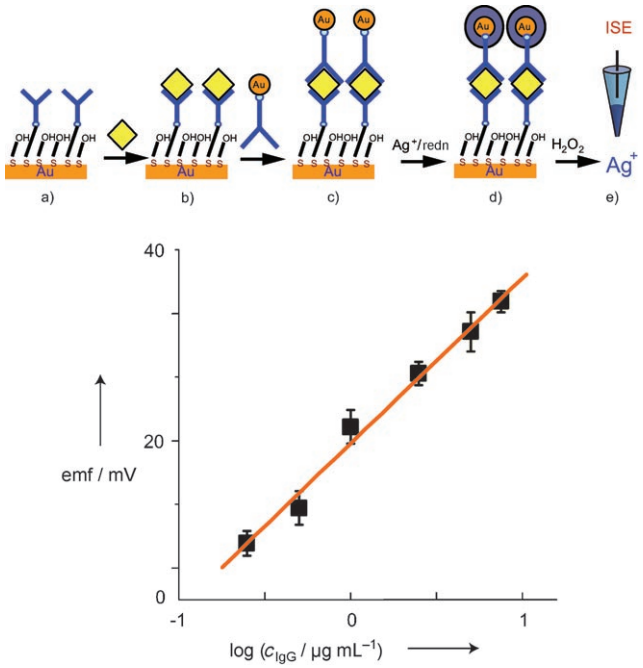



***Figure 8.*** Top: Sandwich immunoassay with potentiometric detection: a) The antibody is immobilized on gold by self-assembly; b) anti-mouse IgG antigen is bound to the antibody; c) a second antibody with Au nanoparticle labels is bound to the antigen; d) Ag is deposited on Au nanoparticles; and e) dissolved $Ag^+$ is detected with an $Ag^+$ ISE. Bottom: Calibration curve of the $Ag^+$ ISE response to IgG.

Adequate reference ionophores are organic bases that interact strongly with $H^+$ but only negligibly with other ions.[26] Another approach involved reference cations such as tetraalkylammonium that show only negligibly small interactions with the ionophores investigated.[27] Finally, one can prepare a reference membrane without the ionophore but with otherwise the same composition as the membrane to be investigated. When the two membranes are combined to create a double membrane, its initial potential in a symmetrical cell reflects the ratio of the ion activities in the two segments.[28,29] As ion-pair formation also influences the activities of free ions, strictly speaking, formal complex formation constants are obtained that involve the ratio of ion-pair formation constants of the free and complexed ions. Alternatively, the method can be used to study ion-pair formation in such membranes.[74] So far, the complexation of nearly 100 ionophores has been studied with this approach (see Table 2 for a selection). In contrast to most currently applied techniques for investigating host–guest interactions, the potentiometric methods are extremely suitable for the characterization of strong complexes. As they are rather simple and much less demanding than the other techniques, it is expected that they will be more widely applied in the future by researchers outside the field of potentiometric sensor development.

***Table 2:*** Effective formation constants $\log\beta_{IL}$ for complexes of lipophilic hosts and ionic guests in solvent polymeric membranes.[a]

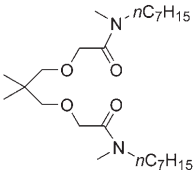
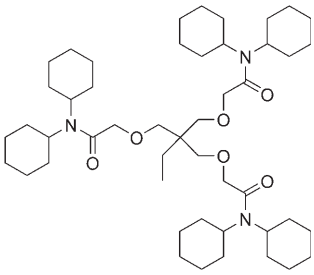
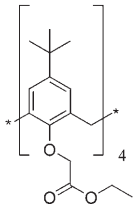
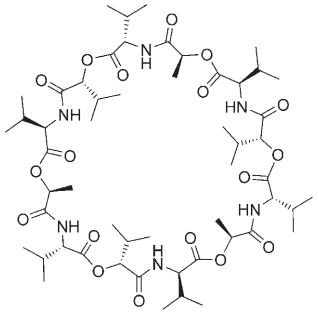
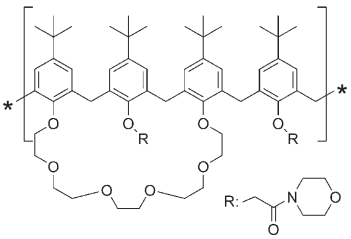
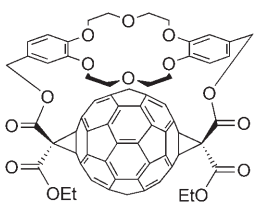
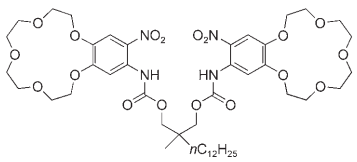
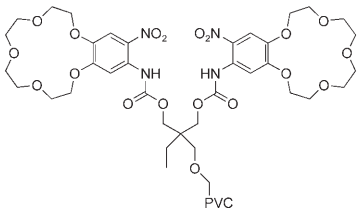
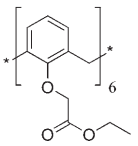
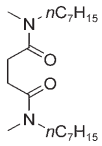
| | | | |
|---|---|---|---|
|  |  |  |  |
| $Li^+$ [2:1] 7.90[84] (DOS); 10.71[84] (NPOE) | $Li^+$ [1:1] 6.7,[85] 7.4[85], 8.24[84] (DOS); 7.40[86] (BBPA)<br>$Na^+$ [1:1] 4.5,[85] 5.1[85] (DOS); 5.75[86] (BBPA)<br>$K^+$ [1:1] 3.2,[85] 2.8[85] (DOS); 4.62[86] (BBPA) | $Na^+$ [1:1] 7.69,[84] 7.60[28] (DOS); 10.27[84] (NPOE) | $K^+$ [1:1] 10.10[84] (DOS); 7.5[29] (DBP); 11.63[84] (NPOE)<br>$Na^+$ [1:1] 4.4[29] (DBP)<br>$NH_4^+$ [1:1] 5.7[29] (DBP) |
|  |  |  |  |
| $K^+$ [1:1] 8.0[87] (NPOE)<br>$Na^+$ [1 : 1] 7.5[87] (NPOE)<br>$Rb^+$ [1:1] 7.3[87] (NPOE) | $K^+$ [1:1] 5.4[88,89] (DOS)<br>$Li^+$ [1:1] 2.9[88,89] (DOS)<br>$Na^+$ [1:1] 4.0[88,89] (DOS)<br>$Cs^+$ [1:1] 3.3[88,89] (DOS) | $K^+$ [1:1] 7.84,[84] 7.75[90] (DOS); 10.04[84] (NPOE)<br>$Li^+$ [1:1] 4.22[28] (DOS)<br>$Na^+$ [1:1] 6.00[28] (DOS) | $K^+$ [1:1] 6.50[90] (DOS)<br>$Na^+$ [1:1] 4.63[90] (DOS) |

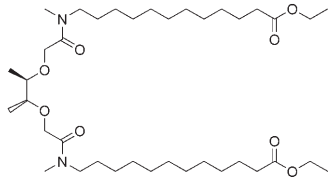
*Table 2* (Continued)



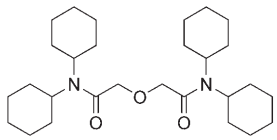
$Cs^+$ [1:1] 8.74[41] (DOS)



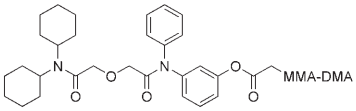
$Mg^{2+}$ [3:1] 9.72[84] (DOS);
13.84[84] (NPOE)



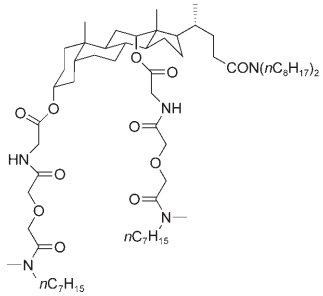
$Ca^{2+}$ [2:1] 19.70[84] (DOS);
24.54,[84] 14.0[91] (NPOE)



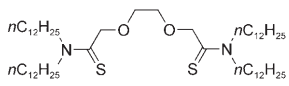
$Ca^{2+}$ [3:1] 25.5[84] (DOS);
29.2,[84] 15.2[91] (NPOE)



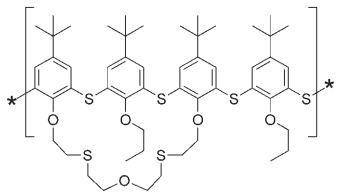

$Ca^{2+}$ [3:1] 16.85[92]
(in MMA–DMA matrix)[b]



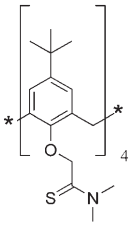

$Ca^{2+}$ [1:1] 8.6[91] (NPOE)



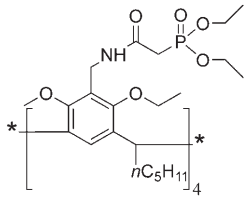
$Cd^{2+}$ [2:1] 16.4[27] (DOS)
$K^+$ [1:1] $< 3$[27] (DOS)
$Ag^+$ [2:1] 19.0[27] (DOS)
$Ca^{2+}$ [1:1] $< 3$[27] (DOS)
$Pb^{2+}$ [2:1] 14.7[27] (DOS)
$Cu^{2+}$ [2:1] 14.8[27] (DOS)



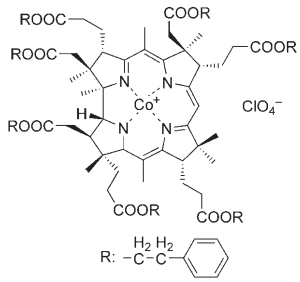
$Ag^+$ [1:1] 10.85,[43] 11.31[43] (NPOE)



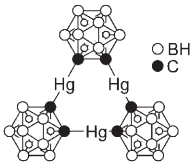
$Pb^{2+}$ [1:1] 15.9,[27] 15.8[93] (DOS);
21.3,[93] 18.4[94] (NPOE)
$Na^+$ [1:1] 3.1[27] (DOS)
$Cu^{2+}$ [1:1] 12.1[27] (DOS)
$Cd^{2+}$ [1:1] 10.0[27] (DOS)



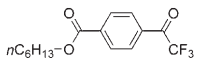
$Eu^{3+}$ [1:1] 31.0[96] (NPOE)
$Na^+$ [1:1] 12.0[96] (NPOE)
$Ca^{2+}$ [1:1] 16.9[96] (NPOE)
$Sr^{2+}$ [1:1] 21.4[96] (NPOE)
$Cu^{2+}$ [1:1] 21.7[96] (NPOE)
$Cd^{2+}$ [1:1] 22.7[96] (NPOE)
$Pb^{2+}$ [1:1] 22.5[96] (NPOE)
$UO_2^{2+}$ [1:1] 25.5[96] (NPOE)



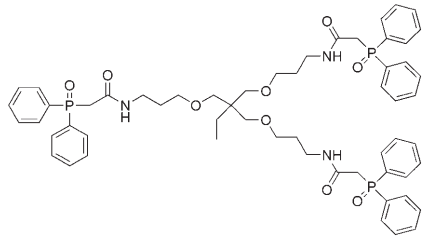
$NO_2^-$ [1:1] 10.58[97] (DOS); 10.59[97]
(NPOE)



$Cl^-$ [2:1] 13.4[98] (DOS)
($\log K_1 = 9.9$, $\log K_2 = 3.5$)



$CO_3^{2-}$ [4:1] 12.8[29] (DBP)
$CH_3COO^-$ [2:1] 5.9[29] (DBP)
benzoate [2:1] 5.3[29] (DBP)
$Cl^-$ [2:1] 3.3[29] (DBP)



$Eu^{3+}$ [1:1] 28.3[95] (NPOE)
$Na^+$ [1:1] 8.4[95] (NPOE)
$Cu^{2+}$ [1:1] 19.8[95] (NPOE)
$Cd^{2+}$ [1:1] 19.1[95] (NPOE)
$Pb^{2+}$ [1:1] 17.4[95] (NPOE)
$UO_2^{2+}$ [1:1] 21.5[95] (NPOE)

[a] The host–guest stoichiometry is given in brackets. The PVC membranes were based on the plasticizers: bis(butylpentyl)adipate (BBPA), bis(2-ethylhexyl)sebacate (DOS), dibutyl phthalate (DBP), dioctyl phthalate (DOP), 2-nitrophenyl octyl ether (NPOE). [b] MMA–DMA: poly(methyl methacrylate)-*co*-(decyl methacrylate).

## 6. Nonclassical Potentiometry

Zero-current concentration polarization at the ISE membrane has been described above as highly undesirable for characterization of the underlying ion-exchange selectivity and for obtaining ultratrace detection limits. It can, however, be very attractive for a number of applications. Probably the most prominent examples that take advantage of zero-current ion fluxes are the ISEs for the polyions heparin, protamine, and a number of other highly charged species briefly mentioned above.[8] In these cases, the high polyion charge would preclude an analytically useful sensitivity of the ISE, since the slope of the calibration curve decreases linearly with the charge of the ion. Analytically useful polyion sensors have been designed by taking advantage of a counterdiffusion process, in which the polyion of interest is depleted locally at the membrane surface during the accumulation process. This makes the response of the ISE dependent on the mass transport of the polyion to the membrane surface and results in calibration slopes significantly larger than those predicted from the Nernst equation [Eq. (3)].[7] Polyion sensors of this kind have been successfully implemented for use in the clinical detection of heparin in undiluted whole-blood samples, thus demonstrating that such nonclassical sensing schemes can be practically useful.[8]

Nonclassical potentiometry may also be attractive in other situations, because concentration polarization at the sample side of the membrane may give more information about the sample than ion activities according to the Nernst equation. Interesting examples include chemical alarm systems with an unusually high sensitivity and without the need for reference electrodes,[75,76] as well as the monitoring of chemical titrations that show larger than classically expected endpoints.[77] Recently, it was shown that thin polymeric membranes can be used to calibrate ISEs from the back side without altering the sample solution in any way.[78,79] In this example, zero-current fluxes in either direction are eliminated almost instantly when the membrane–internal concentration gradient is reduced to zero by the judicious choice of composition of the inner solution.

In recent years, this area of ISE research has been further strengthened by the introduction of current control to induce instrumentally an ion flux across the membrane. Initial examples of this technique involve an imposed current to lower the detection limit.[80–82] More-recent research utilized larger current densities in a multipulse sequence to make many of the above-mentioned sensing principles fully reversible and, therefore, analytically even more useful.[23,76,83]

## 7. Summary and Outlook

The performance of potentiometric sensors has been dramatically improved during the past decade. New applications include the study of host–guest equilibria in lipophilic organic phases and trace analysis in environmental samples. One emerging field is potentiometric bioanalysis with nanoparticle labels or nanopores, which could eventually provide an inexpensive and highly sensitive technique. Another developing field is nonclassical potentiometry including controlled-current measurements.

*The authors gratefully acknowledge the National Institutes of Health (EB002189 and GM07178), the National Science Foundation, and the Swiss National Foundation for financial support of their electrochemical sensor research and Dr. D. Wegmann for careful reading of the manuscript.*

Received: December 15, 2006
Published online: April 24, 2007

[1] C. C. Young, *J. Chem. Educ.* **1997**, *74*, 177–182.
[2] W. E. Morf, *The Principles of Ion-Selective Electrodes and of Membrane Transport*, Elsevier, New York, **1981**.
[3] J. Koryta, K. Stulik, *Ion-Selective Electrodes*, Cambridge University Press, Cambridge, **1983**.
[4] R. P. Buck, E. Lindner, *Anal. Chem.* **2001**, *73*, 88A–97A.
[5] E. Bakker, P. Bühlmann, E. Pretsch, *Chem. Rev.* **1997**, *97*, 3083–3132.
[6] S. C. Ma, M. E. Meyerhoff, V. C. Yang, *Anal. Chem.* **1992**, *64*, 694–697.
[7] B. Fu, E. Bakker, J. H. Yun, V. C. Yang, M. E. Meyerhoff, *Anal. Chem.* **1994**, *66*, 2250–2259.
[8] M. E. Meyerhoff, B. Fu, E. Bakker, J. H. Yun, V. C. Yang, *Anal. Chem.* **1996**, *68*, 168 A-175 A.
[9] E. Bakker, M. E. Meyerhoff, *Anal. Chim. Acta* **2000**, *416*, 121–137.
[10] W. E. Morf, K. Seiler, B. Rusterholz, W. Simon, *Anal. Chem.* **1990**, *62*, 738–742.
[11] M. Lerchi, E. Bakker, B. Rusterholz, W. Simon, *Anal. Chem.* **1992**, *64*, 1534–1540.
[12] P. Bühlmann, E. Pretsch, E. Bakker, *Chem. Rev.* **1998**, *98*, 1593–1687.
[13] S. Mathison, E. Bakker, *Anal. Chem.* **1998**, *70*, 303–309.
[14] T. Sokalski, A. Ceresa, T. Zwickl, E. Pretsch, *J. Am. Chem. Soc.* **1997**, *119*, 11347–11348.
[15] T. Sokalski, T. Zwickl, E. Bakker, E. Pretsch, *Anal. Chem.* **1999**, *71*, 1204–1209.
[16] W. E. Morf, M. Badertscher, T. Zwickl, N. F. de Rooij, E. Pretsch, *J. Phys. Chem. B* **1999**, *103*, 11346–11356.
[17] E. Bakker, E. Pretsch, *Anal. Chem.* **2002**, *74*, 420A–426A.
[18] E. Bakker, E. Pretsch, *TrAC Trends Anal. Chem.* **2005**, *24*, 199–207.
[19] A. Cadogan, Z. Gao, A. Lewenstam, A. Ivaska, D. Diamond, *Anal. Chem.* **1992**, *64*, 2496–2501.
[20] A. Malon, T. Vigassy, E. Bakker, E. Pretsch, *J. Am. Chem. Soc.* **2006**, *128*, 8154–8155.
[21] N. Rubinova, K. Chumbimuni-Torres, E. Bakker, *Sens. Actuators B*, in press.
[22] K. Y. Chumbimuni-Torres, D. Zong, N. Rubinova, Y. Xiang, E. Pretsch, J. Wang, E. Bakker, *J. Am. Chem. Soc.* **2006**, *128*, 13676–13677.
[23] A. Shvarev, E. Bakker, *Anal. Chem.* **2003**, *75*, 4541–4550.
[24] E. Bakker, *Anal. Chem.* **1997**, *69*, 1061–1069.
[25] E. Bakker, E. Pretsch, P. Bühlmann, *Anal. Chem.* **2000**, *72*, 1127–1133.
[26] E. Bakker, E. Pretsch, *Anal. Chem.* **1998**, *70*, 295–302.
[27] A. Ceresa, E. Pretsch, *Anal. Chim. Acta* **1999**, *395*, 41–52.
[28] Y. Mi, E. Bakker, *Anal. Chem.* **1999**, *71*, 5279–5287.
[29] M. M. Shultz, O. K. Stefanova, S. B. Mokrov, K. N. Mikhelson, *Anal. Chem.* **2002**, *74*, 510–517.
[30] A. Ceresa, A. Radu, S. Peper, E. Bakker, E. Pretsch, *Anal. Chem.* **2002**, *74*, 4027–4036.
[31] E. Bakker, P. Bühlmann, E. Pretsch, *Talanta* **2004**, *63*, 3–20.

[32] E. Bakker, R. K. Meruva, E. Pretsch, M. E. Meyerhoff, *Anal. Chem.* **1994**, *66*, 3021 – 3030.
[33] M. Nägele, E. Bakker, E. Pretsch, *Anal. Chem.* **1999**, *71*, 1041 – 1048.
[34] U. Schefer, D. Ammann, E. Pretsch, U. Oesch, W. Simon, *Anal. Chem.* **1986**, *58*, 2282 – 2285.
[35] T. Sokalski, M. Maj-Zurawska, A. Hulanicki, *Mikrochim. Acta* **1991**, *103*, 285 – 291.
[36] T. Sokalski, A. Ceresa, M. Fibbioli, T. Zwickl, E. Bakker, E. Pretsch, *Anal. Chem.* **1999**, *71*, 1210 – 1214.
[37] G. G. Guilbault, R. A. Durst, M. S. Frant, H. Freiser, E. H. Hansen, T. S. Light, E. Pungor, G. Rechnitz, N. M. Rice, T. J. Rohm, W. Simon, J. D. R. Thomas, *Pure Appl. Chem.* **1976**, *48*, 127 – 132.
[38] R. P. Buck, E. Lindner, *Pure Appl. Chem.* **1993**, *66*, 2527 – 2536.
[39] T. Vigassy, C. G. Huber, R. Wintringer, E. Pretsch, *Anal. Chem.* **2005**, *77*, 3966 – 3970.
[40] W. Qin, T. Zwickl, E. Pretsch, *Anal. Chem.* **2000**, *72*, 3236 – 3240.
[41] A. Radu, S. Peper, C. Gonczy, W. Runde, D. Diamond, *Electroanalysis* **2006**, *18*, 1379 – 1388.
[42] I. Bedlechowicz, M. Maj-Zurawska, T. Sokalski, A. Hulanicki, *J. Electroanal. Chem.* **2002**, *537*, 111 – 118.
[43] Z. Szigeti, A. Malon, T. Vigassy, V. Csokai, A. Grün, K. Wygladacz, N. Ye, C. Xu, V. J. Chebny, I. Bitter, R. Rathore, E. Bakker, E. Pretsch, *Anal. Chim. Acta* **2006**, *572*, 1 – 10.
[44] T. Vigassy, R. E. Gyurcsányi, E. Pretsch, *Electroanalysis* **2003**, *15*, 1270 – 1275.
[45] A. C. Ion, E. Bakker, E. Pretsch, *Anal. Chim. Acta* **2001**, *440*, 71 – 79; A. C. Ion, E. Bakker, E. Pretsch, *Anal. Chim. Acta* **2002**, *452*, 329.
[46] S. Plaza, Z. Szigeti, M. Geisler, E. Martinoia, E. Pretsch, *Anal. Biochem.* **2005**, *347*, 10 – 16.
[47] Z. Szigeti, I. Bitter, K. Tóth, C. Latkoczy, D. J. Fliegel, D. Günther, E. Pretsch, *Anal. Chim. Acta* **2005**, *532*, 129 – 136.
[48] A. Malon, A. Radu, W. Qin, Y. Qin, A. Ceresa, M. Maj-Zurawska, E. Bakker, E. Pretsch, *Anal. Chem.* **2003**, *75*, 3865 – 3871.
[49] L. A. Currie, *Pure Appl. Chem.* **1995**, *67*, 1699 – 1723.
[50] R. E. Gyurcsányi, E. Pergel, R. Nagy, I. Kapui, B. T. T. Lan, K. Tóth, I. Bitter, E. Lindner, *Anal. Chem.* **2001**, *73*, 2104 – 2111.
[51] Z. Szigeti, T. Vigassy, E. Bakker, E. Pretsch, *Electroanalysis* **2006**, *18*, 1254 – 1265.
[52] R. C. Thomas, W. Simon, M. Oehme, *Nature* **1975**, *258*, 754 – 756.
[53] J. H. Shim, J. Kim, G. S. Cha, H. Nam, R. J. White, H. S. White, R. B. Brown, *Anal. Chem.*, in press.
[54] R. W. Cattrall, H. Freiser, *Anal. Chem.* **1971**, *43*, 1905 – 1906.
[55] D. Liu, R. K. Meruva, R. B. Brown, M. E. Meyerhoff, *Anal. Chim. Acta* **1996**, *321*, 173 – 183.
[56] P. C. Hauser, D. W. L. Chiang, G. A. Wright, *Anal. Chim. Acta* **1995**, *302*, 241 – 248.
[57] M. Fibbioli, W. E. Morf, M. Badertscher, N. F. de Rooij, E. Pretsch, *Electroanalysis* **2000**, *12*, 1286 – 1292.
[58] M. Fibbioli, K. Bandyopadhyay, S.-G. Liu, L. Echegoyen, O. Enger, F. Diederich, P. Bühlmann, E. Pretsch, *Chem. Commun.* **2000**, 339 – 340.
[59] M. Fibbioli, K. Bandyopadhyay, S.-G. Liu, L. Echegoyen, O. Enger, F. Diederich, D. Gingery, P. Bühlmann, H. Persson, U. W. Suter, E. Pretsch, *Chem. Mater.* **2002**, *14*, 1721 – 1729.
[60] E. Grygolowicz-Pawlak, K. Wygladacz, S. Sek, R. Bilewicz, Z. Brzozka, E. Malinowska, *Sens. Actuators B* **2005**, *111–112*, 310 – 316.
[61] J. Bobacka, *Electroanalysis* **2006**, *18*, 7 – 18.
[62] A. Michalska, A. Konopka, M. Maj-Zurawska, *Anal. Chem.* **2003**, *75*, 141 – 144.
[63] A. Michalska, C. Appaih-Kusi, L. Y. Heng, S. Walkiewicz, E. A. H. Hall, *Anal. Chem.* **2004**, *76*, 2031 – 2039.
[64] J. Sutter, E. Lindner, R. E. Gyurcsányi, E. Pretsch, *Anal. Bioanal. Chem.* **2004**, *380*, 7 – 14.
[65] J. Sutter, A. Radu, S. Peper, E. Bakker, E. Pretsch, *Anal. Chim. Acta* **2004**, *523*, 53 – 59.
[66] L. Sundfors, R. Bereczki, J. Bobacka, K. Tóth, A. Ivaska, R. E. Gyurcsányi, *Electroanalysis* **2006**, *18*, 1372 – 1378.
[67] K. Y. Chumbimuni-Torres, N. Rubinova, A. Radu, L. T. Kubota, E. Bakker, *Anal. Chem.* **2006**, *78*, 1318 – 1322.
[68] L. Y. Heng, E. A. H. Hall, *Anal. Chem.* **2000**, *72*, 42 – 51.
[69] S. Peper, I. Tsagkatakis, E. Bakker, *Anal. Chim. Acta* **2001**, *442*, 25 – 33.
[70] L. Y. Heng, K. Tóth, E. A. H. Hall, *Talanta* **2004**, *63*, 73 – 87.
[71] A. Ceresa, E. Bakker, B. Hattendorf, D. Günther, E. Pretsch, *Anal. Chem.* **2001**, *73*, 343 – 351.
[72] V. I. Slaveykova, K. J. Wilkinson, A. Ceresa, E. Pretsch, *Environ. Sci. Technol.* **2003**, *37*, 1114 – 1121.
[73] R. E. Gyurcsányi, T. Vigassy, E. Pretsch, *Chem. Commun.* **2003**, 2560 – 2561.
[74] Y. Qin, E. Bakker, *Anal. Chem.* **2001**, *73*, 4262 – 4267.
[75] T. Vigassy, W. E. Morf, M. Badertscher, A. Ceresa, N. F. de Rooij, E. Pretsch, *Sens. Actuators B* **2001**, *76*, 477 – 482.
[76] S. Makarychev-Mikhailov, A. Shvarev, E. Bakker, *J. Am. Chem. Soc.* **2004**, *126*, 10548 – 10549.
[77] S. Peper, A. Ceresa, E. Bakker, E. Pretsch, *Anal. Chem.* **2001**, *73*, 3768 – 3775.
[78] K. Tompa, K. Birbaum, A. Malon, T. Vigassy, E. Bakker, E. Pretsch, *Anal. Chem.* **2005**, *77*, 7801 – 7809.
[79] A. Malon, E. Bakker, E. Pretsch, *Anal. Chem.* **2007**, *79*, 632 – 638.
[80] E. Pergel, R. E. Gyurcsányi, K. Tóth, E. Lindner, *Anal. Chem.* **2001**, *73*, 4249 – 4253.
[81] E. Lindner, R. E. Gyurcsányi, R. P. Buck, *Electroanalysis* **1999**, *11*, 695 – 702.
[82] W. E. Morf, M. Badertscher, T. Zwickl, N. F. de Rooij, E. Pretsch, *J. Electroanal. Chem.* **2002**, *526*, 19 – 28.
[83] A. Shvarev, E. Bakker, *J. Am. Chem. Soc.* **2003**, *125*, 11192 – 11193.
[84] Y. Qin, Y. Mi, E. Bakker, *Anal. Chim. Acta* **2000**, *421*, 207 – 220.
[85] M. Bochenska, I. Korczagin, *Polish J. Chem.* **2002**, *76*, 601 – 606.
[86] K. N. Mikhelson, J. Bobacka, A. Ivaska, A. Lewenstam, M. Bochenska, *Anal. Chem.* **2002**, *74*, 518 – 527.
[87] M. Bochenska, A. Zielinska, R. Pomecko, V. Hubscher-Bruder, F. Arnaud-Neu, *J. Inclusion Phenom. Macrocyclic Chem.* **2005**, *52*, 129 – 134.
[88] J.-P. Bourgeois, L. Echegoyen, M. Fibbioli, E. Pretsch, F. Diederich, *Angew. Chem.* **1998**, *110*, 2203 – 2207; *Angew. Chem. Int. Ed.* **1998**, *37*, 2118 – 2121.
[89] J.-P. Bourgeois, P. Seiler, M. Fibbioli, E. Pretsch, F. Diederich, L. Echegoyen, *Helv. Chim. Acta* **1999**, *82*, 1572 – 1595.
[90] R. Bereczki, R. E. Gyurcsányi, B. Agai, K. Tóth, *Analyst* **2005**, *130*, 63 – 70.
[91] M. H. Lee, C. L. Yoo, J. S. Lee, I.-S. Cho, B. H. Kim, G. S. Cha, H. Nam, *Anal. Chem.* **2002**, *74*, 2603 – 2607.
[92] Y. Qin, S. Peper, A. Radu, A. Ceresa, E. Bakker, *Anal. Chem.* **2003**, *75*, 3038 – 3045.
[93] M. Telting-Diaz, E. Bakker, *Anal. Chem.* **2001**, *73*, 5582 – 5589.
[94] M. Püntener, T. Vigassy, E. Baier, A. Ceresa, E. Pretsch, *Anal. Chim. Acta* **2004**, *503*, 187 – 194.
[95] M. M. Reinoso-Garcia, D. Janczewski, D. N. Reinhoudt, W. Verboom, E. Malinowska, M. Pietrzak, C. Hill, J. Báca, B. Grüner, P. Selucky, C. Grüttner, *New J. Chem.* **2006**, *30*, 1480 – 1492.
[96] E. Malinowska, L. Górski, D. Wojciechowska, M. M. Reinoso-Garcia, W. Verboom, D. N. Reinhoudt, *New J. Chem.* **2003**, *27*, 1440 – 1445.
[97] Y. Qin, E. Bakker, *Talanta* **2002**, *58*, 909 – 918.
[98] A. Ceresa, Y. Qin, S. Peper, E. Bakker, *Anal. Chem.* **2003**, *75*, 133 – 140.