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Modern Potentiometry**

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Abstract

For most chemists, potentiometry with ion-selective electrodes (ISEs) probably just means pH measurements with a glass electrode. Only 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 known that potentiometry went through a silent revolution during the last decade. The lower detection limit and the discrimination of interfering ions (the selectivity coefficients) have been improved in many cases by a factor of up to 10^6 and 10^{10}, respectively. This opens up new fields of application including environmental trace analysis and potentiometric biosensing. Another important novel application covered in this review is the determination of complex formation constants between lipophilic hosts and ionic guests.

Keywords

ion-selective electrodes; trace measurements; host-guest complexes; miniaturization; bioanalysis

1. The New Wave of Potentiometry

Potentiometric sensors based on liquid or polymer membrane materials are an established technology that successfully spearheaded the integration of sensing devices in the clinical laboratory for the automated testing of physiological samples for key electrolytes such as potassium, sodium, calcium, chloride and pH.[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 yet understood. The subsequent explanation of the response mechanism as a non-equilibrium ion-exchange/counterdiffusion process[7,8] helped launch the field of non-classical potentiometry.[9]

In parallel, success with optical sensors with regard to reaching low detection limits down to sub-nanomolar levels[10] put into question the unattractive detection limits of higher than micromolar levels observed with the corresponding ion-selective electrodes (ISEs) based on

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the very same materials.[11,12] The detection limit of potentiometric sensors, it turned out, was also dictated by non-equilibrium diffusion processes across the membrane,[13,14] which could be described in some analogy to the polyion sensors mentioned above.[15,16] Understanding and eliminating the undesired zero-current ion fluxes of ions from the membrane into the sample solution helped to lower the detection limits of ISEs to ultra-trace levels.[14,17,18] Subsequently, research has continued in direction of miniaturization and simplification of the fabrication process by incorporating suitable solid rather than aqueous inner contacts[19] in order to show that potentiometry is a very useful technology to assess ultra-low total ion quantities in small sample volumes.[20,21] This is especially attractive when 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 IESs 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 up to 10 orders of magnitude than 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 of further developments in this attractive field.

2. Ion Selectivities

The selectivity of a polymer membrane based ISE may be understood from an empirical or mechanistic perspective, and there has been a significant debate of the importance of either. In the context of the design and characterization of molecular hosts, membrane materials, and achieving 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}, where the subscripts I and J refer to the primary (analyte) ion and the interfering ion, respectively. Smaller values of the selectivity coefficients translate into a better selectivity for I. It 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, for instance, the selectivity coefficient is described as:[2]

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

where K_{IJ} is the ion-exchange constant of the uncomplexed ions between the aqueous (aq) and membrane phase (m), describing the following equilibrium:

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

and β_{IL} and β_{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}, with more lipophilic primary ions I^{z+} giving smaller selectivity coefficients. Clearly, host molecules (ionophores) binding much more strongly the primary than the interfering ions are necessary to achieve a selectivity pattern that significantly deviates from that of a simple ion-exchanger based membrane, whose selectivity is dictated by K_{IJ} alone.

The selectivity coefficient is experimentally accessible by recording separate calibration curves for each of the ions of interest and observing Nernstian calibration slopes. For the measurement of the primary ion, the following relationship between electromotive force, *emf*, and ion activity, a_I, is expected:

$$emf = E_I^0 + \frac{2.303RT}{zF}\log a_I \quad (3)$$

where *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 as

$$\log K_{IJ}^{pot} = \frac{zF}{2.303RT}(E_J^0 - E_I^0) \quad (4)$$

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:

$$emf = E_I^0 + \frac{2.303RT}{zF}\log(a_I + K_{IJ}^{pot}a_J) \quad (5)$$

Here, the meaning of the selectivity coefficient is apparent as a weighting factor for the interfering ion. Response functions for two ions of different charges or in case of relevant ion fluxes are described with more complex of equations.[32,33]

The historical challenge of obtaining selectivity coefficients that truly reflect the underlying ion-exchange selectivitiy [Eq. (1)] originated in incomplete ion-exchange upon exposure of the ISE membrane to interfering ions. This was especially problematic with strongly discriminated interfering ions. It was overcome either by working with membranes that had never been exposed to the primary ion before measurement (see Figure 1),[24] by adding a complexing agent for the primary ion to the aqueous phase,[34,35] or by using membranes that exhibited a strong ion flux in direction of the inner solution, effectively prohibiting 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 re-evaluated systems, the selectivity coefficients can sometimes reach values on the order of 10^{-10} to 10^{-15}, many orders of magnitude better than those observed according to 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 is caused by interfering ions, hence its value is defined by the concentration of other ions in the sample and the corresponding selectivity coefficients, K_{IJ}^{pot}, 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 $a_I(\mathrm{DL}) = K_{IJ}^{pot} a_J^{z_I/z_J}$. Note that this IUPAC definition[37,38] does not correspond to that of all other analytical methods [49] (also by IUPAC) where 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 according to the expression given above.[18]

Unfortunately, at submicromolar concentrations of the analyte ion, detection limits according to the above expression cannot be fully achieved. While they are still related to the selectivity and the concentration of interfering ions, the relationship is much more complicated[30] because of the sample being contaminated by the sensing membrane. The concentration of ions in an ISE membrane is in the order of 10^{-2}–10^{-3} mol/kg. Therefore, leaching of a small fraction of them into the sample and/or a slow transport of primary ions from the inner solution to the sample is capable of biasing the response of ISE membranes at submicromolar 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 ca. 10^{-6} M. For the same reason, the relevance of interfering ions had been heavily overestimated. What was supposed to be interference, was in fact due to the presence of the above-mentioned micromolar concentration of primary ions. After having discovered the real cause,[13,14] a series of different methods have been designed to reduce this bias.[51] Today, it is clear that it cannot be entirely eliminated and that the lower detection limit at submicromolar concentrations is always less good than expected from the interferences by other ions alone.[30] Since, however, many selectivity coefficients have turned out to be really very low (down to ca. 10^{-15}), detection limits around 10^{-8}–10^{-10} M have already been found for more than ten ions (see Table 1).

4. Miniaturization

Conventional ISEs are based on polymeric membranes (in most cases, plasticized poly(vinyl chloride), PVC) of a diameter of 5–10 mm and are usually, on their inner side, in contact 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] current development mainly goes in direction of membrane dimensions of about 0.1–1 mm. This is the typical size of ISE membranes used in blood electrolyte analysis, for which about 100 μL of blood, serum, or plasma are used for about ten parallel measurements on a single sample.[1]

More recent efforts have focused on the construction of ISEs of this size, which have improved lower detection limits to be 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 since, in contrast to most other techniques, the analyte is not consumed during measurements. Because conventional reference electrodes cannot be used in such small samples, a second miniaturized ISE membrane is utilized as reference, which responds to an ion whose activity is kept constant. In a recent example, plasticized PVC membranes prepared in micropipette tips have been 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 (see Figures 3 and 4).[20] Alternatively, 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 allow for simpler fabrication and currently 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. This was due to the lack of a defined redox couple between the membrane and the inner electrode[55,56] as well as to 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 (cf. Figure 5).[58–60] As a more versatile possibility, conducting polymers have been extensively investigated during recent years.[61] Already more than ten years ago, they have been shown to be excellent ion-to-electron transducers in so-called all-solid-state electrodes.[19] However, their use with ISEs exhibiting submicromolar 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 be investigated more lately.[64–66] If the presence of a water film is avoided, the same good, or even better, lower detection limits can be achieved with miniaturized solid-contact ISEs than with 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 regarding the response time and possible formation of the above water film but a disadvantage as to the conditioning time. Although many details and the best procedure of preparation are still to be established, it seems that miniaturized solid-contact ISEs represent the preferred way of constructing the upcoming ISE generation.

5. Applications

For decades, besides pH determinations, clinical analyses have been the most important practical application of ISEs. Since the physiological ranges of relevant ions are rather narrow, the precision and accuracy must be better than 2–3%, which is rather demanding given the small sample amounts and such complex media as whole blood.[1] As a more recent clinical application, the determination of heparin and its antidote protamine has emerged.[8] Due to their high charges z (−70 or +30 for heparin or protamine, respectively), the sensitivity, i.e., the slope of the corresponding sensor response function (59.2/z mV/decade), would normally be negligibly small so that non-classical potentiometry must be used to assess these clinically important polyions (see below).[7]

Various practical applications of ISEs with recently improved lower detection limits are actually being developed. Their utility for trace metal analysis in drinking water has been documented by obtaining good agreement with results from ICPMS measurements.[47,71] Since 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 during potentiometric measurements is in its free form. The pH dependence of the response of a Pb^{2+}-ISE to 10 ppb of Pb^{2+} illustrates this (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 ICPMS (Figure 7).[71]

The ISEs with improved lower detection limits have also been successfully applied in bio-uptake studies of Pb^{2+} and Cd^{2+}.[46,72]

One emerging application of miniaturized ISEs is potentiometric biosensing using nanoparticle labels. This has been 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^{+}-ISE (Figure 8).[22] This assay showed good selectivity and a detection limit of about

12.5 pmol of IgG in a 50 μμL sample (Figure 9).[22] A further possible utility of such miniaturized ISEs is the sensitive detection of biorecognition-

The measurement of complex formation constants in lipophilic phases is another recent application of ISEs, which might be attractive for studying host-guest interactions. The potential difference at the phase boundary membrane/solution is a direct function of the activity of ions, a_i(aq)/a_i(mem), 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, on complex formation constants. Since complex formation also influences the phase boundary potential on the inner side of the membrane and, in addition, the ISE response depends on the relative lipophilicity of the ions as well (see Eq. (1)), some 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. Adequate reference ionophores are organic bases that strongly interact with H^+ but only negligibly with other ions.[26] As another approach, reference cations such as tetraalkylammonium have been used, which show only negligibly small interactions with the ionophores investigated.[27] Finally, one can prepare a reference membrane without the ionophore but otherwise having the same composition as the membrane to be investigated. When the two membranes are united 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] Since 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 also be used to study ion-pair formations 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 not limited to complexes of moderate strength. Since they are rather simple and much less demanding than the other techniques, it is expected that in the future, they will be more widely applied in this field.

6. Non-Classical Potentiometry

Zero-current concentration polarization at the ISEmembrane has been described above as highly undesirable for characterizing the underlying ion-exchange selectivity and for reaching ultra-trace detection limits. They can be very attractive for a number of applications, however. 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 electrode slope decreases linearly with the charge of the ion. Analytically useful polyion sensors have been designed by taking advantage of a counterdiffusion process, where the polyion of interest is locally depleted at the membrane surface during the accumulation process. This makes the response of the ISE dependent on mass transport limitation of the polyion to the membrane surface, and result in electrode slopes significantly larger than 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, demonstrating that such non-classical sensing schemes can be practically useful.[8]

Non-classical potentiometry may also be attractive in other situations, since a concentration polarization at the sample side of the membrane may give more information about the sample than ion activities according to the Nernst equation [Eq. (3)]. Interesting examples include chemical alarm systems with an unusually high sensitivity and without the need of reference electrodes[75,76] as well as monitoring chemical titrations showing 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 of the membrane are almost instantly eliminated when the membrane-internal concentration gradient is reduced to zero by a judicious choice of the composition of the inner solution.

In recent years, this direction in ISE research has been further strengthened by the introduction of current control to instrumentally induce an ion flux across the membrane. Initial examples of this technique use 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 last decade. New applications include the study of host-guest equilibria in lipophilic organic phases and trace analysis in environmental samples. One emerging new field is potentiometric bioanalysis using nanoparticle labels or nanopores, which could eventually provide an inexpensive and highly sensitive technology. Another ongoing development is the field of non-classical potentiometry including controlled current measurements.

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References

1. Young CC. J Chem Educ 1997;74:177–182.
2. Morf, WE. The Principles of Ion–Selective Electrodes and of Membrane Transport. Elsevier; New York: 1981.
3. Koryta, J.; Stulik, K. Ion–Selective Electrodes. Cambridge University Press; Cambridge, GB: 1983.
4. Buck RP, Lindner E. Anal Chem 2001;73:88A–97A.
5. Bakker E, Bühlmann P, Pretsch E. Chem Rev 1997;97:3083–3132. [PubMed: 11851486]
6. Ma SC, Meyerhoff ME, Yang VC. Anal Chem 1992;64:694–697. [PubMed: 1580363]
7. Fu B, Bakker E, Yun JH, Yang VC, Meyerhoff ME. Anal Chem 1994;66:2250–2259. [PubMed: 8080104]
8. Meyerhoff ME, Fu B, Bakker E, Yun JH, Yang VC. Anal Chem 1996;68:168A–175A.
9. Bakker E, Meyerhoff ME. Anal Chim Acta 2000;416:121–137.
10. Morf WE, Seiler K, Rusterholz B, Simon W. Anal Chem 1990;62:738–742.
11. Lerchi M, Bakker E, Rusterholz B, Simon W. Anal Chem 1992;64:1534–1540.
12. Bühlmann P, Pretsch E, Bakker E. Chem Rev 1998;98:1593–1687. [PubMed: 11848943]
13. Mathison S, Bakker E. Anal Chem 1998;70:303–309.
14. Sokalski T, Ceresa A, Zwickl T, Pretsch E. J Am Chem Soc 1997;119:11347–11348.
15. Sokalski T, Zwickl T, Bakker E, Pretsch E. Anal Chem 1999;71:1204–1209.
16. Morf WE, Badertscher M, Zwickl T, de Rooij NF, Pretsch E. J Phys Chem B 1999;103:11346–11356.
17. Bakker E, Pretsch E. Anal Chem 2002;74:420A–426A. [PubMed: 11811417]
18. Bakker E, Pretsch E. Trends Anal Chem 2005;24:199–207.
19. Cadogan A, Gao Z, Lewenstam A, Ivaska A, Diamond D. Anal Chem 1992;64:2496–2501.
20. Malon A, Vigassy T, Bakker E, Pretsch E. J Am Chem Soc 2006;128:8154–8155. [PubMed: 16787077]

21. Rubinova N, Chumbimuni-Torres K, Bakker E. Sens Actuators B. in press
22. Chumbimuni-Torres KY, Zong D, Rubinova N, Xiang Y, Pretsch E, Wang J, Bakker E. J Am Chem Soc 2006;128:13673–13677.
23. Shvarev A, Bakker E. Anal Chem 2003;75:4541–4550. [PubMed: 14632062]
24. Bakker E. Anal Chem 1997;69:1061–1069.
25. Bakker E, Pretsch E, Bühlmann P. Anal Chem 2000;72:1127–1133. [PubMed: 10740849]
26. Bakker E, Pretsch E. Anal Chem 1998;70:295–302.
27. Ceresa A, Pretsch E. Anal Chim Acta 1999;395:41–52.
28. Mi Y, Bakker E. Anal Chem 1999;71:5279–5287. [PubMed: 10596210]
29. Shultz MM, Stefanova OK, Mokrov SB, Mikhelson KN. Anal Chem 2002;74:510–517. [PubMed: 11838668]
30. Ceresa A, Radu A, Peper S, Bakker E, Pretsch E. Anal Chem 2002;74:4027–4036. [PubMed: 12199570]
31. Bakker E, Bühlmann P, Pretsch E. Talanta 2004;63:3–20.
32. Bakker E, Meruva RK, Pretsch E, Meyerhoff ME. Anal Chem 1994;66:3021–3030. [PubMed: 7978299]
33. Nägele M, Bakker E, Pretsch E. Anal Chem 1999;71:1041–1048.
34. Schefer U, Ammann D, Pretsch E, Oesch U, Simon W. Anal Chem 1986;58:2282–2285.
35. Sokalski T, Maj-Zurawska M, Hulanicki A. Mikrochim Acta 1991;114:285–291.
36. Sokalski T, Ceresa A, Fibbioli M, Zwickl T, Bakker E, Pretsch E. Anal Chem 1999;71:1210–1214.
37. Guilbault GG, Durst RA, Frant MS, Freiser H, Hansen EH, Light TS, Pungor E, Rechnitz G, Rice NM, Rohm TJ, Simon W, Thomas JDR. Pure Appl Chem 1976;48:127–132.
38. Buck RP, Lindner E. Pure Appl Chem 1993;66:2527–2536.
39. Vigassy T, Huber CG, Wintringer R, Pretsch E. Anal Chem 2005;77:3966–3970. [PubMed: 15987098]
40. Qin W, Zwickl T, Pretsch E. Anal Chem 2000;72:3236–3240. [PubMed: 10939393]
41. Radu A, Peper S, Gonczy C, Runde W, Diamond D. Electroanalysis 2006;18:1379–1388.
42. Bedlechowicz I, Maj-Zurawska M, Sokalski T, Hulanicki A. J Electroanal Chem 2002;537:111–118.
43. Szigeti Z, Malon A, Vigassy T, Csokai V, Grün A, Wygladacz K, Ye N, Xu C, Chebny VJ, Bitter I, Rathore R, Bakker E, Pretsch E. Anal Chim Acta 2006;572:1–10. [PubMed: 17723454]
44. Vigassy T, Gyurcsányi RE, Pretsch E. Electroanalysis 2003;15:1270–1275.
45. Ion AC, Bakker E, Pretsch E. Anal Chim Acta 2001;440:71–79.2002, 452, 329
46. Plaza S, Szigeti Z, Geisler M, Martinoia E, Pretsch E. Anal Biochem 2005;347:10–16. [PubMed: 16266684]
47. Szigeti Z, Bitter I, Tóth K, Latkoczy C, Fliegel DJ, Günther D, Pretsch E. Anal Chim Acta 2005;532:129–136.
48. Malon A, Radu A, Qin W, Qin Y, Ceresa A, Maj–Zurawska M, Bakker E, Pretsch E. Anal Chem 2003;75:3865–3871. [PubMed: 14572055]
49. Currie LA. Pure Appl Chem 1995;67:1699–1723.
50. Gyurcsányi RE, Pergel E, Nagy R, Kapui I, Lan BTT, Tóth K, Bitter I, Lindner E. Anal Chem 2001;73:2104–2111. [PubMed: 11354497]
51. Szigeti Z, Vigassy T, Bakker E, Pretsch E. Electroanalysis 2006;18:1254–1265.
52. Thomas RC, Simon W, Oehme M. Nature 1975;258:754–756. [PubMed: 1207762]
53. Shim JH, Kim J, Cha GS, Nam H, White RJ, White HS, Brown RB. Anal Chem. submitted
54. Cattrall RW, Freiser H. Anal Chem 1971;43:1905–1906.
55. Liu D, Meruva RK, Brown RB, Meyerhoff ME. Anal Chim Acta 1996;321:173–183.
56. Hauser PC, Chiang DWL, Wright GA. Anal Chim Acta 1995;302:241–248.
57. Fibbioli M, Morf WE, Badertscher M, de Rooij NF, Pretsch E. Electroanalysis 2000;12:1286–1292.
58. Fibbioli M, Bandyopadhyay K, Liu S-G, Echegoyen L, Enger O, Diederich F, Bühlmann P, Pretsch E. Chem Commun 2000;5:339–340.

59. Fibbioli M, Bandyopadhyay K, Liu S-G, Echegoyen L, Enger O, Diederich F, Gingery D, Bühlmann P, Persson H, Suter UW, Pretsch E. Chem Mater 2002;14:1721–1729.
60. Grygolowicz–Pawlak E, Wygladacz K, Sek S, Bilewicz R, Brzozka Z, Malinowska E. Sens Actuators B 2005;111–112:310–316.
61. Bobacka J. Electroanalysis 2006;18:7–18.
62. Michalska A, Konopka A, Maj–Zurawska M. Anal Chem 2003;75:141–144. [PubMed: 12530830]
63. Michalska A, Appaih–Kusi C, Heng LY, Walkiewicz S, Hall EAH. Anal Chem 2004;76:2031–2039. [PubMed: 15053668]
64. Sutter J, Lindner E, Gyurcsányi R, Pretsch E. Anal Bioanal Chem 2004;380:1–14. [PubMed: 15309369]
65. Sutter J, Radu A, Peper S, Bakker E, Pretsch E. Anal Chim Acta 2004;523:53–59.
66. Sundfors L, Bereczki R, Bobacka J, Tóth K, Ivaska A, Gyurcsányi RE. Electroanalysis 2006;18:1372–1378.
67. Chumbimuni–Torres KY, Rubinova N, Radu A, Kubota LT, Bakker E. Anal Chem 2006;78:1318–1322. [PubMed: 16478128]
68. Heng LY, Hall EAH. Anal Chem 2000;72:42–51. [PubMed: 10655633]
69. Peper S, Tsagkatakis I, Bakker E. Anal Chim Acta 2001;1:25–33.
70. Heng LY, Tóth K, Hall EAH. Talanta 2004;63:73–87.
71. Ceresa A, Bakker E, Hattendorf B, Günther D, Pretsch E. Anal Chem 2001;73:343–351. [PubMed: 11199988]
72. Slaveykova VI, Wilkinson KJ, Ceresa A, Pretsch E. Environ Sci Technol 2003;37:1114–1121. [PubMed: 12680663]
73. Gyurcsányi RE, Vigassy T, Pretsch E. Chem Commun 2003:2560–2561.
74. Qin Y, Bakker E. Anal Chem 2001;73:4262–4267. [PubMed: 11569818]
75. Vigassy T, Morf WE, Badertscher M, Ceresa A, de Rooij NF, Pretsch E. Sens Actuators B 2001;76:477–482.
76. Makarychev–Mikhailov S, Shvarev A, Bakker E. J Am Chem Soc 2004;126:10548–10549. [PubMed: 15327306]
77. Peper S, Ceresa A, Bakker E, Pretsch E. Anal Chem 2001;73:3768–3775. [PubMed: 11510846]
78. Tompa K, Birbaum K, Malon A, Vigassy T, Bakker E, Pretsch E. Anal Chem 2005;77:7801–7809. [PubMed: 16316191]
79. Malon A, Bakker E, Pretsch E. Anal Chem. in press
80. Pergel E, Gyurcsányi RE, Tóth K, Lindner E. Anal Chem 2001;73:4249–4253. [PubMed: 11569816]
81. Lindner E, Gyurcsányi RE, Buck RP. Electroanalysis 1999;11:695–702.
82. Morf WE, Badertscher M, Zwickl T, de Rooij NF, Pretsch E. J Electroanal Chem 2002;526:19–28.
83. Shvarev A, Bakker E. J Am Chem Soc 2003;125:11192–11193. [PubMed: 16220929]
84. Qin Y, Mi Y, Bakker E. Anal Chim Acta 2000;421:207–220.
85. Bochenska M, Korczagin I. Polish J Chem 2002;76:601–606.
86. Mikhelson KN, Bobacka J, Ivaska A, Lewenstam A, Bochenska M. Anal Chem 2002;74:518–527. [PubMed: 11838669]
87. Bochenska M, Zielinska A, Pomecko R, Hubscher–Bruder V, Arnaud–Neu F. J Inclusion Phenom Macrocyclic Chem 2005;52:129–134.
88. Bourgeois J-P, Echegoyen L, Fibbioli M, Pretsch E, Diederich F. Angew Chem Int Ed Engl 1998;37:2118–2121.
89. Bourgeois J-P, Seiler P, Fibbioli M, Pretsch E, Diederich F, Echegoyen L. Helv Chim Acta 1999;82:1572–1595.
90. van Eis MJ, Pérez Núñez I, Muslinkina LA, Alvarado RJ, Pretsch E, Echegoyen L, Diederich F. J Chem Soc, Perkin Trans 2;2001:1890–1892.
91. van Eis MJ, Seiler P, Muslinkina LA, Badertscher M, Pretsch E, Diederich F, Alvarado RJ, Echegoyen L, Pérez Núñez I. Helv Chim Acta 2002;85:2009–2055.
92. Bereczki R, Gyurcsányi RE, Agai B, Tóth K. Analyst 2005;130:63–70. [PubMed: 15614355]

93. Lee MH, Yoo CL, Lee JS, Cho I-S, Kim BH, Cha GS, Nam H. Anal Chem 2002;74:2603–2607. [PubMed: 12069244]
94. Qin Y, Peper S, Radu A, Ceresa A, Bakker E. Anal Chem 2003;75:3038–3045. [PubMed: 12964748]
95. Telting–Diaz M, Bakker E. Anal Chem 2001;73:5582–5589. [PubMed: 11816591]
96. Püntener M, Vigassy T, Baier E, Ceresa A, Pretsch E. Anal Chim Acta 2004;503:187–194.
97. Reinoso–Garcia MM, Janczewski D, Reinhoudt DN, Verboom W, Malinowska E, Pietrzak M, Hill C, Báca J, Grüner B, Selucky P, Grüttner C. New J Chem 2006;30:1480–1492.
98. Malinowska E, Górski L, Wojciechowska D, Reinoso–Garcia MM, Verboom W, Reinhoudt DN. New J Chem 2003;27:1440–1445.
99. Qin Y, Bakker E. Talanta 2002;58:909–918.
100. Ceresa A, Qin Y, Peper S, Bakker E. Anal Chem 2003;75:133–140. [PubMed: 12530829]
101. Makarychev–Mikhailov S, Legin A, Mortensen J, Levitchev S, Vlasov Y. Analyst 2004;129:213–218. [PubMed: 14978522]

Biographies

Eric Bakker is a professor of chemistry at Purdue University in West Lafayette, Indiana. After earning his Ph.D. 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. This includes potentiometric and pulsed voltammetric sensors as well as fluorescent bead-based assay concepts. He has coauthored about 150 publications and review articles on this topic.

Ernö Pretsch studied chemistry at the Technical University Budapest and the ETH Zurich, where he also received his Ph.D. in 1968. At the ETH, he has worked as a research associate and, since 1991, as a Titularprofessor. His current research interests focus on potentiometric sensors in view of optimizing their lower detection limit, selectivity behavior, and rugged construction. He is also interested in the computer-aided interpretation of molecular spectra including NMR spectra prediction. He is elected external member of the Hungarian Academy of Sciences, Contributing Editor of Trends in Analytical Chemistry, and member of the Editorial Board of 6 further journals in the field of analytical chemistry or chemometrics. He is co-author of about 270 scientific papers and 9 books.

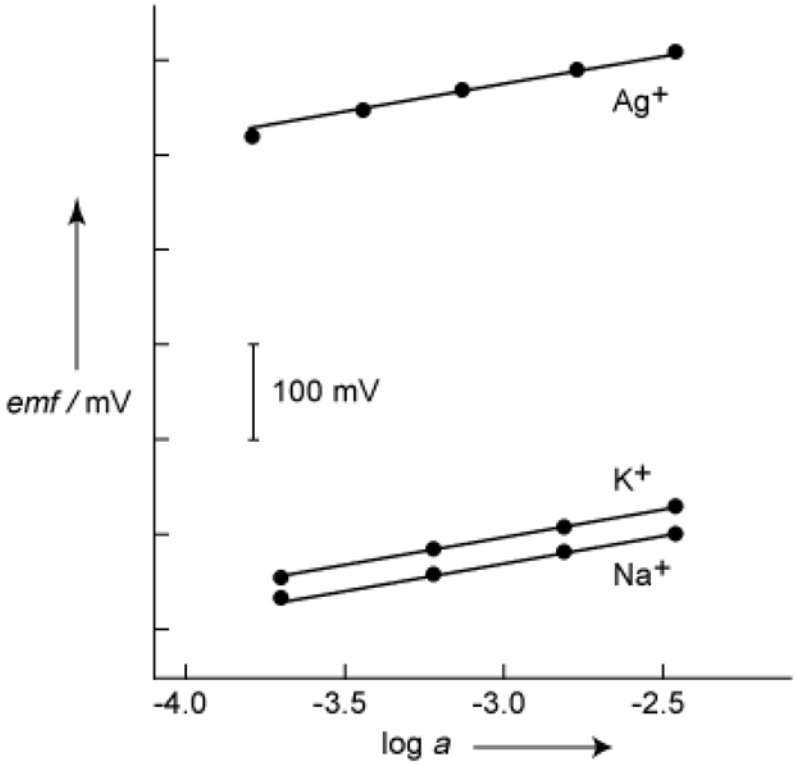


Figure 1.

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

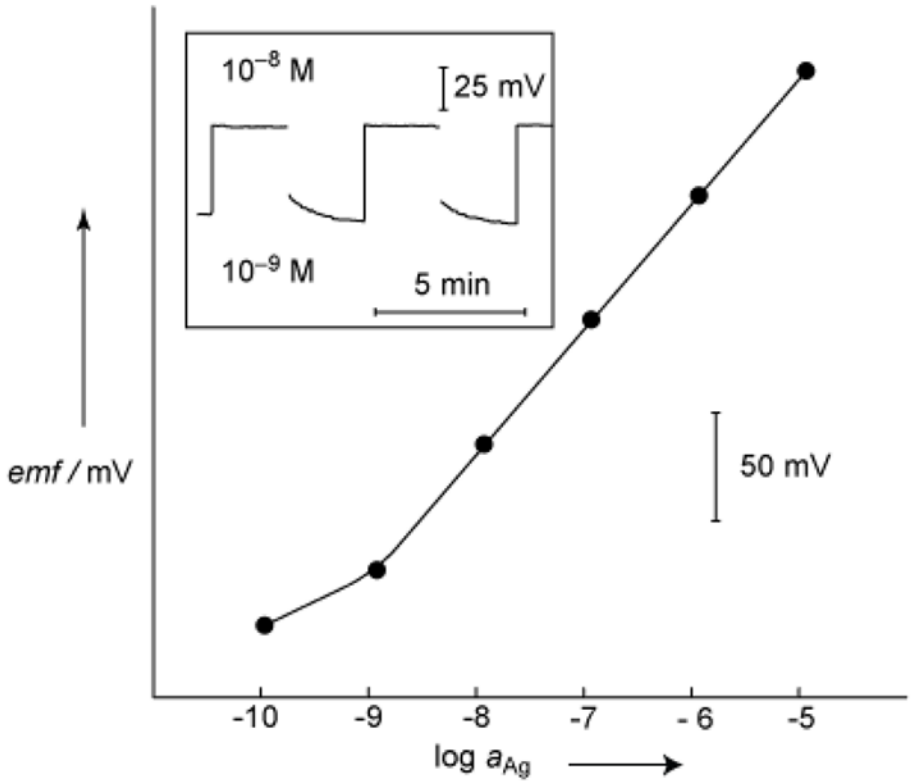


Figure 2.
Calibration curve of a Ag^+-selective polymer membrane electrode, exhibiting a subnanomolar detection limit.[21] Inset: Responses upon repeated exposure to 1 and 10 nanomolar levels of silver nitrate.

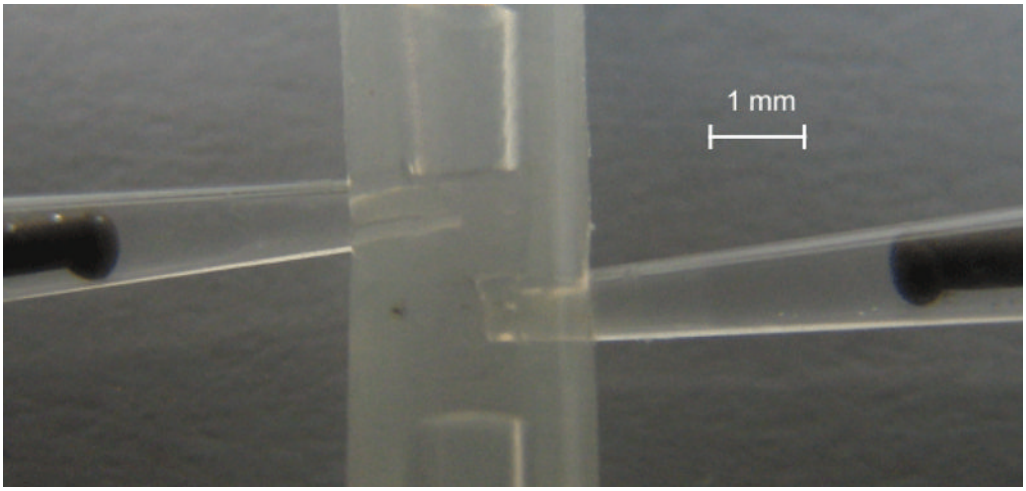


Figure 3.
Picture of the 3-μL measuring cell. A Ca^{2+}-ISE (left, indicator electrode) and a Na^{+}-ISE reference electrode (right) are inserted into a 1-mm i.d. silicone tubing and put in contact with the aqueous sample plug of 3 μL).[20]

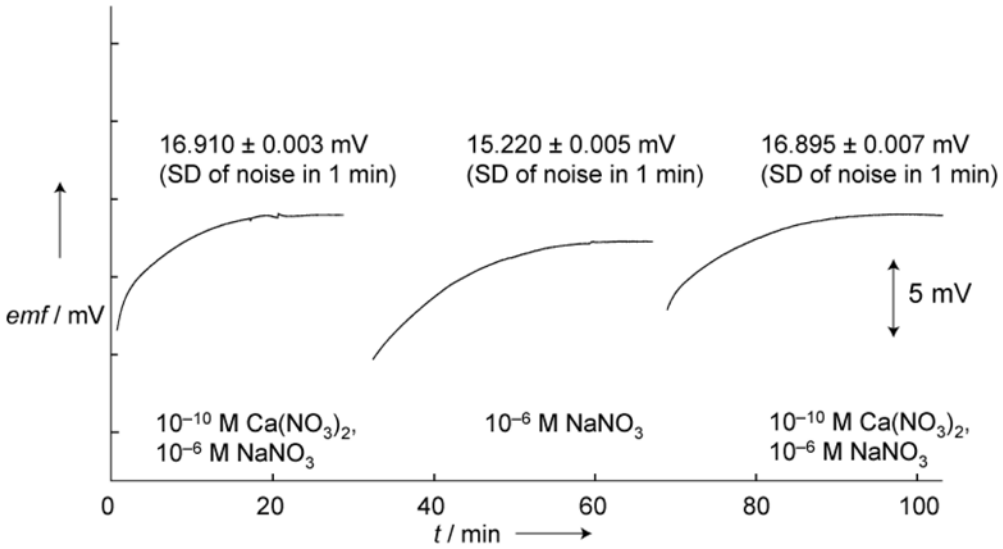


Figure 4.

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

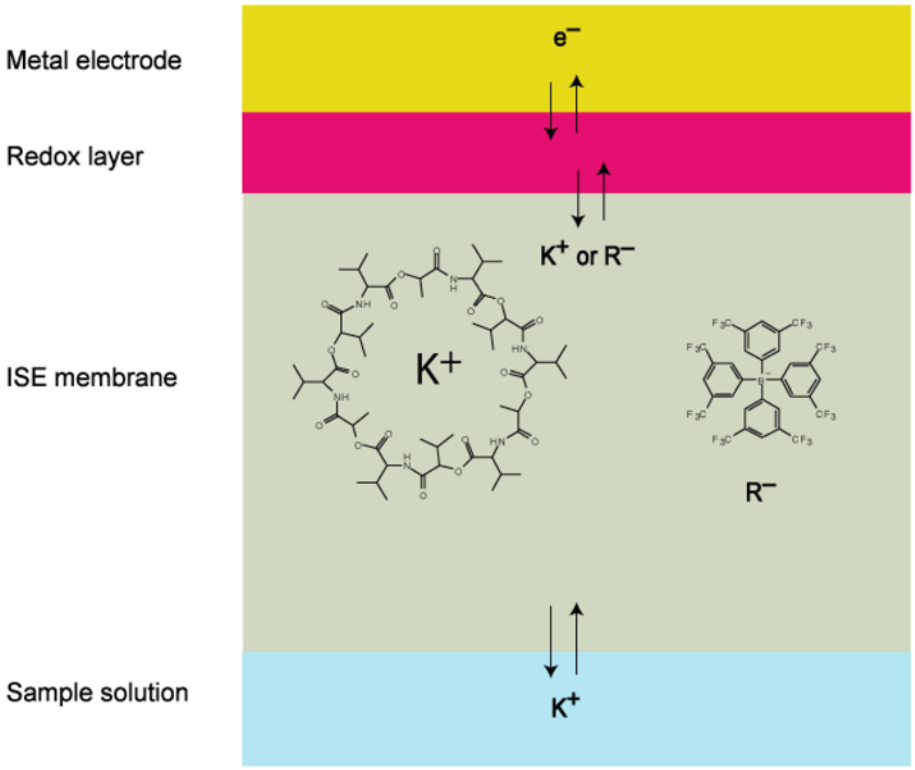


Figure 5.
Schematic representation of a solid-contact ISE. The measuring current (in the order of fA) is transported by ions in the solutions and the ISE membrane and by electrons in the metal. The two processes are coupled in the redox layer (a conducting polymer or a redox-active self-assembled monolayer). 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.

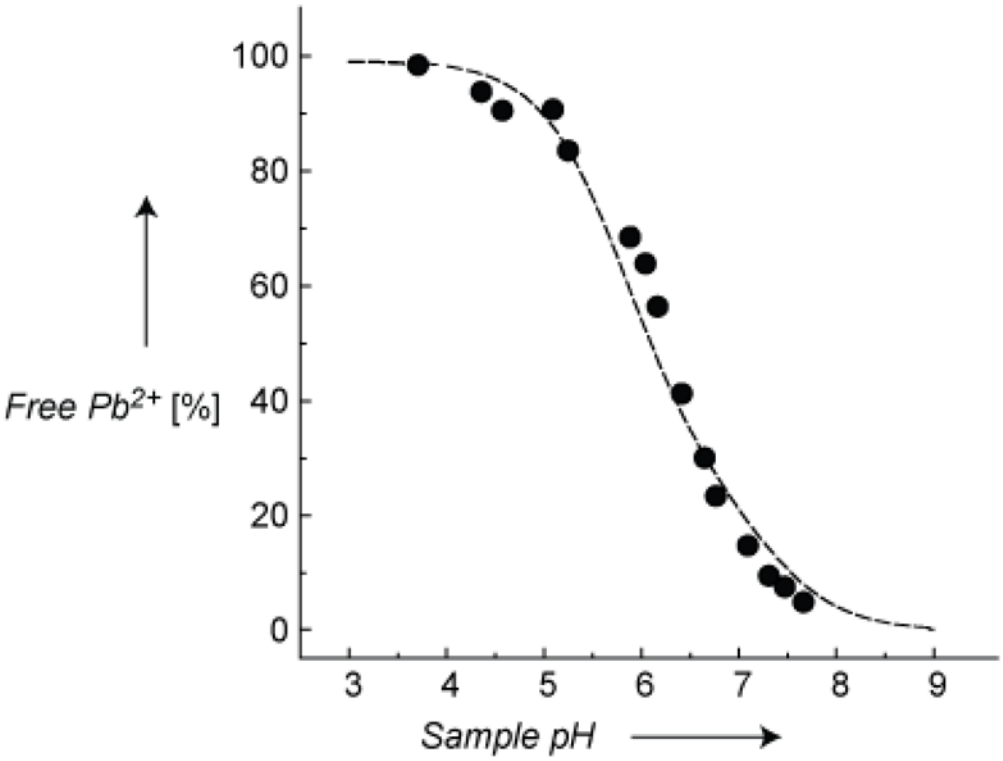


Figure 6.
Potentiometric determination of the fraction of uncomplexed Pb^{2+} as a function of pH in a drinking water sample spiked with 10 ppb of Pb^{2+}. Dashed line: calculated free Pb^{2+} activity for a total carbonate concentration of 4.14 mM.[71]

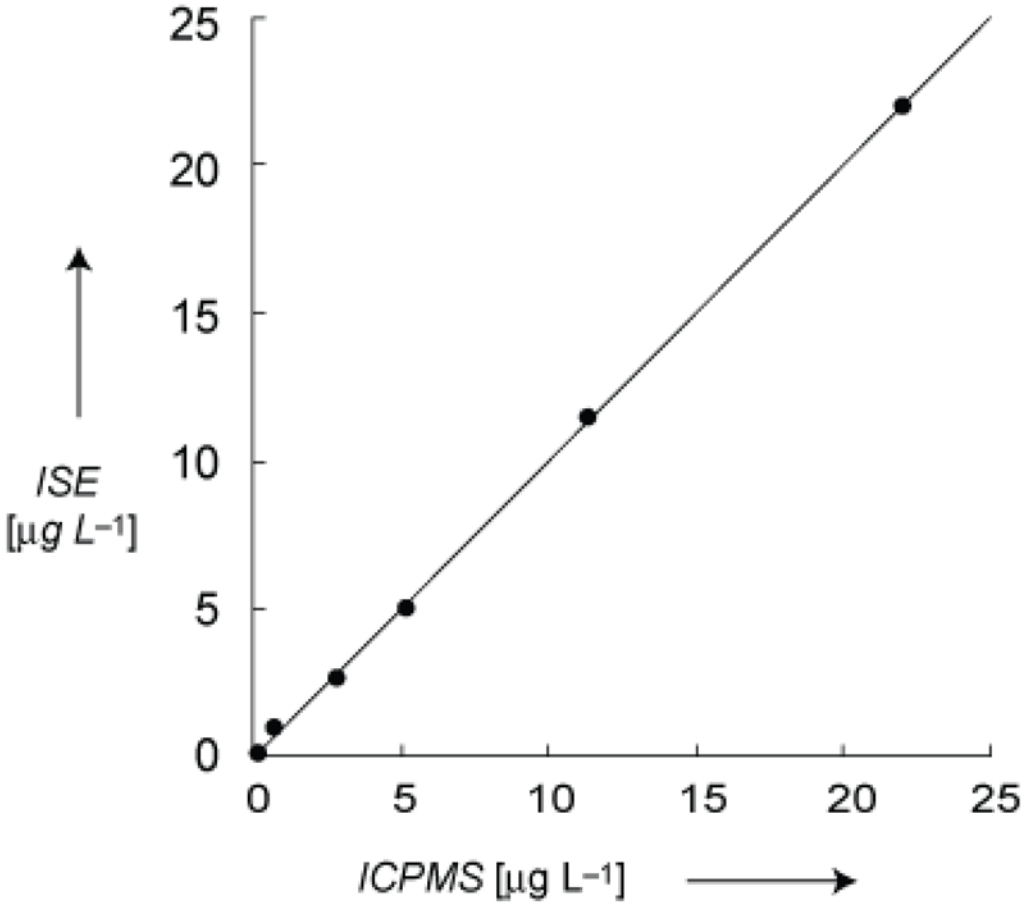


Figure 7.
Comparison of Pb^{2+} activity values of environmental samples obtained by potentiometry at pH 4.0 with those by ICPMS.[71]

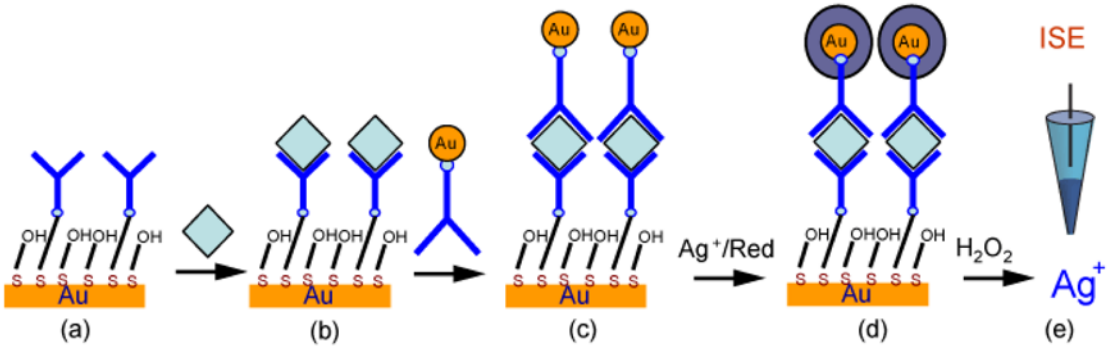


Figure 8.

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.

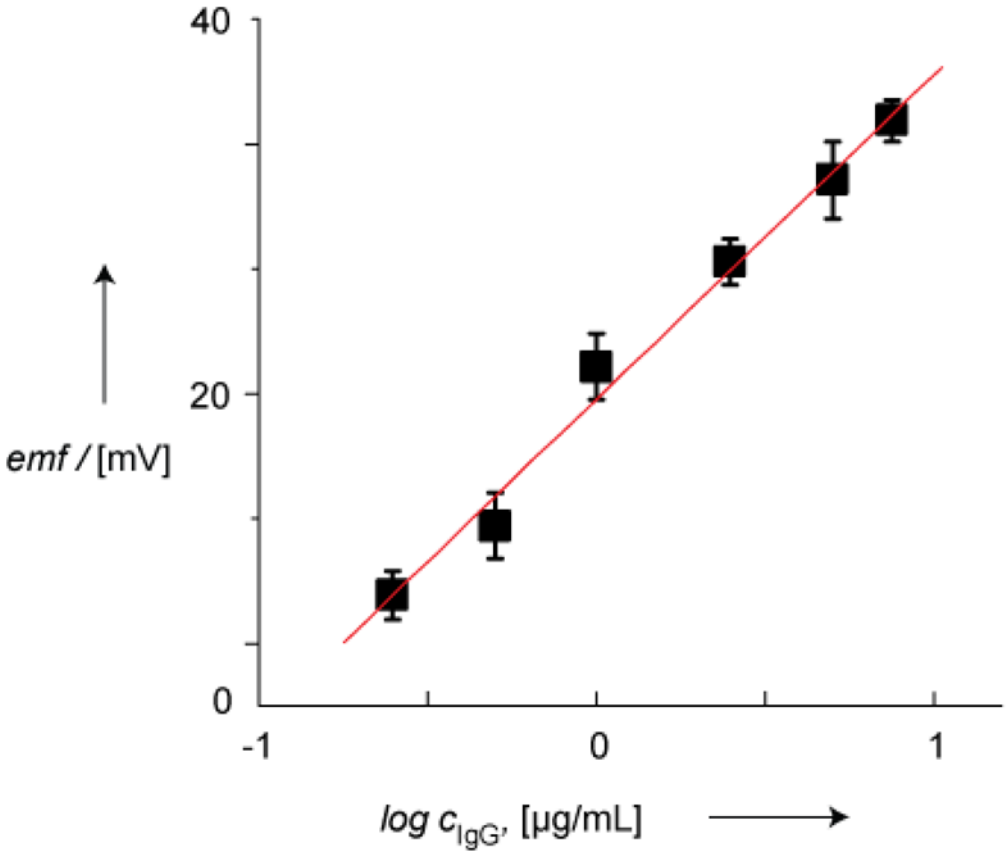


Figure 9.
Calibration curve of the Ag^+-ISE response to IgG.

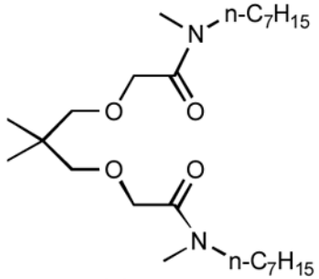
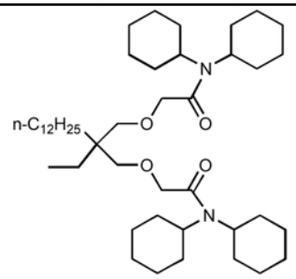
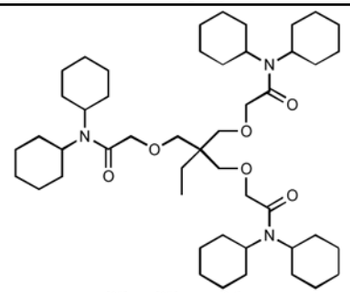
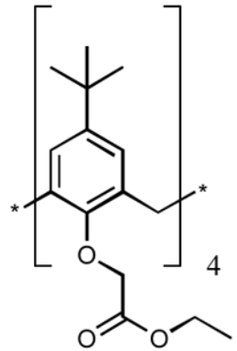
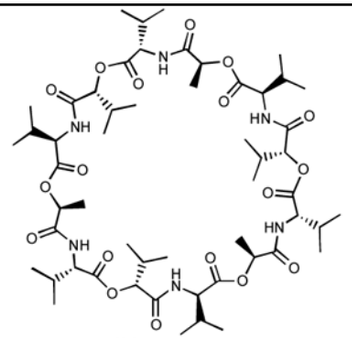
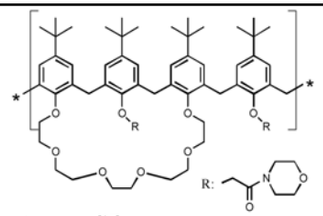
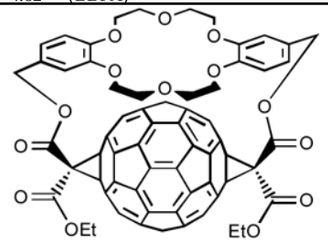
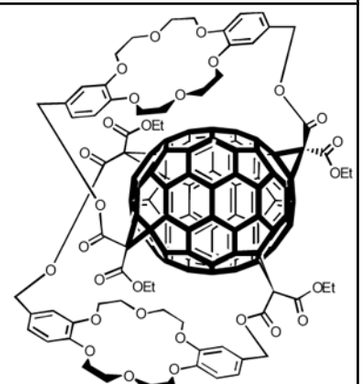
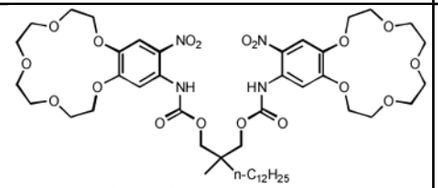
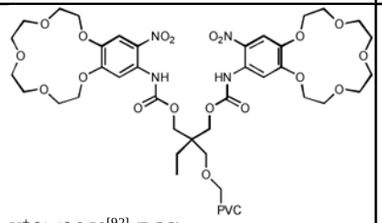
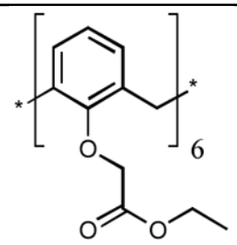
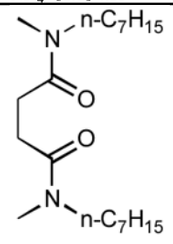
Table 1

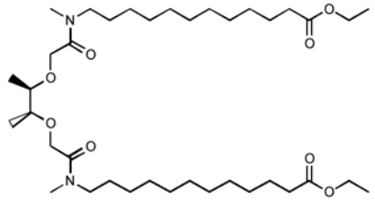
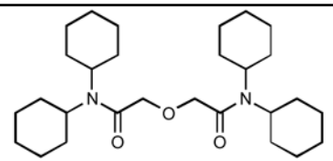
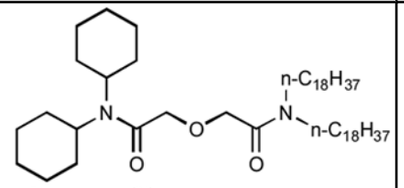
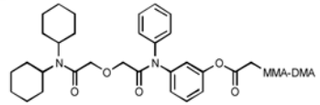
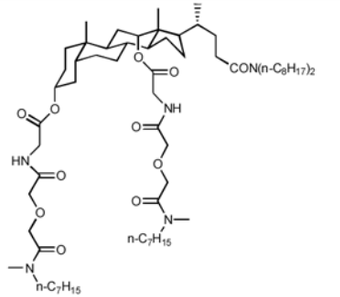
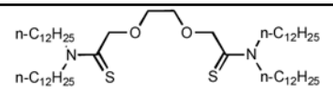
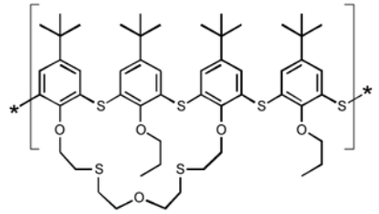
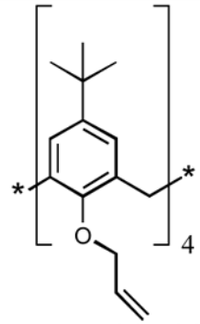
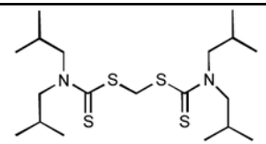
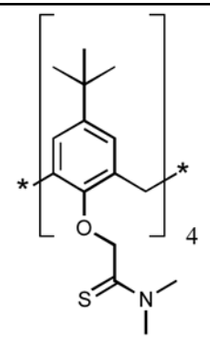
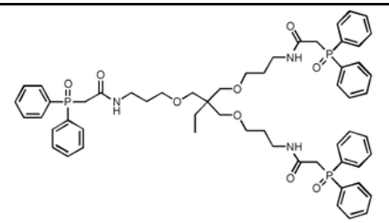
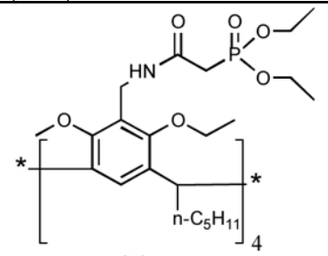
Unbiased selectivity coefficients and lower detection limits of selected ion-selective electrodes.

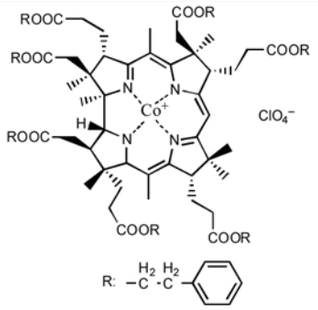
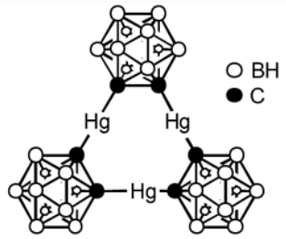
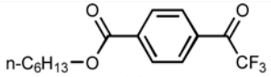
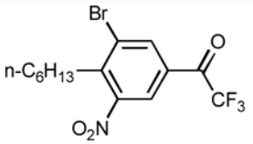
Ion	Detection limit [M]	Selectivity coefficients, log K_{IJ}^{pot}	Ref.
Na^+	3×10^{-8}	H^+: −4.8; K^+: −2.7; Ca^{2+}: −6.0	[39]
K^+	5×10^{-9}	Na^+: −4.2; Mg^{2+}: −7.6; Ca^{2+}: −6.9	[40]
NH_4^+	2×10^{-8}		[40]
Cs^+	8×10^{-9}	Na^+: −4.7; Mg^{2+}: −8.7; Ca^{2+}: −8.5	[41]
Ca^{2+}	ca. 10^{-10}	H^+: −4.9;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

Table 2

Effective formation constants, log β_{IL}, for complexes of lipophilic hosts and ionic guests in solvent polymeric membranes with the given host-guest stoichiometry [in brackets].[a]

 Li^+ [2:1] 7.90[84] (DOS); 10.71[84] (NPOE)	 Li^+ [1:1] 5.9,[85] 7.0[85] (DOS) Na^+ [1:1] 4.1,[85] 5.2[85] (DOS) K^+ [1:1] 3.1,[85] 4.1[85] (DOS)	 Li^+ [1:1] 6.7,[85] 7.4[85], 8.24[84] (DOS); 7.40[86] (BBPA) Na^+ [1:1] 4.5,[85] 5.1[85] (DOS); 5.75[86] (BBPA) 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) Na^+ [1:1] 4.4[29] (DBP) NH_4^+ [1:1] 5.7[29] (DBP)	 K^+ [1:1] 8.0[87] (NPOE) Na^+ [1:1] 7.5[87] (NPOE) Rb^+ [1:1] 7.3[87] (NPOE)	 K^+ [1:1] 5.4[88,89] (DOS) Li^+ [1:1] 2.9[88,89] (DOS) Na^+ [1:1] 4.0[88,89] (DOS) Cs^+ [1:1] 3.3[88,89] (DOS)	 K^+ [1:1] 5.96;[90,91] [1:2] 11.31[90,91] (DOS) H^+ [1:1] 2.94[90,91] (DOS) Na^+ [1:1] 4.82[90,91] (DOS) NH_4^+ [1:1] 4.39[90,91] (DOS)
 K^+ [1:1] 7.84,[84] 7.75[92] (DOS); 10.04[84] (NPOE)	 K^+ [1:1] 6.50[92] (DOS)		

Li^+ [1:1] 4.22[28] (DOS) Na^+ [1:1] 6.00[28] (DOS)	Na^+ [1:1] 4.63[92] (DOS)	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[93] (NPOE)	 Ca^{2+} [3:1] 25.5[84] (DOS); 29.2,[84] 15.2[93] (NPOE)	 Ca^{2+} [3:1] 22.06[84] (DOS); 27.39[84] (NPOE)	 Ca^{2+} [3:1] 16.85[94] (in MMA-DMA^b matrix)
 Ca^{2+} [1:1] 8.6[93] (NPOE)	 Cd^{2+} [2:1] 16.4[27] (DOS) H^+ [1:1] <3[27] (DOS) Na^+ [1:1] <3[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)	 Ag^+ [1:1] 5.86,[43] 6.93[43] (NPOE)
 Ag^+ [2:1] 12.42,[28] 12.6[27] (DOS) H^+ [1:1] <3[27] (DOS) Na^+ [2:1] 2.8[28] (DOS) K^+ [1:1] <3[27] (DOS) Mg^{2+} [1:1] <3[27] (DOS) Ca^{2+} [1:1] <3[27] (DOS) Pb^{2+} [1:1] <3[27] (DOS) Cu^{2+} [1:1] <3[27] (DOS) Cd^{2+} [1:1] <3[27] (DOS)	 Pb^{2+} [1:1] 15.9,[27] 15.8[95] (DOS); 21.3,[95] 18.4[96] (NPOE) H^+ [1:1] <3[27] (DOS) Na^+ [1:1] 3.1[27] (DOS) K^+ [1:1] <3[27] (DOS) Mg^{2+} [1:1] <3[27] (DOS) Ca^{2+} [1:1] <3[27] (DOS) Cu^{2+} [1:1] 12.1[27] (DOS)	 Eu^{3+} [1:1] 28.3[97] (NPOE) Na^+ [1:1] 8.4[97] (NPOE) Cu^{2+} [1:1] 19.8[97] (NPOE) Cd^{2+} [1:1] 19.1[97] (NPOE) Pb^{2+} [1:1] 17.4[97] (NPOE) UO_2^{2+} [1:1] 21.5[97] (NPOE)	 Eu^{3+} [1:1] 31.0[98] (NPOE) Na^+ [1:1] 12.0[98] (NPOE) K^+ [1:1] 10.2[98] (NPOE) Mg^{2+} [1:1] 16.5[98] (NPOE) Ca^{2+} [1:1] 16.9[98] (NPOE) Sr^{2+} [1:1] 21.4[98] (NPOE) Ag^+ [1:1] 8.9[98] (NPOE) Cu^{2+} [1:1] 21.7[98] (NPOE) Cd^{2+} [1:1] 22.7[98] (NPOE) Pb^{2+} [1:1] 22.5[98] (NPOE) UO_2^{2+} [1:1] 25.5[98] (NPOE)

	Cd^{2+} [1:1] 10.0[27] (DOS)		
 NO_2^- [1:1] 10.58[99] (DOS); 10.59[99] (NPOE)	 Cl^- [2:1] 13.4[100] (DOS) (log K_1 = 9.9, log K_2 = 3.5)	 CO_3^{2-} [4:1] 12.8[29] (DBP) $CH3COO^-$ [2:1] 5.9[29] (DBP) Benzoate [2:1] 5.3[29] (DBP) Cl^- [2:1] 3.3[29] (DBP)	 CO_3^{2-} [3:1] 14.4[101] (DOS); 13.6[101] (NPOE)

[a] The PVC membranes were based on the following 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).